Curcumin Ameliorates Chronic Renal Failure in 5/6 Nephrectomized Rats by Regulation of the mTOR/HIF-1α/VEGF Signaling Pathway

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Previous studies implicated the mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α (HIF-1α)/vascular endothelial growth factor (VEGF) pathway in renal fibrosis and found that curcumin could suppress the expression of mTOR. Therefore, the aim of the present study was to investigate the therapeutic effects of curcumin against chronic renal failure (CRF) in a rat model induced by 5/6 nephrectomy through inhibition of mTOR/HIF-1α/VEGF signaling. A total of 70 male Sprague–Dawley rats were divided into seven groups: a sham group, a CRF group, and five treatment groups. Except for the sham rats, all rats underwent 5/6 nephrectomy to induce CRF. The 5/6 nephrectomized rats received treatment with curcumin vehicle, everolimus vehicle, curcumin, everolimus, or the combination of curcumin and everolimus. Everolimus, a specific inhibitor of mTOR, was used as a positive control. At the end of treatment, blood biochemical indexes, proteinuria and the kidney index were detected. Moreover, histological change was examined by hematoxylin and cosin staining, and protein expression levels were detected by Western blotting. The blood biochemical indexes, proteinuria, and kidney index were increased in the CRF group as compared to the sham group, which was accompanied by marked activation of the mTOR/HIF-1α/VEGF pathway. However, curcumin, as well as everolimus, restored or ameliorated these changes. These results indicate that activation of the mTOR/HIF-1α/VEGF signaling pathway plays an important role in the occurrence and development of CRF, and that curcumin has renoprotective effects by blocking activation of this pathway.

Key words chronic renal failure; mammalian target of rapamycin; hypoxia-inducible factor-1α; vascular endothelial growth factor

INTRODUCTION

Chronic renal failure (CRF), defined as a glomerular filtration rate (GFR) of <15 mL/min/1.73 m², is characterized by glomerular sclerosis, tubular atrophy, and the irreversible and progressive loss of nephrons, which is associated with severe renal damage and a series of symptoms or metabolic disorders, and is considered as one of the three most common causes of death.1-3 Renal replacement therapies with hemodialysis, hemodiafiltration, or kidney transplantation are regarded as the most efficient strategies for the treatment of CRF. However, almost 3.2 million patients die prematurely each year globally because of the lack of access to such therapies.4 Thus, there is an urgent need to further elucidate the molecular mechanisms underlying CRF to develop new treatment strategies.

Accumulating evidence suggests that renal fibrosis, including glomerular sclerosis and interstitial fibrosis, is closely associated with CRF, although it is not entirely clear whether renal interstitial changes are initial steps in the development of CRF or rather the consequence of secondary functional and structural changes.4-6) Such changes are regulated by the mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α (HIF-1α)/vascular endothelial growth factor (VEGF) pathway.7-9) In this pathway, mTOR, a downstream mediator of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, plays a key role in the proliferation and angiogenesis of endothelial cells via input from intracellular and extracellular signals to regulate downstream protein synthesis.9,10) When in a phosphorylated state, mTOR phosphorylates Thr70 of eukaryotic translation initiation factor 4E (eIF-4E)-binding protein-1 (4E-BP1) and Thr389 of p70 S6 kinase (P70S6K), which is followed by the upregulation of downstream proteins, such as HIF-1α and VEGF;12,13) HIF-1α is involved in the induction of renal hypoxia and tubulointerstitial injury, which result in the loss of peritubular capillaries, interstitial fibrosis, apoptosis, epithelial–mesenchymal transdifferentiation (EMT), and the continuous evolution of phenotypic expression from a simple cyst to epithelial hyperplasia and eventual tumor formation.14,15) VEGF promotes endothelial proliferation, migration, and tube formation by endothelial cells. Thus, inhibition of the mTOR/HIF-1α/VEGF pathway may be a promising therapeutic strategy against the renal interstitial changes in CRF.

