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Original Article

AKT/foxo3a signal pathway mediates the protective mechanism of resveratrol on renal interstitial fibrosis and oxidative stress in rats with unilateral ureteral obstruction

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Abstract: Objective: To explore whether protein kinase B (serine/threonrine kinase, AKT)/forkhead box protein O3a (foxo3a) pathway mediates the protective mechanism of resveratrol (RSV) on renal interstitial fibrosis (RIF) and oxidative stress. Methods: Sprague-Dawley (SD) rats were grouped into Sham group, unilateral ureteral obstruction (UUO) group and UUO + RSV group. HE staining was used to test the pathological damage of RIF intervened by RSV, biochemical analyzer was used to measure serum renal injury indexes (creatinine, Cr, blood urea nitrogen, Bun), and enzyme-linked immunosorbent assay (ELISA) was used to detect oxidative stress indexes (malondialdehyde, MDA; glutathione, GSH; superoxide dismutase, SOD). AKT/FoxO3a signaling pathway markers and renal interstitial indexes were measured by western blot analysis. Results: Compared with Sham group, HE staining in UUO group showed significant RIF pathological damage; Cr and Bun indexes were increased, and AKT/FoxO3a signal pathway was activated, as indicated by increased p-AKT/AKT and p-FoxO3a/FoxO3a; TGF-β1 and α-SMA protein levels in fibrosis indexes were increased, while E-cadherin decreased; MDA was increased, GSH and SOD were decreased in oxidative stress indexes, while those in UUO + RSV group were improved. Conclusion: AKT/foxo3a signaling pathway mediates the protective mechanism of RSV on RIF and oxidative stress in UUO rats, and RSV can improve RIF and oxidative stress in UUO rats by inhibiting AKT/foxo3a signaling pathway.

Keywords: AKT/foxo3a signaling pathway, resveratrol, unilateral ureteral obstruction rats, renal interstitial fibrosis, oxidative stress

Introduction

Renal interstitial fibrosis (RIF) is a common pathological feature in many kinds of chronic kidney diseases, and it is also one of the reasons for fundamental pathological change in end-stage kidney disease [1]. RIF is the key to the progression of chronic kidney disease, which has a close correlation with the decline of renal function, and acts in the necrosis, degeneration, transdifferentiation of renal tubular epithelial cells and the deposition and generation of extracellular matrix [2]. Unilateral ureteral obstruction (UUO) is a classic RIF model, which leads to kidney dysfunction in young people and the elderly. Although the patients were treated in time, urinary tract obstruction can still lead to irreversible nephron damage, increase oxidative stress and promote inflammatory cell infiltration [3, 4]. Therefore, how to inhibit the development of RIF is particularly important.

Resveratrol (RSV) is a natural polyphenol antioxidant, which is an antibiotic and can protect against fungal infection when plants are in harsh environment or attacked by pathogens [5]. Studies have shown that RSV has anti-cancer, anti-oxidant and anti-inflammatory effects, and has many health benefits [6]. RSV can improve renal injury and renal fibrosis by inhibiting inflammatory process and lipid peroxida-

tion, and can also inhibit epithelial-mesenchymal transition of renal injury and renal fibrosis by activating SIRT1 [7]. Other researches indicate that RSV can prevent and treat muscle atrophy caused by chronic kidney disease through inhibiting the expression of MuRF1 signaling pathway. Therefore, we speculated that RSV could protect UUO rat model from RIF by inhibiting the expression of a certain signal pathway. Forkhead box O3A (Foxo3a), as a key protein involved in the regulation of centralized basic cell function, has been widely studied clinically, and it shows that the efficacy of foxo3a is carefully regulated by phosphorylation. AKT can phosphorylate foxo3a and inactivate it, resulting in foxo3a remaining in cytoplasm and inhibiting the transcription of target gene [9]. Wang Z et al. [10] explained that pyrroloquinoline quinine could improve the oxidation of renal tubular epithelial cells induced by high glucose and promote apoptosis by regulating PI3K (phosphatidylinositol 3-kinase)/Akt/FoxO3a signaling pathway. Through the above research, we speculated that RSV could protect UUO rat model by inhibiting AKT/foxo3a signaling pathway.

Thus, a UUO rat model was established to observe the improvement effect of RSV on RIF pathological damage and whether RSV could play a protective role by mediating AKT/foxo3a.

