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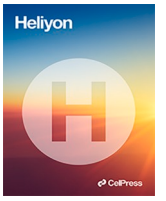

Review article

Research progress on the mechanism of renal interstitial fibrosis in obstructive nephropathy

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ABSTRACT

Renal fibrosis is a common result for various chronic kidney diseases developing to the end stage. It is a pathological process characterized by the destruction of normal kidney structure and the subsequent replacement with fibrous tissue, which primarily involves fibroblast proliferation and extracellular matrix deposition. Obstruction is a common cause of renal fibrosis, and obstructive renal fibrosis is a common disease in urology. Obstructive renal fibrosis, characterized by its insidious onset, is the result of a complex interplay of multiple factors. These factors encompass renal tubular epithelial cell injury, the presence of a hypoxic microenvironment in affected kidney tissue, inflammatory cell infiltration, release of inflammatory mediators, and the release of renal fibrosis growth factors, among others. This paper reviews the research progress on the mechanism and treatment of renal interstitial fibrosis.

1. Introduction

In the pathological process of chronic kidney disease evolving to the end stage, the main manifestations include accumulation of excess extracellular matrix (ECM) in the renal interstitium, destruction of renal structure and impaired function [1–3]. Obstructive nephropathy is a common disease in urology, which involves abnormal structure and function of the urinary system, poor drainage of urine, and hydronephrosis, resulting in destruction of normal structure and function of the kidney, renal function decline and even exhaustion. The pathogenesis of obstructive renal fibrosis begins with an elevation of pressure in the collecting system, leading to the injury of renal tubular epithelial cells. This process is accompanied by inflammatory cell infiltration, the release of inflammatory mediators, and the activation of fibroblasts in the renal interstitium. These events culminate in renal interstitial fibrosis, causing the destruction of kidney structure and impairing its overall function [4–6]. The most significant pathological feature of obstructive nephropathy is renal interstitial fibrosis, the degree of which has close relation to the patient's prognosis. This suggests that the key to protect renal function in patients with obstructive nephropathy lies in how to delay the process of renal interstitial fibrosis [7]. Currently, surgery remains the primary treatment option for obstructive nephropathy as it aims to alleviate the obstruction and restore normal urine flow. However, for patients who are unable to undergo surgery, lack indications for surgical intervention, or experience

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irreversible renal function decline even after surgical removal of the obstruction, effective treatment options are still lacking. Therefore, it is of clinical significance to investigate the mechanism of renal interstitial fibrosis in obstructive nephropathy, examine how to protect renal function. This article will summarize the latest research progress in the pathogenesis and treatment of obstructive kidney disease, in order to propose the latest research conclusions on the diagnosis and treatment of obstructive kidney fibrosis, and provide theoretical guidance for the treatment of obstructive kidney disease.

The mechanism of obstructive renal fibrosis mainly involves damage to renal tubular cells (hypoxic environment of renal tissue, mechanical forces), inflammation, and other pathways (Transforming Growth Factor Beta-1 (TGF-β1), Explanation of small molecule RNA, methylation, and other aspects).

The primary objectives of this review are twofold: firstly, to provide a comprehensive overview of the mechanisms underlying the development of obstructive renal fibrosis (Fig. 1); secondly, to discuss recent advancements in the treatment of obstructive renal fibrosis (Fig. 2).. (created with BioRender.com)

The treatment of renal interstitial fibrosis in obstructive nephropathy mainly includes two aspects: gene therapy and drug therapy, among which drug therapy is also divided into TGF-β1 pathway related drugs and other pathway related drugs.

2. The mechanism of renal interstitial fibrosis in obstructive nephropathy

2.1. Renal tubular epithelial cell injury

The reduction of blood flow in peritubular capillariescan lead to ischemic and hypoxic injury of renal tubular epithelial cells, followed by release of inflammatory mediators, which is an important link in the occurrence of renal interstitial fibrosis caused by obstructive nephropathy. The transformation of renal tubular epithelial cells into mesenchymal fibroblasts is a crucial mechanism contributing to the progression of renal fibrosis. Waasdorp et al. [8]found that in mice with unilateral ureteral obstruction (UUO) and deficient protease-activated receptor-1 (PAR-1), the aggregation of macrophages and fibroblasts was significantly reduced with the production of monocyte chemoattractant protein-1 and TGF-β1. PAR-1 can drive the epithelial-mesenchymal transition (EMT) of tubular epithelial cells (TECs) in vitro, and aggravate renal interstitial fibrosis in UUO mice.

Renal interstitial fibrosis is a common kidney injury caused by a variety of chronic kidney diseases and multiple factors. Xie et al.