Curcumin [(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a polyphenolic compound isolated from the rhizomes of *Curcuma longa* (turmeric) and exhibits a wide range of therapeutic properties with protective effects against many diseases, such as rheumatoid arthritis, tumor, and epilepsy, among others.16-18) For CRF, previous studies indicated that curcumin had renoprotective effects through the deactivation of multiple hypertrophic signaling pathways and blocking of inflammatory signals even when administered at a later stage of disease.19,21) These findings encouraged us to examine the pharmacological effects of curcumin in 5/6 nephrectomy-induced CRF in a rat model, mainly focusing on the regulation of the mTOR/HIF-1α/VEGF pathway. Overall, the findings of this study lay a foundation for the development of new therapeutic strategies for treatment of CRF.
MATERIALS AND METHODS

Chemicals and Reagents Sodium carboxymethylcellulose (CMC-Na) was purchased from Shanghai Aladdin Bio-Checm Technology Co., Ltd. (Shanghai, China). Curcumin and everolimus were purchased from Biomol GmbH (Hamburg, Germany). The following antibodies were obtained from Abcam (Cambridge, U.K.): rabbit anti-mTOR, rabbit anti-phosphorylated mTOR (at serine 2448), rabbit anti-P70S6K1, rabbit anti-phosphorylated P70S6K1 (at threonine 389), rabbit anti-4E-BP1, rabbit anti-phosphorylated 4E-BP1 (at threonine 70), rabbit anti-HIF-1α, rabbit anti-VEGF, rabbit anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH), and goat anti-rabbit immunoglobulin (IgG). Hydroxyproline assay kit was obtained from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). The whole-cell protein extraction kit was obtained from Nanjing Keygen Biotech. Co., Ltd. (Nanjing, China). The enhanced bicinchoninic acid (BCA) protein assay kit was obtained from Beyotime Institute of Biotechnology (Shanghai, China).

Animals A total of 70 male Sprague–Dawley rats, weighing 180–200 g, were purchased from the Animal Experiment Center of Tianjin Medical University (Tianjin, China) and treated in accordance with the guidelines of the National Institutes of Health for the humane treatment of animals. The rats were housed under a 12-h light/dark cycle at 22 ± 2°C with free access to food and water. All animal procedures were approved by the Institute of Radiation Medicine of the Chinese Academy of Medical Sciences and conducted in accordance with the ethical principles for Experiments on Animals as well as international standards.

Five-Sixths (5/6) Nephrectomy All surgical procedures were conducted under isoflurane anesthesia and sterile conditions. CRF was induced in rats by performing 5/6 nephrectomy as described previously.22,23 Briefly, after the renal artery was temporarily occluded, 2/3 of the left kidney were ligated and excised. Bleeding was controlled by compression, until it stopped. The muscle and skin incisions were closed with polypropylene sutures. The animals were returned to the breeding room to recover. One week later, a right flank incision was made, the renal vessels and ureter were tied, and the right kidney was excised. The animals were returned to the breeding room to recover for one week.

Grouping and Treatment As shown by the in vivo experimental design presented in Fig. 1, the rats were assigned to a sham group (n = 10), CRF group (n = 10), curcumin vehicle group (C− group, n = 10), everolimus vehicle group (E− group, n = 10), curcumin group (C+ group, n = 10), everolimus group (E+ group, n = 10), or curcumin plus everolimus group (C+ + E+ group, n = 10). All rats underwent 5/6 nephrectomy except rats in the sham group. The rats in the C− and C+ + E+ groups were gavaged daily with 75 mg/kg of curcumin (suspended in 0.5% CMC-Na) for 6 weeks.23 The rats in the C− group were gavaged daily with the vehicle (0.5% CMC-Na) only for 6 weeks. The rats in the E− and C+ + E+ groups were subcutaneously injected with 2 mg/kg of everolimus (suspended in 0.9% saline) daily for 6 weeks.24 The rats in the E− group were subcutaneously injected with the vehicle (0.9% saline) daily for 6 weeks.

