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Research Article

Antifibrotic Effects of Scutellarin on the Kidney in a Mouse Model of Unilateral Ureteral Obstruction

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Abstract

Background and Objective: Renal interstitial fibrosis (RIF) is a prevalent and irreversible process that drives the progression of chronic kidney disease (CKD) to end-stage renal failure and is characterized by significant deposition of fibrotic matrix proteins. The unilateral ureteral obstruction (UUO) model induces rapid tubulointerstitial fibrosis and is widely used to study antifibrotic interventions. Scutellarin, an active flavonoid derived from *Erigeron breviscapus*, has demonstrated efficacy in alleviating symptoms of various chronic diseases, including stroke, neurodegenerative disorders, and cardiovascular and renal diseases. However, the impact of scutellarin on renal fibrosis in obstructive nephropathy remains unclear. Thus, this study evaluated the effects of scutellarin on fibrosis and renal function in a UUO mouse model. **Materials and Methods**: Male C57BL/6 mice underwent UUO surgery and received oral scutellarin (21 mg/kg/day) for 3 days before and 5 days after surgery. Renal fibrosis was assessed by immunohistochemistry (IHC; collagen I) and Western blotting (WB; alpha-smooth muscle actin (α-SMA), fibronectin (FN), collagen I). Kidney function was evaluated by urinary protein (BCA assay), serum blood urea nitrogen (BUN), and serum creatinine (Scr). Data were analyzed using GraphPad Prism 8; $p < 0.05$ was considered statistically significant. **Results**: UUO induced significant interstitial fibrosis, as evidenced by increased collagen I deposition and elevated protein levels of α-SMA, FN, and collagen I. Scutellarin treatment significantly attenuated these changes, reducing the collagen I IHC-positive area to 0.63-fold and the α-SMA, FN, and collagen I protein levels (WB, normalized to glyceraldehyde-3-phosphate dehydrogenase) to 0.21-, 0.45-, and 0.54-fold of UUO levels, respectively (all $p < 0.01$). Concurrently, scutellarin significantly lowered proteinuria, BUN, and Scr compared with the UUO group (all $p < 0.0001$). **Conclusion**: Scutellarin ameliorated renal fibrosis and dysfunction in the UUO mouse model, associated with downregulation of key fibrosis-related proteins. These findings support further preclinical investigation of scutellarin as a potential antifibrotic agent in kidney disease.

Keywords: renal fibrosis; scutellarin; *Erigeron breviscapus*; ureteral obstruction; antifibrotic agents; alpha-SMA protein; fibronectin; collagen type I

1. Introduction

Chronic kidney disease (CKD) affects millions worldwide and frequently progresses to end-stage renal disease, requiring dialysis or transplantation. Renal interstitial fibrosis (RIF) characterized by excessive extracellular matrix (ECM) deposition and loss of functional parenchyma is the final common pathway underlying CKD progression, regardless of the initial etiology [1]. RIF disrupts renal architecture through fibroblast activation and ECM accumulation, leading to impaired glomerular filtration and tubular function [2]. Given its irreversible nature and central role in CKD, halting or reversing RIF has become a critical focus in nephrology research.

Myofibroblast activation is a pivotal event in RIF pathogenesis [3]. These specialized cells, characterized by the expression of alpha-smooth muscle actin (α-SMA) and fibronectin (FN), are the primary source of pathological ECM [4]. Both markers correlate strongly with the onset and severity of renal fibrosis. Myofibroblasts are highly responsive to transforming growth factor beta 1 (TGF-β1), a master regulator of their differentiation and ECM production [5]. Upon TGF-β1 stimulation, they proliferate and secrete abundant ECM components particularly collagen I and FN which accumulate in the tubulointerstitium, replacing normal parenchyma [6]. This fibrotic deposition not only compromises kidney function but also fosters a profibrotic microenvironment that perpetuates myofibroblast activation and disease progression [7].