Data and methods

Animal data

Materials: Thirty clean Sprague-Dawley (SD) rats aged 6-8 weeks were obtained from experimental animal center, and kept in clean environment with good ventilation. Before the experiment, all the animals were fed for one week in the environment with indoor humidity of 48-59% and temperature of 21-26°C. The experiment conformed to the ethics committee, and the experimental process followed the Guiding Principles for the Protection and Use of Experimental Animals [11]. Ethical batch number: LL2020 (Review) 108 (A15).

Model preparation and grouping

Thirty rats were grouped into Sham group, UUO group (disease group) and UUO + RSV group.

Modeling [12]: The instruments were disinfected before operation, and 1% pentobarbital sodium (40 mg/kg) was injected into the abdominal cavity of rats for anesthesia. The rats were fixed on the rat plate in prone position. Routine disinfection was performed, and an abdominal incision was made to fully expose the kidney and separate the left ureter. In UUO group and UUO + RSV group, the ureter was ligated with sterile silk thread, and then the ureter was cut in the middle of the two knots. The muscles and skin were sutured layer by layer, and sterile gauze was applied after disinfection. In Sham group, only the left ureter was separated without ligation, and then the abdominal cavity was sutured. The next steps were the same.

Administration: The UUO + RSV group was given 20 mg/kg resveratrol (Amyjet Scientific, Wuhan, China, SIH-264-100MG) for 14 consecutive days. Sham group and UUO group were given normal saline. The rats were treated by intragastric administration.

Sample collection and processing

On the 14th day after the operation, the rats were anesthetized with 1% pentobarbital sodium at a dose of 40 mg/kg. 5 mL of venous blood from three groups of rats was extracted, centrifuged at 1500×g, and stored in a refrigerator at -80°C for 10 min. They were then decapitated. An abdominal median incision was made to expose and remove the kidney, and the renal capsule was carefully removed to release hydronephrosis. They were kept in a refrigerator at -80°C for subsequent experiments.

Outcome measures

HE staining and pathological changes of kidney tissue: The gross pathological changes of lung tissue were tested, the kidney tissue was immersed in 4% neutral buffered formaldehyde solution (Solarbio Technology Co., Ltd., Beijing, China, DF0113), fixed for 24 h, embedded in paraffin, and sectioned continuously at 4 μm. After routine HE staining, the pathological changes of kidney tissue were observed under light microscope, and the score of renal tubular injury was calculated. Ten high-power visual fields (×200) were applied for each specimen under light microscope. Renal tubular necrosis and vacuolar degeneration <10% were scored as 1 point, <25% as 2 points, <50% as 3 points, <75% as 4 points, and ≥75% as 5 points.

Western blot experiment: The kidney tissue stored at -80°C was ground under liquid nitrogen, washed twice by PBS, and then added with RIPA lysate (Amyjet Scientific Co., Ltd., Wuhan, China, 28192) for ultrasonic lysis to obtain the total protein. The concentration was tested by BCA protein detection kit (Vazyme-innovation in enzyme technology, Nanjing, China, E112-01/02). A 10 μg of total protein was taken for SDS-PAGE gel electrophoresis (Shanghai Qiming Biotechnology Co., Ltd., Shanghai, China, BM0687), and the protein was transferred to PVDF membrane (Absin Bioscience Inc, Shanghai, China, abs932). Transforming growth factor beta 1 (TGF-β1, Abcam, ID cat: ab215715, 1:600), E-cadherin (Abcam, ID cat: ab40772, 1:1000), alpha smooth muscle actin (α-SMA, Abcam, ID cat: ab21027, 1:2000), p-AKT (Abcam, ID cat: ab38449, 1:1000), AKT (Abcam, ID cat: ab8805, 1:1000), p-foxo3a (Abcam, ID cat: ab154786, 1:1000), Fox03a (Abcam, ID cat: ab109629, 1:1000) and β-actin (Abcam, ID cat: ab115777, 1:200) antibodies were added according to the instructions, and the membrane was washed the next day. Horseradish peroxidase labeled secondary antibody (ABBKINE, Wuhan, China, A21010) (1:2000) was added, incubated at room temperature for 1 h, the membrane was rinsed, and ECL reagent (Keygene Biotech Co., Ltd., Jiangsu, China, KGP1201) was applied for development. Image Lab was applied for semi-quantitative analysis. The gray ratio of target protein to β-actin was applied as the expression level.