Biochemical Indexes and Sample Collection Before and after 6-week treatment, the rats were housed in metabolic cages with free access to food and water, and 24 h urine samples were collected. Systolic blood pressure (SBp) was determined by the tail-cuff method and the rats were weighed. Then, plasma was collected under anesthesia with intraperitoneal injection of 50 mg/kg of sodium pentobarbital. After 6-week treatment, the remaining kidneys were dissected out and stored at −80°C until used. The concentrations of urinary protein and serum urea, blood urea nitrogen (BUN), and serum creatinine (Scr) were determined with an automatic biochemical analyzer (Olympus AU5421; Olympus Corporation, Tokyo, Japan). The kidneys were divided into 2 parts: one (n = 5 per group) was fixed in 10% neutral-buffered formalin for histopathological examination and the other (n = 5 per group) was stored at −80°C for subsequent determination of protein expression.

Hydroxyproline Content Assay We detected the kidney fibrosis through assessing hydroxyproline content in the kidney tissues using hydroxyproline assay kit according to the manufacturer’s instructions.

Histological Examination A portion of the kidney was fixed with 10% formalin, embedded in paraffin, and cut into 3 μm-thick sections, which were stained with hematoxylin and eosin for histological examination. The glomerular diameter and inside diameter of tubules were determined.

Western Blotting Total protein in the remaining kidneys was extracted using a whole-cell protein extraction kit. The total protein concentration was determined with the enhanced BCA protein assay kit in accordance with the manufacturer’s instructions. The proteins were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and electrotransferred onto an Immobilon® polyvinylidene difluoride (PVDF; Sigma-Aldrich Corporation, St. Louis, MO, U.S.A.) membrane. Then, the PVDF membrane was blocked with 5% non-fat milk for 1 h at 37°C and incubated with the following primary antibodies overnight at 4°C: rabbit anti-mTOR (dilution, 1:800), rabbit anti-phosphorylated mTOR (at serine 2448, 1:1000), rabbit anti-Ribosomal Protein S6 Kinases, 70-kDa (P70S6K1) (1:1000), rabbit anti-phosphorylated P70S6K1 (at threonine 389, 1:1000), rabbit anti-4E-BP1 (1:1000), rabbit anti-phosphorylated 4E-BP1 (at threonine 70, 1:1000), rabbit

![Fig. 1. Experimental Design](image-url)
anti-HIF-1α (1:1000), rabbit anti-VEGF (1:1000), and rabbit anti-GAPDH (1:3000). Afterward, the PVDF membrane was washed three times with tris-buffered saline-Tween 20 and incubated with horseradish peroxidase-conjugated goat anti-rabbit IgG (1:4000) for 2 h at room temperature. Finally, the PVDF membrane was developed using enhanced chemiluminescence substrate reagent. Each protein expression was normalized using the protein expression from CRF group or C− group.

Statistical Analysis Data were expressed as the mean ± standard error of the mean. Data were statistically analyzed using the unpaired Student’s t-test or one-way ANOVA followed by the post-hoc Tukey’s test. The analyses and graphics were generated using GraphPad Prism statistical software (GraphPad Software Inc., La Jolla, CA, U.S.A.). A probability (p) value of <0.05 was considered to be statistically significant.

RESULTS

The Effect of Curcumin on Body Weight and Biochemical Indexes in 5/6 Nephrectomized Rats Before treatment, 5/6 nephrectomized rats were randomly divided into C− group, E− group, C+ group, E+ group and C+ + E+ group, and their body weight and biochemical indexes were detected. As shown in Table 1, body weight and biochemical indexes had no statistical significance among those groups. Nephrectomized rats (CRF group) had significantly lower body weight and higher biochemical indexes (24-h urine volume, SBp, 24-h urine protein, BUN, Scr and serum urea) compared with the sham group (p < 0.05, Table 2). Treatment with curcumin vehicle (C− group) or everolimus vehicle (E− group) could not affect body weight and biochemical indexes compared with CRF group (p > 0.05, Table 2). However, treatment with curcumin (C+ group) or everolimus (E+ group) could significantly increase body weight and decrease biochemical indexes (24-h urine volume, SBp, 24-h urine protein, BUN, Scr and serum urea) compared with corresponding vehicle group (p < 0.05, Table 2). In addition, higher body weight and lower levels of biochemical indexes (24-h urine volume, SBp, 24-h urine protein, BUN, Scr and serum urea) were detected in the C+ + E+ group when compared with the C− group and E+ group (p < 0.05, Table 2).