The unilateral ureteral obstruction (UUO) mouse model is a well-established and widely used experimental

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system in nephrology research [8]. It rapidly induces renal fibrosis, inflammatory cell infiltration, oxidative stress, and ECM accumulation in the kidney, providing a reproducible platform for evaluating antifibrotic interventions [9,10]. Although UUO does not fully recapitulate the slow progression of human CKD, it reliably models key aspects of fibrogenesis relevant to multiple CKD etiologies.

Scutellarin, a bioactive flavonoid derived from the traditional Chinese medicinal herb *Erigeron breviscapus*, has attracted considerable attention in recent years due to its diverse pharmacological properties. Initially recognized for its cardiovascular benefits, including enhancing cardiac function and exerting antithrombotic effects [11], scutellarin has since been shown to possess a wide range of therapeutic activities in various preclinical models. Studies have demonstrated its anti-inflammatory [12,13], antioxidative [14,15], and antiapoptotic [16] effects, which contribute to its protective role in multiple disease states. In the context of fibrosis, scutellarin has shown promising results in ameliorating pulmonary fibrosis [17]. It achieves this by reducing collagen deposition in lung tissues and inhibiting the expression of inflammatory factors such as NLR family pyrin domain containing 3 (NLRP3), interleukin 1β (IL-1β), and Interleukin-18 (IL-18) [18]. These inflammatory mediators play crucial roles in promoting the epithelial mesenchymal transition (EMT), a process by which epithelial cells acquire a mesenchymal phenotype and contribute to fibrosis development [19]. Moreover, scutellarin has been shown to suppress α-SMA expression in a diabetic nephropathy mouse model [20], suggesting its potential in mitigating renal fibrosis through the inhibition of myofibroblast activation, however, its effects on fibrosis in the context of obstructive nephropathy remain unclear.

Based on this evidence, we hypothesized that scutellarin may attenuate renal fibrosis and dysfunction in the UUO model. Consequently, we investigated its effects on functional parameters, histological fibrosis, and the expression of key ECM and fibroblast activation markers.

2. Materials and Methods

2.1 Animals and the UUO Mouse Model

Six-week-old male C57BL/6J mice were purchased from the Experimental Animal Center of the Heshuo Business Department (Kunming, Yunnan, China). All animals were housed in a specific pathogen-free facility under controlled conditions (temperature: 22 $\pm$ 2 °C, humidity: 50 $\pm$ 10%) with a 12-h light/dark cycle and *ad libitum* access to standard chow and water. Only male mice were used in order to minimize hormonal variability and ensure consistent fibrotic responses. After a 2-week acclimatization period, mice were randomly assigned to three groups (n = 6 per group): sham, UUO, and scutellarin-treated UUO.

Scutellarin (purity $\geq$98%, HPLC verified; CAS No. 27749-61-5) was purchased from Chengdu Must Bio-Technology Co., Ltd. (Chengdu, Sichuan, China). The compound was freshly suspended in 0.5% (w/v) sodium carboxymethyl cellulose (CMC-Na) solution and administered to mice via oral gavage at a dose of 21 mg/kg/day. This dosage was selected based on prior preclinical studies and pilot dose-response experiments. Control animals received an equal volume of 0.5% CMC-Na vehicle alone. Mice in the scutellarin group received treatment for 3 consecutive days prior to surgery and continued for 5 days post-surgery, with the final dose administered approximately 2 h before euthanasia.

The UUO model was established by ligation of the left ureter at two sites using 6-0 silk suture through a left flank incision under anesthesia with sodium pentobarbital (50 mg/kg, i.p., 10 mg/mL). Sham-operated mice underwent identical surgical exposure without ureteral ligation. On day 6 post-surgery, all mice were euthanized with sodium pentobarbital (150 mg/kg, i.p., 10 mg/mL), and the left kidneys, serum, and urine were collected for subsequent analyses.

All procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the ARRIVE guidelines.