Determination of renal injury index and oxidative stress index: Venous blood stored at -80°C was taken. Serum renal function indexes (creatinine (cr), urea nitrogen (BUN)) of three groups of rats were measured by automatic chemiluminescence immunoassay (Wuhan Easy Diagnosis Biomedicine Co., Ltd, item number: CF10). ELISA [13] was applied to detect the expression level of indexes, such as malondialdehyde (MDA), glutathione (GSH) and superoxide dismutase (SOD), with reference to instructions of MDA, GSH and SOD kits (Yaji Biotechnology Co., Ltd., Shanghai, China, YS065-59B, YS06420B, YS06598B).

Statistical analysis

GraphPad 6 was applied for visualizing the pictures. Data were represented as mean ± SD. Single factor analysis of variance was applied in multiple group comparison, and LSD-t test was used for post hoc comparison. Repeated measurement analysis of variance was employed for multiple time points, and Bonferroni was applied for post hoc testing. $P<0.05$ indicated statistically significant differences.

Results

Comparison of pathological scores and morphology of kidney in three groups of rats

Compared with Sham group, the scores of tubulointerstitial injury in UUO group were elevated ($P<0.05$), while the scores of tubulointerstitial injury in UUO + RSV group were decreased after RSV intervention ($P<0.05$). HE staining showed that the glomerular structure of Sham group rats was clear and complete, and the renal tubules were arranged orderly after 14 days of modeling. In UUO group, the renal tissue showed that the brush edge of renal tubule fell off, the renal tubule shrank, the basement membrane thickened, and inflammatory cell infiltration and fibrosis appeared. However, after RSV intervention, the degree of renal tubular injury, inflammatory cell infiltration and fibrosis in UUO + RSV group decreased (**Figure 1**).

RSV improved kidney injury in UUO rats

We examined the effect of RSV on renal function of UUO model rats and found that compared with Sham group, the levels of renal functions such as Cr and Bun in UUO group increased ($P<0.05$), while Cr and Bun in UUO + RSV group decreased after RSV intervention ($P<0.05$) (**Figure 2**).

RSV improved oxidative stress in UUO rats

We examined the effect of RSV on oxidative stress indicators in UUO model rats and found that compared with Sham group, the protein expression level of MDA in UUO group was higher, while the levels of GSH and SOD were lower in UUO group ($P<0.05$). However, after RSV intervention, the MDA level significantly decreased while the GSH and SOD levels evidently increased in UUO + RSV group (**Figure 3**).

RSV reduced renal fibrosis in UUO rats

We examined the effect of RSV on renal fibrosis indexes in UUO model rats and found that com-

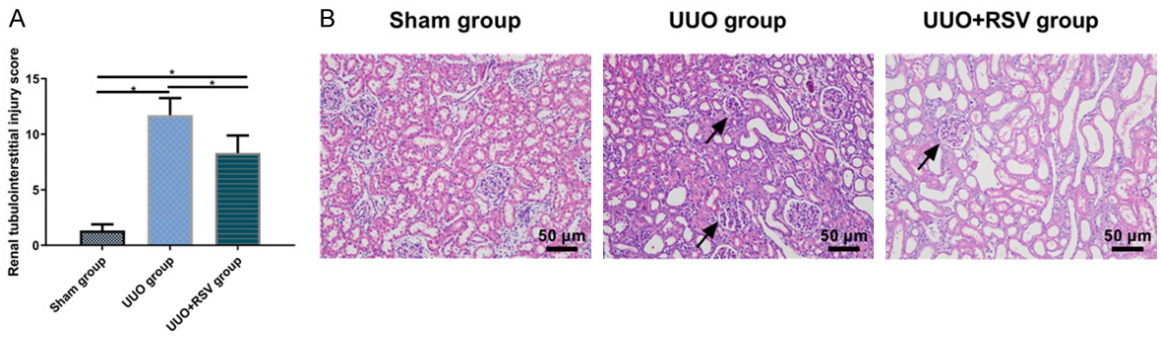

Figure 1. Comparison of pathological scores and morphology of kidney among three groups of rats. A: Effect of RSV on tubulointerstitial injury score of UUO model (n=10, one-way ANOVA test was used, LSD-t was used as a post-test). B: Effect of RSV on HE staining of renal pathological morphology in UUO model. Note: *P<0.05, compared with the Sham group or comparison between the two groups.