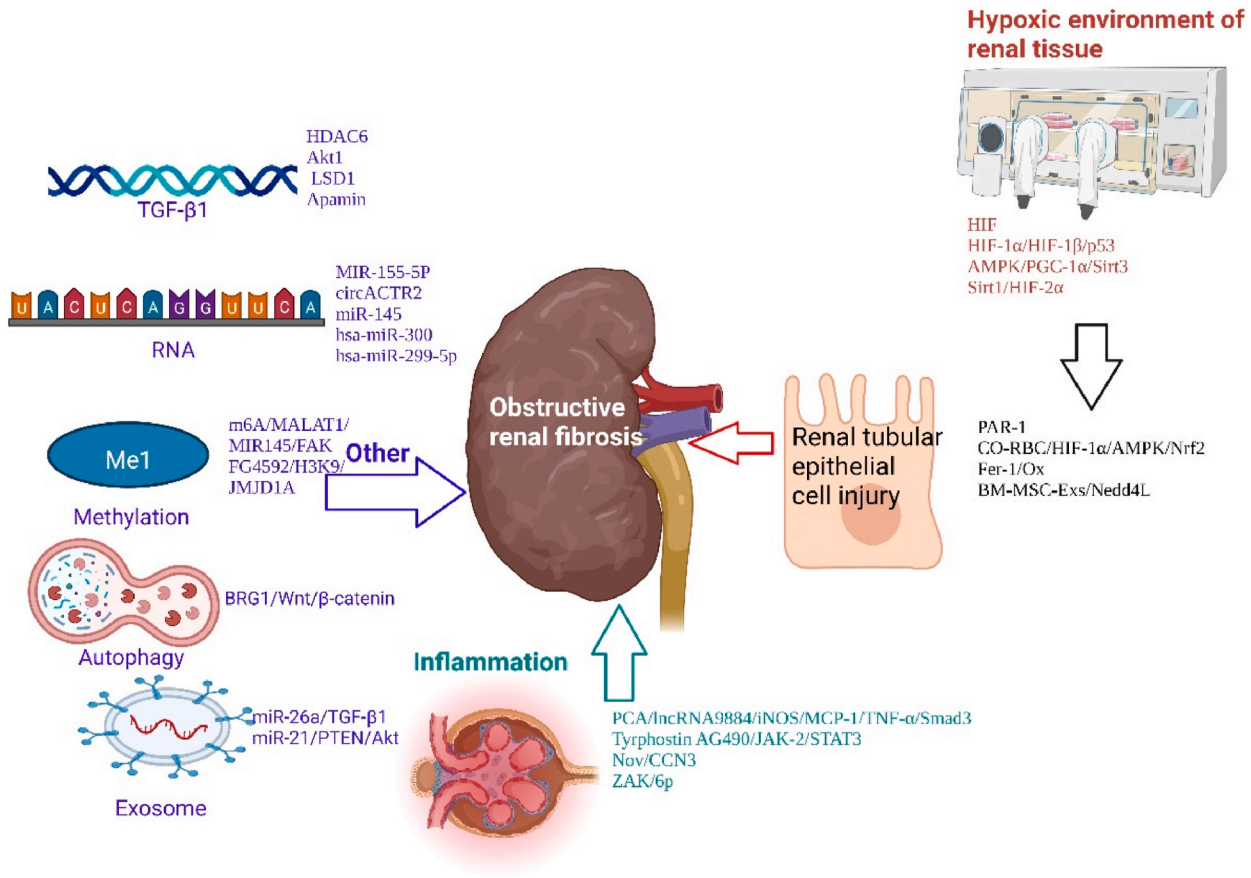

Fig. 1. The mechanism of renal interstitial fibrosis in obstructive nephropathy.