2.2 Immunohistochemical Staining

Mouse renal tissues were fixed in 4% paraformaldehyde, dehydrated through graded ethanol, and embedded in paraffin. Four-micrometer sections were deparaffinized, rehydrated, and incubated in 3% hydrogen peroxide for 30 min to block endogenous peroxidase activity. Antigen retrieval was performed by heating slides in citrate-based antigen unmasking solution (boiling, 5 min). Sections were blocked in 5% goat serum for 60 min at room temperature and then incubated overnight at 4 °C with primary antibody against collagen I (1:200, 14695-1-AP; Proteintech, Wuhan, Hubei, China). After washing three times with phosphate-buffered saline, sections were incubated with horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG secondary antibody (1:500, ab6721; Abcam, Cambridge, UK) for 50 min at room temperature. Immunoreactivity was visualized using a diaminobenzidine (DAB) chromogen substrate kit (ZSGB-BIO, Beijing, China), followed by hematoxylin counterstaining. Stained slides were imaged using the Leica microscope system (Leica Microsystems, Wetzlar, Germany), and collagen I positive areas (%) were quantified using ImageJ software (National Institutes of Health [NIH], Bethesda, MD, USA).

2.3 Western Blotting Analysis

Renal cortical tissues were homogenized in ice-cold lysis buffer containing protease and phosphatase inhibitors (KeyGen Biotech, Nanjing, Jiangsu, China). The bicinchoninic acid (BCA) assay was implemented to quantify the extracted protein concentrations. Equal amounts of protein were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis and electrotransferred to PVDF membranes (Roche Applied Sciences, Penzberg,

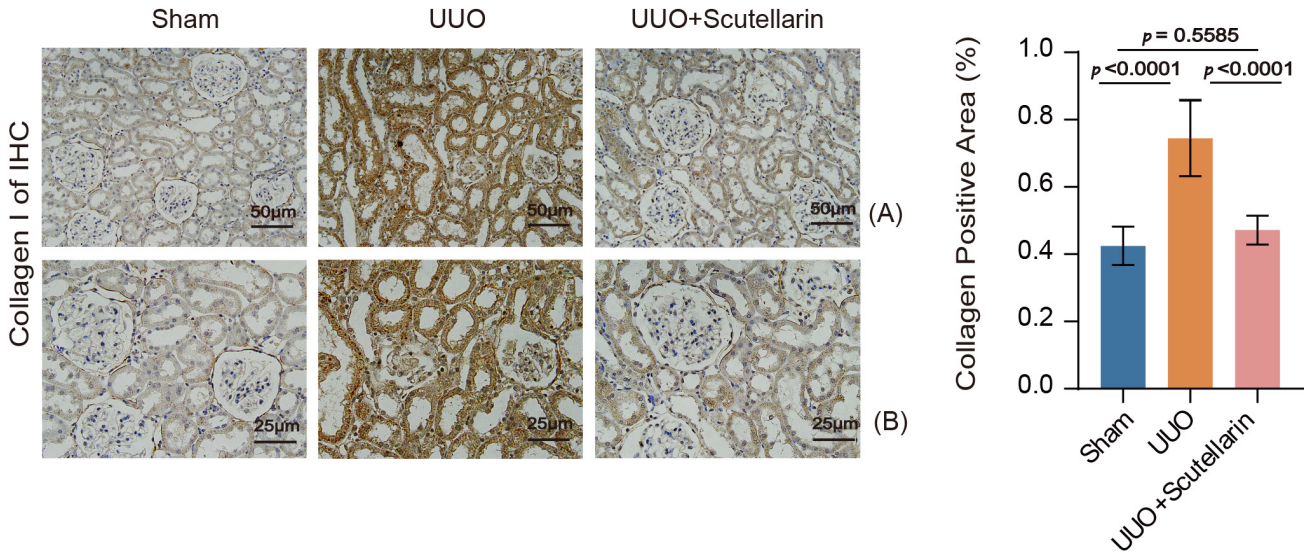

Fig. 1. Scutellarin therapy alleviated collagen deposition caused by UUO in mouse kidneys. Collagen positive area (%) was quantified by IHC. Data are shown as the mean ± SD (n = 6 per group). UUO, unilateral ureteral obstruction; IHC, immunohistochemistry. Scale bars: 50 μm (A) and 25 μm (B).