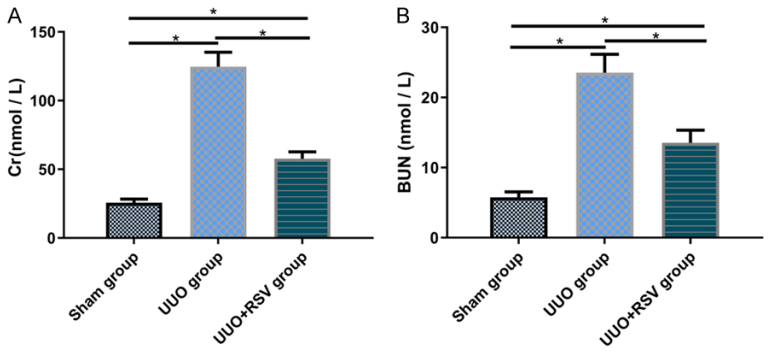

Figure 2. RSV decreased kidney injury in UUO rats. Effect of RSV on serum Cr (A) and BUN (B) in UUO model (n=10, one-way ANOVA test was used, LSD-t was used as a post-test). Note: *P<0.05, compared with the Sham group or comparison between the two groups.

pared with Sham group, the levels of TGF-β1 and α-SMA in UUO group were evidently higher, while that of E-cadherin was evidently lower in UUO group. After RSV intervention, the TGF-β1 and α-SMA levels evidently decreased and the E-cadherin level significantly increased in UUO + RSV group (**Figure 4**).

Effect of RSV on AKT/FoxO3a signaling pathway in kidney tissue of UUO rats

We tested AKT/FoxO3a signaling pathway and pathway-related proteins to verify the effect of RSV on AKT and FoxO3a, and no evident difference was found in AKT and FoxO3a among the three groups (P>0.05). There were, however, significant differences in the expression of p-Akt and p-foxo3a among the three groups (P<0.05). Compared with Sham group, p-AKT and p-FoxO3a in UUO group increased evidently, but after RSV intervention, those in UUO + RSV group decreased evidently (P<0.05) (**Figure 5**).

Discussion

RIF is the basic pathological change of chronic renal failure (CRF). Studies have shown that many pathophysiological changes including abnormal accumulation of extracellular matrix, infiltration of inflammatory cells, apoptosis and oxidative stress will lead to fibrosis [14, 15]. The degree of RIF has a significant influence on the therapeutic effect of patients with CRF, and inhibiting and reversing fibrosis is helpful for delaying the progression of CRF [16]. In this study, RSV treatment was given to UUO rats, and the mechanism of improving renal fibrosis in UUO rats was observed, which provided theoretical basis for RSV to effectively improve RIF.

RSV is a natural polyphenol, which has anti-inflammatory, antioxidant and cytoprotective effects. It has been clinically proven to have extensive pharmacological effects and plays a protective role in various types of kidney diseases, such as diabetic kidney diseases and kidney damage caused by sepsis [17]. Studies have shown that RSV has low toxicity and the ability to regulate various molecular signaling pathways involved in cancer progression, so it is considered as an excellent anticancer drug clinically [18]. The tubulointerstitial injury score of UUO rats increased evidently after