Table 1. Body Weight and Biochemical Indexes before Treatment in the 5/6 Nephrectomized Rats

<table>
<thead>
<tr>
<th></th>
<th>C−</th>
<th>E−</th>
<th>C+</th>
<th>E+</th>
<th>C+ + E+</th>
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<tr>
<td>Body weight (g)</td>
<td>221.5 ± 11.9</td>
<td>219.2 ± 14.3</td>
<td>225.9 ± 12.2</td>
<td>218.7 ± 6.3</td>
<td>220.4 ± 10.5</td>
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<tr>
<td>24-h Urine volume (mL)</td>
<td>18.5 ± 5.2</td>
<td>21.3 ± 17.7</td>
<td>20.6 ± 3.8</td>
<td>21.3 ± 2.8</td>
<td>19.9 ± 4.0</td>
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<tr>
<td>SBp (mmHg)</td>
<td>101.6 ± 8.9</td>
<td>109.5 ± 6.8</td>
<td>112.0 ± 7.2</td>
<td>113.8 ± 10.3</td>
<td>106.4 ± 7.5</td>
</tr>
<tr>
<td>24-h Urine protein (mg/24h)</td>
<td>210.3 ± 22.9</td>
<td>208.9 ± 17.9</td>
<td>212.8 ± 17.7</td>
<td>199.0 ± 50.6</td>
<td>213.2 ± 17.6</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>41.2 ± 6.3</td>
<td>38.9 ± 21.1</td>
<td>41.6 ± 4.7</td>
<td>40.2 ± 3.9</td>
<td>39.1 ± 2.7</td>
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<tr>
<td>Scr (mg/dL)</td>
<td>0.809 ± 0.158</td>
<td>0.786 ± 0.101</td>
<td>0.812 ± 0.007</td>
<td>0.799 ± 0.125</td>
<td>0.806 ± 0.2143</td>
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<tr>
<td>Serum urea (mg/dL)</td>
<td>82.5 ± 4.3</td>
<td>78.6 ± 6.8</td>
<td>86.8 ± 7.9</td>
<td>84.6 ± 2.4</td>
<td>80.7 ± 3.3</td>
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</table>

Table 2. Body Weight and Biochemical Indexes after 6-week Treatment in the Various Groups

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>CRF</th>
<th>C−</th>
<th>E−</th>
<th>C+</th>
<th>E+</th>
<th>C+ + E+</th>
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<tr>
<td>Body weight (g)</td>
<td>324.0 ± 14.0</td>
<td>216.5 ± 5.8</td>
<td>222.5 ± 13.2</td>
<td>216.2 ± 7.1</td>
<td>240.1 ± 10.2</td>
<td>243.5 ± 7.4</td>
<td>272.3 ± 17.7</td>
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<tr>
<td>24-h Urine volume (mL)</td>
<td>13.0 ± 3.0</td>
<td>31.4 ± 5.0</td>
<td>31.8 ± 3.3</td>
<td>31.3 ± 2.1</td>
<td>24.0 ± 2.9</td>
<td>24.3 ± 2.2</td>
<td>17.1 ± 2.3</td>
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<tr>
<td>SBp (mmHg)</td>
<td>95.8 ± 3.8</td>
<td>143.8 ± 6.7</td>
<td>142.6 ± 7.5</td>
<td>142.8 ± 4.7</td>
<td>123.3 ± 7.5</td>
<td>118.5 ± 7.2</td>
<td>107.4 ± 6.3</td>
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<tr>
<td>24-h Urine protein (mg/24h)</td>
<td>308.9 ± 106.7</td>
<td>468.7 ± 34.7</td>
<td>481.5 ± 28.3</td>
<td>453.3 ± 37.9</td>
<td>248.9 ± 43.0</td>
<td>269.7 ± 45.6</td>
<td>191.6 ± 29.7</td>
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<tr>
<td>BUN (mg/dL)</td>
<td>34.5 ± 3.9</td>
<td>57.9 ± 3.8</td>
<td>59.6 ± 5.2</td>
<td>55.7 ± 4.1</td>
<td>42.1 ± 3.8</td>
<td>39.3 ± 4.4</td>
<td>32.1 ± 3.7</td>
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<tr>
<td>Scr (mg/dL)</td>
<td>0.520 ± 0.058</td>
<td>0.918 ± 0.061</td>
<td>0.913 ± 0.556</td>
<td>0.931 ± 0.071</td>
<td>0.612 ± 0.057</td>
<td>0.552 ± 0.071</td>
<td>0.471 ± 0.043</td>
</tr>
<tr>
<td>Serum urea (mg/dL)</td>
<td>70.5 ± 5.5</td>
<td>134.1 ± 12.9</td>
<td>126.0 ± 13.0</td>
<td>134.2 ± 17.8</td>
<td>84.6 ± 6.2</td>
<td>88.3 ± 7.0</td>
<td>69.0 ± 6.9</td>
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</table>