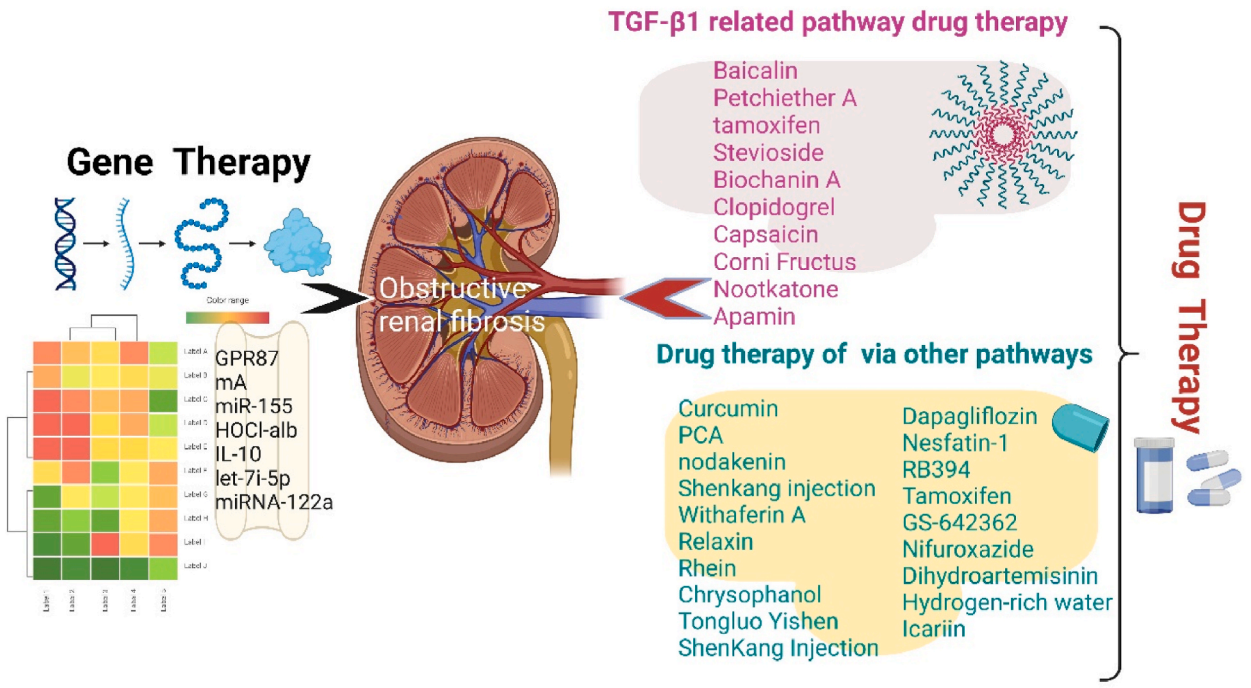

Fig. 2. Treatment of renal interstitial fibrosis in obstructive nephropathy.

[9]showed that the apoptosis of renal tubular epithelial cells and interstitial fibrosis were significantly reduced after Ferrostatin-1 (Fer-1) treatment. It is widely recognized that Fer-1, an inhibitor of ferroptosis, exerts inhibitory effects on Ox-induced tubular epithelial cell damage, fibrosis, and the formation of calcium oxalate (CaOx) stones. Interestingly, mesenchymal stem cell (MSC)-derived exosomes are considered as a new approach to treat tissue damage, and studies have found that bone marrow mesenchymal stem cell-derived exosomes (BM-MSC-Exs) can mitigate renal fibrosis by preventing TGF-β1-induced epithelial-mesenchymal transition (EMT) of renal tubular epithelial cells through regulating the trafficking of neural precursor cell expressed, developmentally down-regulated 4-like (Nedd4L) protein [10]. Currently, there exists a controversial debate regarding whether epithelial-mesenchymal transition (EMT) serves as the basis and marker of renal fibrosis. Some researchers argue that damage to renal tubular epithelial cells can trigger EMT and subsequently lead to renal fibrosis [11–13]. On the other hand, there are those who believe that damage to renal tubular epithelial cells does not directly induce the transformation of EMT into fibroblasts. Instead, it may result in certain phenotypic changes that provide fibrogenic stimuli for the transition of fibroblasts into myofibroblasts [14,15]. Further comprehensive research and confirmation are required to resolve this controversy and gain a deeper understanding of the underlying mechanisms.

In addition, renal tissue in a hypoxic environment can cause damage to renal tubular epithelial cells, leading to obstructive renal fibrosis. The obstruction causes higher pressure in the renal pelvis and brings changes in renal hemodynamics. Renal tubular epithelial cells may undergo ischemia-hypoxic necrosis due to the low blood flow, leading to the release of excessive oxygen free radicals and inflammatory factors, and cell apoptosis in hypoxic environment [16]. Hypoxia-inducible factor (HIF) encompasses various subtypes, including Hypoxia-Inducible Factor 1-Alpha (HIF-1α) and Hypoxia-Inducible Factor 1-Beta (HIF-1β), which play a pivotal role in linking inflammation and cancer. These subtypes exhibit elevated expression levels under conditions of hypoxia and ischemia [17]. Liu et al. [18]found significantly increased expression of HIF-1α in kidney tissue of UUO model mice. During hypoxia, the up-regulation of p53 induced by HIF-1α hampers cell cycle progression, resulting in G2/M cell cycle arrest. This, in turn, activates fibrotic signaling pathways mediated by transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF), ultimately promoting the production of extracellular matrix and contributing to the development of renal fibrosis. Many scholars have found that renal tubular epithelial cells of UUO model mice with HIF-1α knockout can reduce the infiltration of inflammatory cells and deposition of renal interstitial collagen, thus slowing down the process of UUO-induced renal fibrosis [19–21]. In addition, Mei et al. [22] found that the HIF-1α induced by hypoxia in high glucose cells was significantly higher than that in normal glucose cells. Inhibition of HIF-1 attenuated hypoxia-induced fibronectin expression in hyperglycemic cells, while UUO induced higher HIF-1α expression as well as fibrosis in diabetic mouse kidneys compared to non-diabetic kidneys. In conclusion, the results suggest that diabetes may predispose renal tissue and cells to fibrosis by enhancing HIF-1α activation.