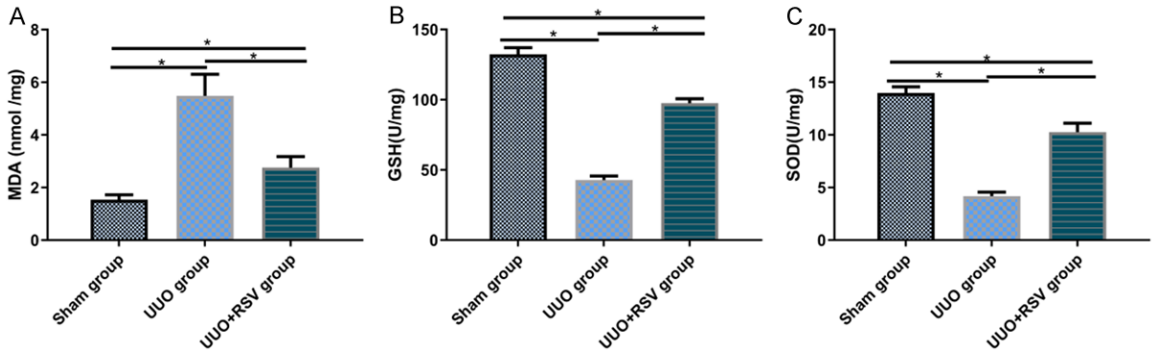

Figure 3. RSV decreased oxidative stress in UUO rats. Effect of RSV on MAD (A), GSH (B) and SOD (C) protein expression in UUO model (n=10, one-way ANOVA test was used, LSD-t was used as a post-test). Note: *P<0.05, compared with the Sham group or comparison between the two groups.

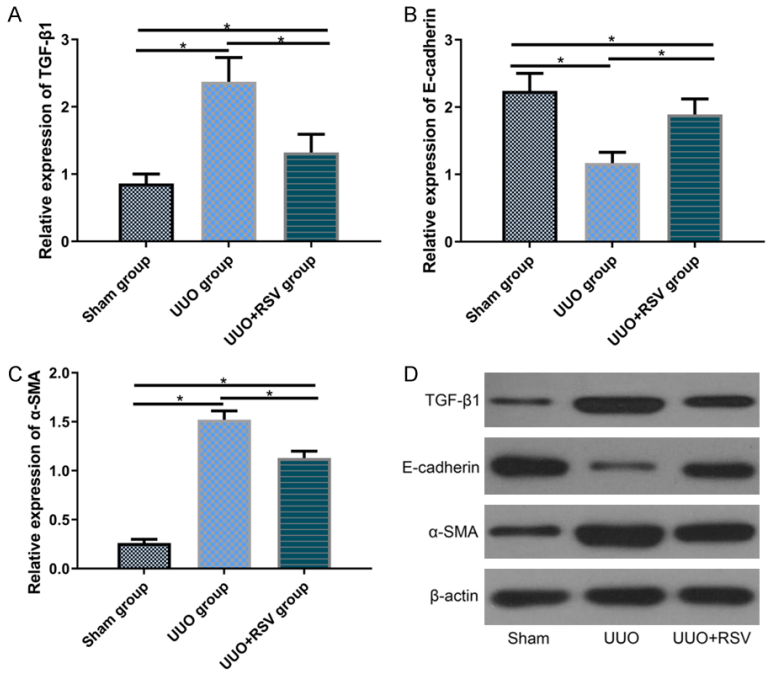

Figure 4. RSV reduced renal fibrosis in UUO rats. A-C: Effect of RSV on the protein expression of TGF-β1, E-cadherin and α-SMA in UUO model (n=10, one-way ANOVA test was used, LSD-t was used as a post-test). D: Protein map. Note: *P<0.05, compared with the Sham group or comparison between the two groups.

induction, and HE staining showed that the brush edge of renal tubules fell off, the renal tubules shrank, the basement membrane thickened, and inflammatory cell infiltration and fibrosis appeared in the renal tissue of UUO rats. However, after RSV intervention, the scores of tubulointerstitial injury in UUO rats were evidently reduced, and the degree of tubulointerstitial injury, inflammatory cell infiltration and fibrosis was evidently reduced. It indicated that RSV had a good inhibitory effect on RIF, thus protecting kidney. Studies have shown that [19], the expression of Cr and BUN in serum of uremic rats was evidently increased, and RSV could effectively reduce the expression of Cr and BUN in serum of uremic rats. Compared with Sham group, the renal function levels of Cr and Bun in UUO group were evidently enhanced, while those in UUO + RSV group evidently reduced after RSV intervention. The results showed that RSV could obviously improve the renal function of RIF rats.