CRF chronic renal failure; C− curcumin vehicle group; E− everolimus vehicle group; C+ curcumin group; E+ everolimus group; C+ + E+ curcumin plus everolimus group; SBp systolic blood pressure; BUN blood urea nitrogen; Scr serum creatinine. a) p < 0.05 vs. sham group; b) p < 0.05 vs. C− group; c) p < 0.05 vs. E− group; d) p < 0.05 vs. C+ group; e) p < 0.05 vs. E+ group.
inside diameter of tubules and hydroxyproline content when compared with curcumin vehicle (C− group) \( (p < 0.05, \text{Figs. 2A–D}) \), which is similar with everolimus. Moreover, combined treatment with curcumin and everolimus (C+ + E+ group) was more effective than single treatment with curcumin (C+ group) or everolimus (E+ group) \( (p < 0.05, \text{Figs. 2A–D}) \).

**The Effect of Curcumin on mTOR/HIF-1α/VEGF Pathway in 5/6 Nephrectomized Rats**

As shown in Fig. 3, the expression levels of p-mTOR, mTOR, p-P70S6K1, P70S6K1, P-4E-BP1, 4E-BP1, HIF-1α, and VEGF were higher in the CRF group than in the sham group \( (p < 0.05, \text{Fig. 3}) \). Treatment with curcumin (C+ group) or everolimus (E+ group) could significantly decrease the expression levels of p-mTOR, mTOR, p-P70S6K1, P70S6K1, P-4E-BP1, 4E-BP1, HIF-1α, and VEGF compared with corresponding vehicle group \( (p < 0.05, \text{Fig. 3}) \). Moreover, inhibiting effect of combined treatment with curcumin and everolimus (C+ + E+ group) on mTOR/HIF-1α/VEGF pathway was better than single treatment with curcumin (C+ group) or everolimus (E+ group) \( (p < 0.05, \text{Fig. 3}) \).

**DISCUSSION**

In the present study, the mTOR/HIF-1α/VEGF pathway was activated in CRF rats by 5/6 nephrectomy. Additionally, curcumin as well as everolimus, a selective inhibitor of mTOR, had a renoprotective effect against CRF by suppressing activation of the mTOR/HIF-1α/VEGF pathway, which was accompanied by increase of kidney function and inhibition of kidney injury. These results suggest that treatment with curcumin ameliorated 5/6 nephrectomy-induced CRF in rats.

Renal fibrosis, including glomerular sclerosis and interstitial fibrosis, is considered to play a crucial role in the pathogenesis of CRF. The accumulation of matrix proteins in the glomerulus is termed glomerulosclerosis, while tubulointerstitial...
fibrosis describes the presence of matrix proteins replacing the tubules or surrounding interstitium. The molecular mechanisms underlying renal fibrosis are not completely known, although VEGF is known to play an important role in this pathogenesis. For example, Ardura et al. suggested that the profibrogenic effect of parathyroid hormone-related protein (PTHrP) partially accounts for the promotion of EMT of renal tubulointerstitial cells through interaction with VEGF, and this effect is elicited by high expression levels of PTHrP and VEGF in the obstructed kidney at a later time. Hakroush et al. also reported that increased renal tubular expression of VEGF is associated with fibrosis, cyst formation, and glomerular diseases. Consistent with the findings of these studies, we observed interstitial inflammatory cell infiltration, glomerular hypertrophy, tubular dilation, as well as fibrosis in the kidneys of 5/6 nephrectomized rats, which was accompanied by an increase in VEGF expression. VEGF, also known as VEGF-A, is a member of the family of heparin-binding growth factors, which includes placental growth factor, VEGF-B, VEGF-C, and VEGF-D. VEGF is essential for mammalian vascular development via stimulation of endothelial cell proliferation and differentiation. In the kidney, podocytes, distal tubules, collecting ducts, and proximal tubules produce VEGF, which plays an important role in the development and integrity of the nephron and renal interstitium.