Bavaria, Germany). Membranes were blocked in 5% non-fat milk in Tris-buffered saline containing 0.1% Tween 20 (TBST) for 1 h at room temperature and then incubated overnight at 4 °C with primary antibodies targeting α-SMA (1:5000, 14395-1-AP; 42 kDa), FN (1:2000, 66042-1-Ig; 220–250 kDa), collagen 1 (1:1000, 14695-1-AP; 130 kDa), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (1:5000, 60004-1-Ig; 37 kDa) (all from Proteintech, Wuhan, Hubei, China). After three washes with TBST, the membranes were incubated with HRP-conjugated secondary antibodies: membranes probed with rabbit primary antibodies were incubated with goat anti-rabbit IgG (1:5000, ab6721; Abcam, Cambridge, England, UK), whereas those probed with mouse primary antibodies were incubated with goat anti-mouse IgG (1:5000, ab6789; Abcam, Cambridge, England, UK) for 1 h at room temperature. Proteins were visualized using enhanced chemiluminescence reagent (Thermo Fisher Scientific, Waltham, MA, USA), and densitometric ratios normalized to GAPDH were quantified by densitometric analysis with ImageJ software (NIH, Bethesda, MD, USA).

2.4 Biochemical Analysis

At the end of the experiment, urine and blood samples were collected from all mice. Urinary total protein, blood urea nitrogen (BUN) and serum creatinine (Scr) were measured to assess renal function. Total urinary protein concentration was determined using the Pierce BCA Protein Assay Kit (23225; Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. BUN and Scr levels were quantified using an automated biochemical analyzer (Hitachi 7080, Tokyo, Japan) with commercially available enzymatic reagents.

2.5 Statistical Analysis

Data are presented as the mean ± standard deviation (n = 6 independent animals per group). Comparisons among three groups were performed using one-way analysis of variance followed by Tukey's post hoc test using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). $p < 0.05$ was considered statistically significant. Exact values are reported for all significant comparisons in figures or figure legends.

3. Results

3.1 Scutellarin Administration Attenuates the Renal Fibrotic Process and Collagen Accumulation in an UUO Induced Mouse Model

Renal fibrosis in the UUO model is characterized by excessive deposition of ECM components. Immunohistochemistry (IHC) analysis revealed that the interstitial area positive for collagen I was significantly increased in UUO kidneys compared with sham-operated controls ($p < 0.0001$; Fig. 1). Consistently, Western blot analysis showed a 6.06-fold elevation in collagen I protein expression (normalized to GAPDH) in the UUO group relative to the sham group ($p < 0.0001$; Fig. 2c, Table 1). Oral administration of scutellarin significantly reduced both collagen deposition and expression, with the IHC-positive area and collagen I/GAPDH levels decreasing to 0.63-fold and 0.54-fold of UUO values, respectively (both $p < 0.0001$; Table 1). Notably, the scutellarin-treated group did not differ significantly from the sham group ($p = 0.5585$; Fig. 1), suggesting near-complete restoration toward baseline levels.

We further assessed two additional fibrosis-associated proteins: α-SMA and FN, UUO induced a 9.99-fold increase in α-SMA/GAPDH and a 6.05-fold increase in