Previous researches revealed that oxidative stress injury had a correlation with the pathological process of most kidney diseases, such as MDA, GSH, and SOD. MDA is the product of lipid peroxidation, which can reflect the degree of oxidative damage, while GSH and SOD are important antioxidant enzymes in human body [20-22]. Bilgic et al. [23] found that RSV could effectively reduce the expression of Cr and BUN in rats, improve the expression of oxidative stress indicators, and protect kidney tissue from the side effects of risperidone. Xu et al. [24] discovered that RSV could reduce renal ischemia-reperfusion injury, and alleviate renal tubular

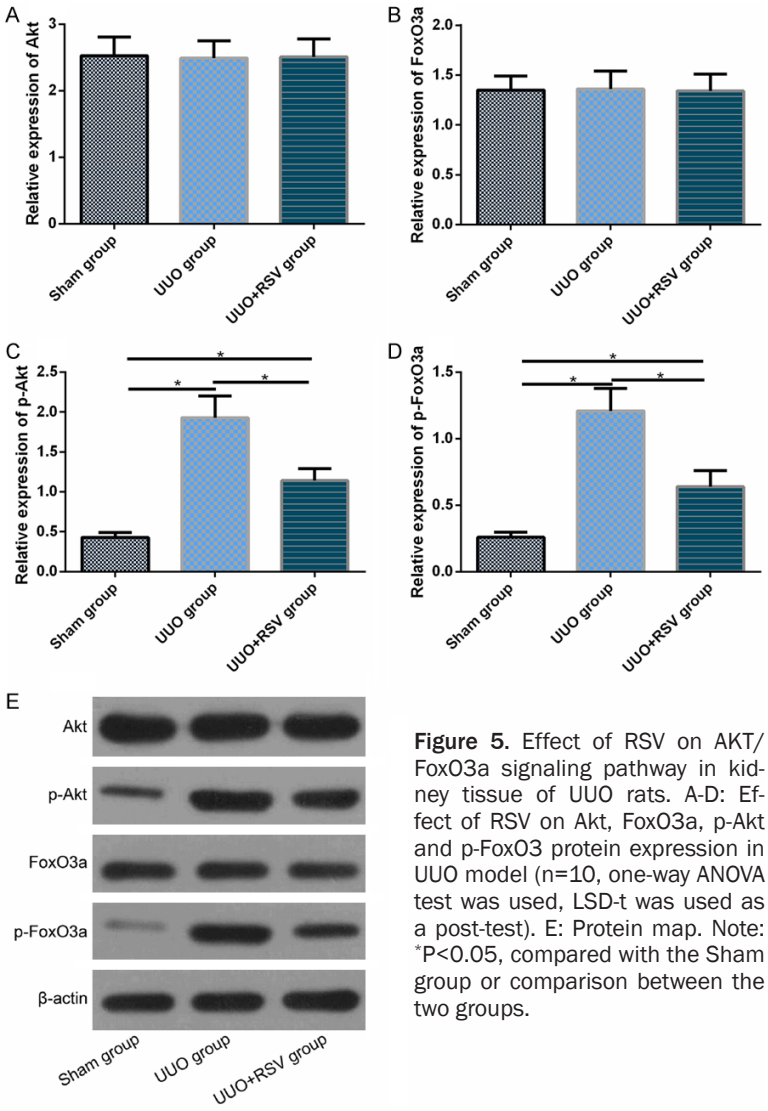

Figure 5. Effect of RSV on AKT/FoxO3a signaling pathway in kidney tissue of UUO rats. A-D: Effect of RSV on Akt, FoxO3a, p-Akt and p-FoxO3 protein expression in UUO model (n=10, one-way ANOVA test was used, LSD-t was used as a post-test). E: Protein map. Note: *P<0.05, compared with the Sham group or comparison between the two groups.

injury and oxidative stress through AKT/NMDA/CaMK/DAPK and NF-κB. Compared with Sham group, MDA in UUO group increased evidently, while GSH and SOD reduced. After RSV intervention, MDA in UUO + RSV group reduced evidently, while GSH and SOD increased. This indicated that RSV could induce the expression of antioxidant enzymes and reduce the damage of kidney caused by oxidative stress. TGF-β1 is an important mediator in the pathology and physiology of renal fibrosis. Some indicated that TGF-β induces tubular epithelial and tubular mesangial cells to transform into fibroblasts, which can down-regulate E-cadherin and up-regulate α-SMA. In a word, inhibiting factors related to fibrosis (such as TGF-β) may control or reverse renal fibrosis [26]. TGF-β1 and α-SMA in UUO group were evidently enhanced, while E-cadherin was reduced. After RSV intervention, TGF-β1 and α-SMA in UUO + RSV group were evidently reduced, while E-cadherin was enhanced. This indicated that RSV could inhibit collagen synthesis and deposition in RIF rats by down-regulating TGF-β1, α-SMA and up-regulating E-cadherin, thus playing an anti-fibrosis role. Studies have shown that many signaling pathways act in the pathogenesis of RIF, such as AKT/foxo3a signaling pathway [27, 28]. Foxo3a belongs to FoxO subfamily of Forkhead transcription factor, and Akt can phosphorylate and inactivate three FoxO proteins, indicating that it can regulate TGF-β induced diabetic nephropathy through AKT/foxo3a pathway, thus playing a role in kidney protection [29]. p-AKT and p-FoxO3a protein in UUO group were evidently lower than those in Sham group and UUO + RSV group. This indicated that RSV intervention increased the phosphorylation of FoxO3a, prevented FoxO3a protein from entering nucleus to play the role of transcription factor, and decreased p-AKT and p-FoxO3a protein, thus playing an anti-fibrosis role.