VEGF is mainly regulated by HIF-1 at the transcriptional level and the activity of HIF-1 is dependent on the availability of the HIF-1α subunit. It is still controversial whether HIF-1α is pro-fibrotic or anti-fibrotic due to its different roles in different renal cells. Liu et al. indicated that pharmacological inhibitors will generally affect all cell types in kidneys, while the inhibition of HIF by genetic methods may only affect specific renal cell types which may contribute distinctly during renal fibrogenesis. In general, HIF-1α is constitutively expressed but rapidly degraded by the ubiquitin-proteasome pathway. However, under the stimulation of growth factors, cytokines, and some oncogenes, HIF-1α expression is increased via activation of the PI3K/Akt pathway. PI3K regulates protein syntheses through its target Akt and downstream phosphatidylinositol 3-kinase (PI3K) reactivation, thereby disrupting the integrity of the eIF-4E/BP1 complex, which is essential for inhibition of cap-dependent mRNA translation, resulting in enhanced HIF-1α protein translation. Moreover, phosphorylated mTOR also phosphorylates Thr389 of P70S6K, which promotes the phosphorylation of its substrate, ribosomal protein S6, and induces HIF-1α protein translation. In the present study, the expression levels of mTOR, p-mTOR (at serine 2448), P70S6K1, p-P70S6K1 (at threonine 389), 4E-BP1, p-4E-BP1 (at threonine 70), and HIF-1α were increased in the kidneys of 5/6 nephrectomized rats, which could promote the expression of VEGF, thereby implicating the mTOR/HIF-1α/VEGF pathway in the development of CRF. Therefore, inhibition of this pathway is a promising and effective treatment strategy. In support of this hypothesis, Nakagawa et al. indicated that everolimus, a specific inhibitor of mTOR, had renoprotective effects via improved proximal tubular function in end-stage renal disease. Analogously, in the present study, everolimus, which was used as a positive control, had suppressed activation of the mTOR/HIF-1α/VEGF pathway and ameliorated abnormalities in body weight, 24-h urine volume, SBp, 24-h urine protein, BUN, Scr, serum urea, glomerular diameter, inside diameter of tubules and hydroxyproline content of the 5/6 nephrectomized rats. Surprisingly, curcumin also produced a similar effect with everolimus in this CRF rat model. These results suggest that the protective effect of curcumin on CRF is dependent on the suppression of the mTOR/HIF-1α/VEGF pathway. Curcumin is the active ingredient of the traditional herbal remedy and dietary spice turmeric (Curcuma longa), which has been shown to suppress activation of the PI3K/Akt/ mTOR signaling pathway in cancers of the breast, lung, bladder, and colon. Additionally, as a potential treatment for renal diseases, curcumin was found to effectively promote the proliferation of renal tubular epithelial cells and possess a remarkable ability to block tubular EMT and maintain the morphology and phenotype of renal tubule epithelium cells via inhibition of the Akt/mTOR pathway. Thus, we speculated that curcumin-induced suppression of mTOR/HIF-1α/VEGF pathway might depend on its inhibitory effect on PI3K/Akt pathway. However, whether curcumin inhibits mTOR/HIF-1α/VEGF pathway in PI3K/Akt pathway-independent manners remains unknown and needs further studies.

In conclusion, the present study focused the renoprotective effects of curcumin on 5/6 nephrectomy-induced CRF rats via inhibition of the mTOR/HIF-1α/VEGF pathway, thereby providing new insights into the effects and molecular mechanisms of curcumin for the treatment of CRF.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES