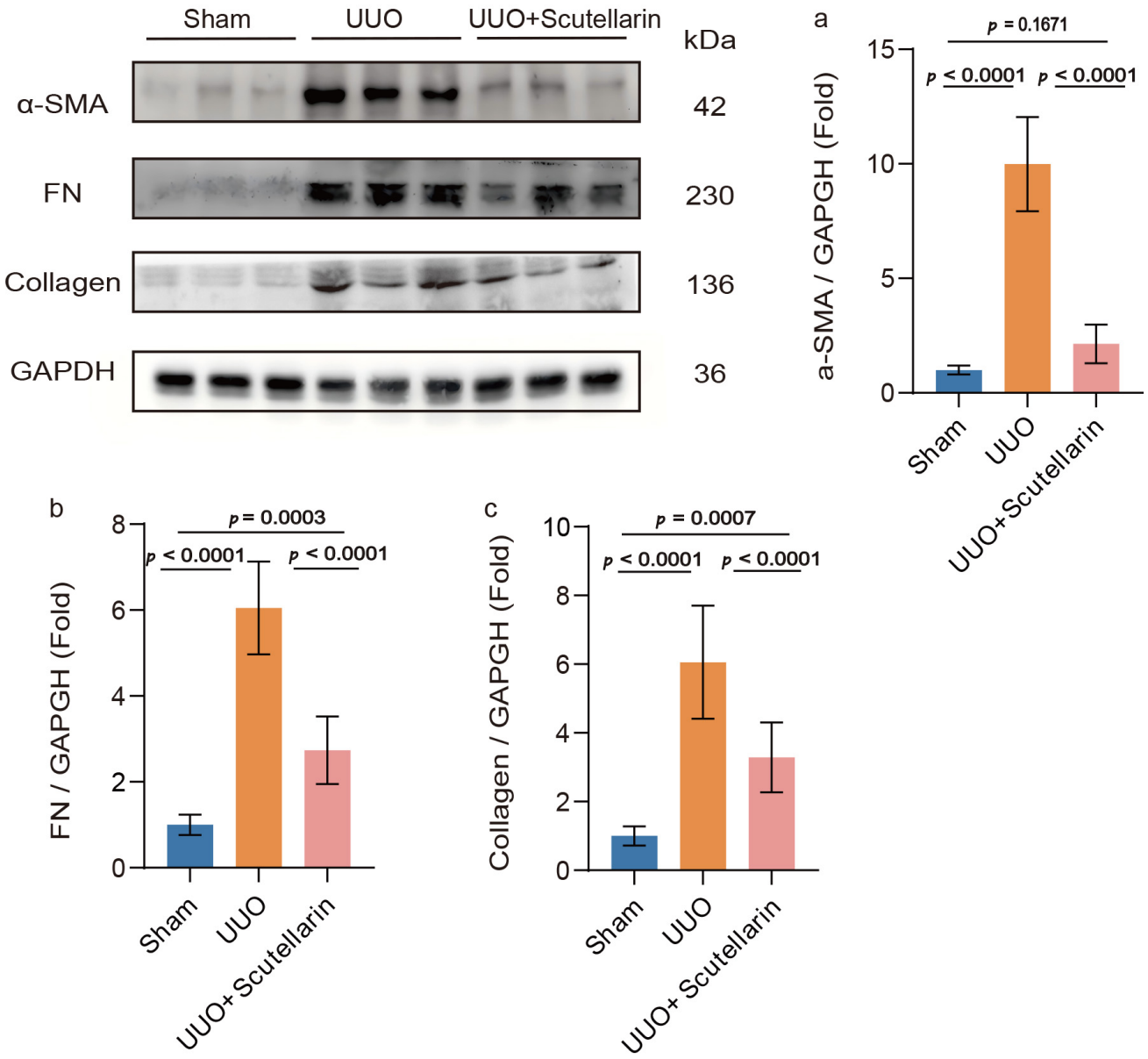

Fig. 2. Scutellarin treatment decreased the levels of fibrosis-related proteins in UUO mouse kidneys. Western blot analysis of (a) α-SMA, (b) FN, and (c) collagen I protein levels, normalized to GAPDH and expressed as fold change relative to the sham group. Data are shown as the mean $\pm$ SD (n = 6 per group).

FN/GAPDH compared with sham controls (both $p <$ 0.0001; Fig. 2a,b; Table 1). Scutellarin treatment significantly suppressed these elevations, reducing α-SMA and FN to 0.21-fold and 0.45-fold of UUO levels, respectively (both $p < 0.0001$; Table 1). Again, no statistically significant difference was observed between the scutellarin and sham groups for α-SMA ($p = 0.1671$, Fig. 2a), reinforcing the notion that scutellarin effectively prevents pathological activation of fibrogenic pathways.

Collectively, scutellarin treatment attenuates UUO-induced renal fibrosis, as evidenced by significant reductions in interstitial collagen I deposition and the expression of key fibrosis-related proteins, including α-SMA and FN.

3.2 Scutellarin Administration Alleviates Renal Functional Impairment in an UUO Induced Mouse Model

Urinary protein, BUN, and Scr are well-recognized biochemical indicators commonly employed to evaluate the extent of kidney damage and assess functional alterations in renal pathologies.

In the UUO group, all three parameters were significantly elevated compared with sham-operated controls ($p < 0.0001$; Fig. 3), consistent with impaired renal excretory function. Oral administration of scutellarin significantly attenuated these changes, with proteinuria, BUN, and Scr levels significantly lower than those in the UUO group ($p <$ 0.0001; Fig. 3, Table 1). Although the values in the scutel-

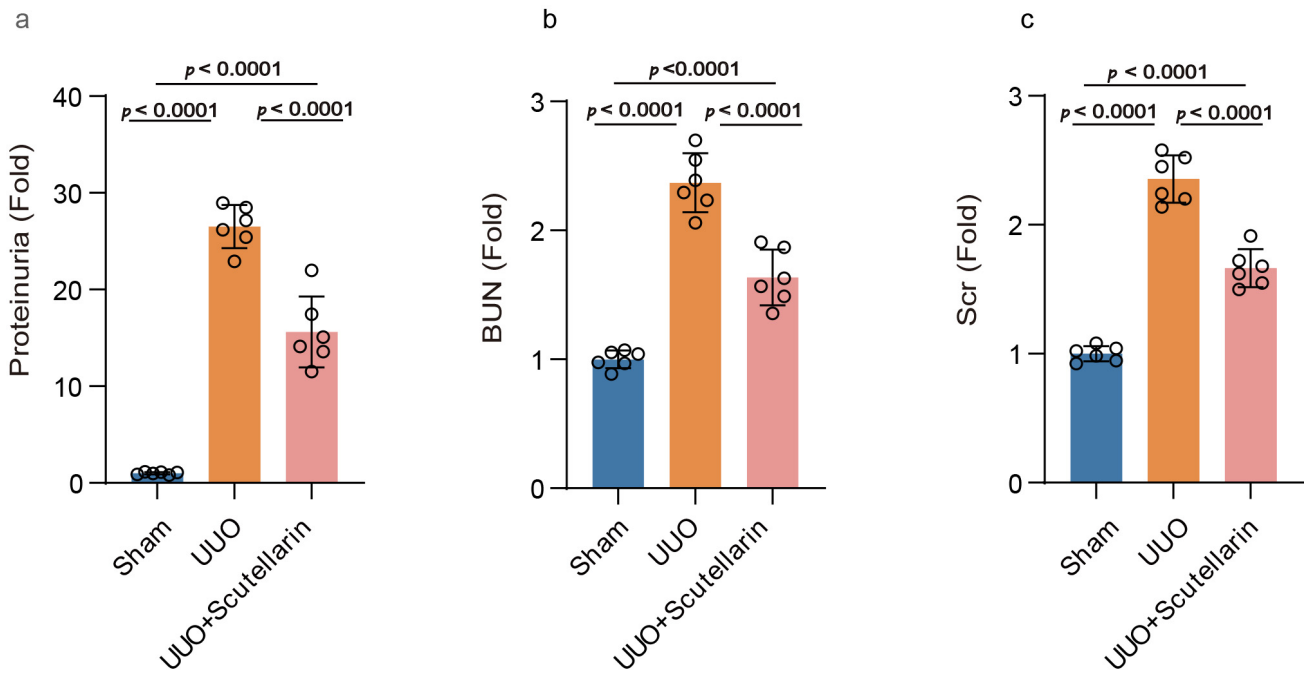

Fig. 3. Scutellarin treatment mitigated renal impairment in UUO mouse kidneys. Levels of (a) urinary protein, (b) BUN, and (c) Scr are expressed as fold change relative to the sham group. Data are shown as the mean ± SD (n = 6 per group).

Table 1. Scutellarin improves renal function and suppresses fibrotic markers in UUO mice.

Parameter	Sham (Mean ± SD)	UUO (Mean ± SD)	UUO+Scutellarin (Mean ± SD)	Fold change (UUO/Sham)	Fold change (Scut/UUO)	*p* value (Scut vs. UUO)
Collagen IHC (%)	0.44 ± 0.06	0.73 ± 0.12	0.46 ± 0.04	1.66	0.63	<0.0001
α-SMA/GAPDH	1.00 ± 0.19	9.99 ± 2.06	2.14 ± 0.84	9.99	0.21	<0.0001
FN/GAPDH	1.00 ± 0.24	6.05 ± 1.08	2.74 ± 0.79	6.05	0.45	<0.0001
Collagen/GAPDH	1.00 ± 0.28	6.06 ± 1.65	3.29 ± 1.02	6.06	0.54	<0.0001
Proteinuria (mg/mL)	0.11 ± 0.01	2.88 ± 0.24	1.70 ± 0.40	26.51	0.59	<0.0001
BUN (mmol/L)	10.51 ± 0.73	24.91 ± 2.40	17.20 ± 2.28	2.37	0.69	<0.0001
Scr (μmol/L)	37.10 ± 2.21	87.37 ± 6.84	61.73 ± 5.44	2.36	0.71	<0.0001

Data are shown as the mean ± standard deviation (n = 6). Proteinuria, BUN, Scr, and collagen I (IHC, %) are absolute values. Western blot data (α-SMA, FN, collagen I) were normalized to GAPDH. Fold changes were calculated as ratio of group means. α-SMA, alpha-smooth muscle actin; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; FN, fibronectin; BUN, blood urea nitrogen; Scr, serum creatinine.

larin group remained higher than those in sham mice, the reductions corresponded to a 41% decrease in proteinuria, 31% decrease in BUN, and 29% decrease in Scr relative to the UUO group (Table 1), indicating partial but significant improvement in renal function.

These results demonstrated that scutellarin treatment ameliorated UUO-induced renal dysfunction, as evidenced by the significant reduction in key biochemical markers of kidney injury.

4. Discussion

In this study, we demonstrated that scutellarin, a major active ingredient derived from the traditional Chinese herb *Erigeron breviscapus*—exerts potent antifibrotic effects on an UUO-induced mouse model of chronic tubulointerstitial fibrosis. Treatment with scutellarin significantly improved kidney function, as reflected by reductions in proteinuria, BUN, and Scr. Histologically, this was accompanied by decreased interstitial collagen deposition, confirmed by both IHC quantification of collagen I (%) and Western blot analysis showing downregulation of collagen I, FN, and α-SMA—three canonical markers of ECM accumulation and myofibroblast activation. These findings align with prior reports of scutellarin-containing formulations improving proteinuria and renal parameters in patients with diabetic kidney disease, suggesting potential translational relevance, although direct clinical validation in fibrotic CKD remains to be established.

The coordinated suppression of α-SMA, FN, and collagen I strongly indicates that scutellarin reduces the ex-

pression of markers associated with myofibroblast activation, which are primary cellular effectors of ECM overproduction in tubulointerstitial fibrosis. While our study did not directly assess upstream signaling events, this pattern of marker reduction is highly consistent with inhibition of the TGF-β1-driven fibrogenic program, a well-established axis in renal fibrosis. TGF-β1 potently induces the expression of α-SMA, FN, and collagen I in renal fibroblasts and promotes EMT-like processes that contribute to myofibroblast pools [21]. Notably, earlier studies demonstrated that scutellarin suppresses TGF-β1 signaling and ameliorates fibrosis in models of diabetic nephropathy and pulmonary injury, with concomitant downregulation of these same markers [17,20]. Thus, although direct measurement of TGF-β1 or Smad phosphorylation was not performed here, the concordance between our molecular findings and established TGF-β1 dependent responses provides a plausible and literature-supported mechanistic framework for scutellarin's antifibrotic action.

This multimodal activity places scutellarin within a broader class of natural compounds derived from traditional Chinese medicine that target renal fibrosis through shared and distinct mechanisms. For instance, baicalin (from *Scutellaria baicalensis*) [22,23] and curcumin (derived from *Curcuma longa*) [24,25] also suppress TGF-β1/Smad signaling and EMT, while concurrently activating the nuclear factor erythroid 2-related factor 2 antioxidant pathway to mitigate oxidative stress-driven fibrogenesis. Similarly, tanshinone IIA (derived from *Salvia miltiorrhiza*) [26,27] inhibits TGF-β1 and NLRP3 inflammasome activation—matching the anti-inflammatory effects in other organs—while also specifically promoting apoptosis in activated myofibroblasts, a mechanism not yet documented for scutellarin. Meanwhile, notoginsenoside R1 (derived from *Panax notoginseng*) [28] improves renal function and reduces fibrotic markers by inhibiting TGF-β1, closely mirroring the functional and molecular outcomes observed in our study. Together, these agents highlight a shared therapeutic strategy: targeting the TGF-β1-EMT-ECM axis while simultaneously ancillary drivers such as inflammation and redox imbalance. Scutellarin distinguishes itself not necessarily by a unique mechanism but by its established clinical use in microvascular complications and favorable safety profile, which may accelerate its repurposing for CKD.

It is important to acknowledge that scutellarin possesses documented anti-inflammatory and antioxidant properties in other organ systems [10,14,15,18], and given that inflammation and oxidative stress can amplify fibrogenic signaling in the obstructed kidney, such ancillary effects may indirectly contribute to the observed benefit. Since direct measurements of redox status, inflammatory cytokines, or inflammasome components were not conducted in our model, the involvement of these pathways is speculative and warrants future investigation.

Unlike current standard-of-care agents (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) that primarily modulate hemodynamics to slow rather than reverse fibrosis [29–31], scutellarin therapeutically targets key structural components of the fibrotic response, evidenced by decreased collagen I deposition and reduced myofibroblast marker expression.

5. Limitations

This study has several limitations that should be acknowledged. First, while the observed downregulation of α-SMA, FN, and collagen I strongly suggests an attenuation of myofibroblast activity, the precise cellular origin of this effect—whether from the inhibition of resident fibroblast activation, EMT, or other cellular sources—remains undetermined due to the lack of lineage tracing or additional specific phenotypic markers. Second, the current experimental design, which administered scutellarin both before and after UUO surgery, does not allow us to distinguish whether the compound prevents the initial development of fibrosis or reverses established fibrotic lesions; this distinction is critical for its potential clinical application. Third, although the UUO model is a well-established tool for studying rapid fibrogenesis, it does not fully recapitulate the complex and slow progression of human CKD. Therefore, the translational relevance of these findings requires further validation in models that better mimic common human CKD etiologies, such as diabetic or hypertensive nephropathy, and ultimately in controlled clinical trials to confirm efficacy and establish optimal dosing regimens.

6. Conclusion

Despite the limitations acknowledged above, Our findings demonstrate that scutellarin attenuates RIF and improves functional parameters in the UUO mouse model, associated with reduced expression of collagen I, α-SMA, and fibronectin. These results support further preclinical evaluation of scutellarin as an antifibrotic agent in kidney disease. Future studies should investigate its effects on additional models that better reflect human CKD pathophysiology, such as diabetic or hypertensive nephropathy, and elucidate the underlying molecular mechanisms, including potential modulation of TGF-β1 signaling. Comprehensive pharmacokinetic and toxicological assessments are required before clinical application. However, because targeting renal fibrosis remains a critical therapeutic goal, natural compounds such as scutellarin represent potential adjunctive therapies for progressive kidney disease.

Availability of Data and Materials

The datasets used in the current study are available from the corresponding author upon reasonable request.

Author Contributions

LG designed the research and contributed to manuscript writing. LG, ZZ, QL and DC performed the research and conducted experiments. LG, DC, CC and ZZ performed data analysis. TY, YW, RC participated in research design, data collection and analysis, interpretation of results, and manuscript writing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Institutional Animal Ethics Committee of Qujing University of Medicine & Health Sciences approved (No. DL2025003) and conducted the study according to the Regulations on the Administration of Laboratory Animals (State Council of China), the Guiding Opinions on the Humane Treatment of Laboratory Animals (MOST, 2006), the Guidelines for Ethical Review of Laboratory Animal Welfare (GB/T 35892-2018), and the ARRIVE 2.0 guidelines.

Acknowledgment

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Conflicts of Interest

The authors declare no conflicts of interest.

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