In this study, we determined the protective mechanism of RSV on RIF and oxidative stress in UUO rats. However, there are still some limitations. First of all, the samples were only tested on animal models, and it is not clear whether there is the same effect in vitro. Second, as a basic study, further research is needed to prove whether RSV can be used in clinical practice. Finally, RSV may also affect the protective mechanism of RIF and oxidative stress in UUO rats through other mechanisms, which need to be proved by further experiments. We hope to improve our research through more experiments in the follow-up report.

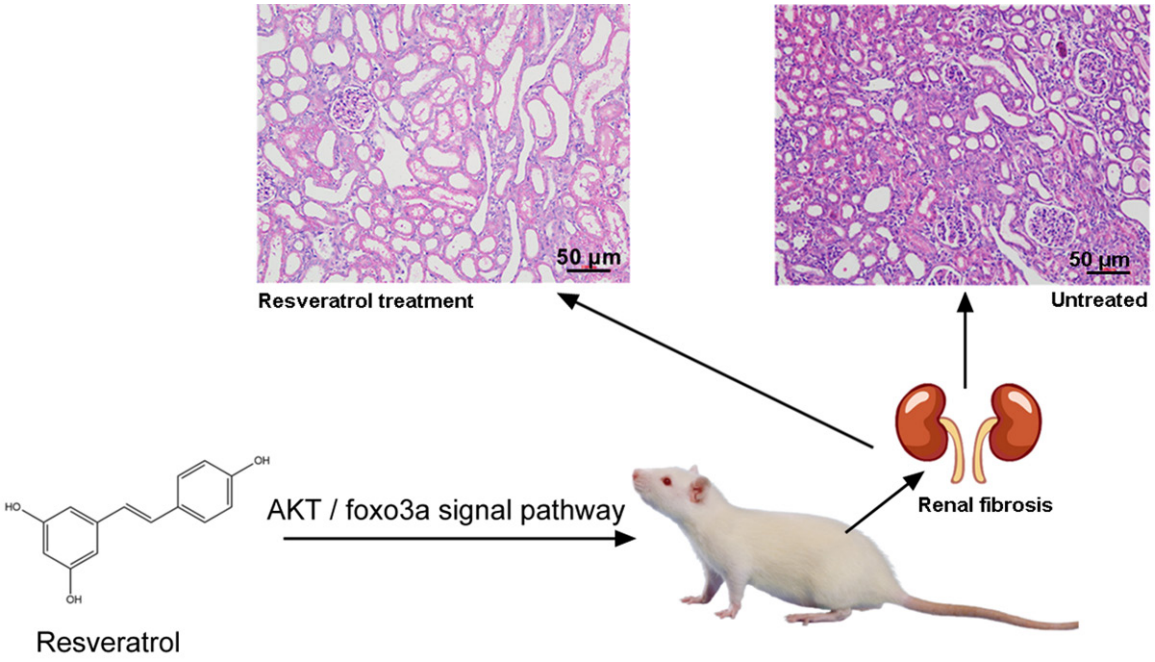

Figure 6. RSV inhibits renal fibrosis in rats mediated by AKT/FoxO3a signaling pathway.

In summary, AKT/foxo3a signal pathway mediates the protective mechanism of RSV on RIF and oxidative stress in UUO rats, and RSV can improve RIF and oxidative stress in UUO rats by inhibiting AKT/foxo3a signal pathway (**Figure 6**).

Disclosure of conflict of interest

None.

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