Furthermore, Yishen Huoxue decoction has been shown to alleviate renal injury and fibrosis induced by UUO (unilateral ureteral obstruction). This effect may be attributed to the modulation of adenosine monophosphate-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor coactivator-1α (PGC-1α)/silent mating-type information regulation 2 homolog 3 (Sirt3) signaling pathway, which is associated with the mitigation of hypoxia-induced oxidative stress [23]. Li et al. [24] found that knockdown of

Sirtuin 1 (SIRT1) in renal interstitial cells led to more severe renal injury and fibrosis in UUO model mice, and hypoxia-inducible factor (HIF)-2α may act as a substrate of Sirt1 to mediate to renoprotective effects. In conclusion, SIRT1 plays a protective role in renal injury and fibrosis, which may be related to inhibition of HIF-2α. After ureteral obstruction occurs, renal metabolic function declines and local renal blood flow decreases, which causes decreased blood supply to renal tubules and insufficient oxygen supply to renal tubular epithelial cells, resulting in ischemic hypoxic necrosis and cell apoptosis; at the same time, hypoxia can also induce the release of a large number of oxygen free radicals, oxygen free radicals have toxic effects on cells, further aggravating the oxidative damage of epithelial cells and inducing renal fibrosis.

The majority of damage to renal tubular epithelial cells is caused by obstruction caused by mechanical forces (shear stress, pressure). There are many reasons for obstructive renal fibrosis obstruction, which can be divided into mechanical obstruction and dynamic obstruction according to the nature of the obstruction. Most of the obstruction is mechanical obstruction. Studies have found that the signal transduction regulation caused by changes in fluid shear stress in renal tubular epithelial cells is closely related to renal physiology and pathology. Renal tubular epithelial cells are obstructed by mechanical forces due to shear stress caused by flow within the nephron. In renal diseases characterized by renal tubular dilation, obstruction, and high filtration, shear stress can undergo alterations, thereby contributing to the development of obstructive renal fibrosis [25]. In their comprehensive review on fibroblast activation and myofibroblast production in obstructive kidney disease, Grande et al. [26] concluded that obstructive kidney disease represents the primary cause of renal failure. After urinary tract obstruction, under the influence of mechanical forces and cytokines produced by renal tubular epithelial cells and infiltrating interstitial cells, fibroblasts are activated, leading to the formation of obstructive kidney fibrosis. In addition, Rohatgi et al. [27] found that biomechanical forces, stretching, and fluid shear stress in renal tubules can cause changes in intracellular signal transduction and gene expression, leading to the pathological biology of obstructive and non-obstructive kidney disease. Gui et al. [28] found that the degree of harmful microenvironment formed by obstructive renal fibrosis was determined by cellular mechanical force. Therefore, balancing cell mechanics and metabolism is crucial for developing treatment strategies to prevent renal fibrosis. The above research indicates that an important factor in the formation of obstructive renal fibrosis is the mechanical force (shear stress, pressure).

2.2. Inflammation

Factors including inflammatory cell infiltration and release of inflammatory mediators play an important role in the occurrence and development of renal interstitial fibrosis caused by obstructive nephropathy, which can lead to changes in renal vascular permeability, local renal tissue structure destruction and damage. Moreover, continuous chronic inflammation and accumulation of fibrotic products can aggravate tubulointerstitial fibrosis (TIF), eventually leading to renal hypofunction and failure. Yang et al. [29] found that protocatechualdehyde (PCA) alleviated the renal fibrosis of obstructive nephropathy by inhibiting the inflammatory response induced by lncRNA9884. PCA not only inhibited abnormal expression of the inflammatory cytokines such as Inducible Nitric Oxide Synthase (iNOS), Monocyte Chemoattractant Protein-1 (MCP-1), Tumor Necrosis Factor alpha (TNF- α) in UUO-induced TECs, but also inhibited the expression of Smad3-dependent LncRNA9884. Gasparitsch et al. [30] discovered that Tyrphostin AG490 (AG490) effectively inhibited Janus kinase-2 (JAK-2) and signal transducer and activator of transcription-3 (STAT3), resulting in a reduction in inflammation and fibrosis in neonatal obstructive nephropathy. Tyrphostin AG490 pharmacologically blocks JAK2/STAT3 to reduce inflammation, renal tubular apoptosis and interstitial fibrosis, suggesting that blocking JAK2/STAT3 may be beneficial to children with congenital obstructive nephropathy. Recombinant Mouse Nephroblastoma Overexpressed Gene(Nov/CCN3) is a secreted multifunctional protein belonging to the CCN family, which is involved in a variety of physiological and pathological processes, such as angiogenesis, inflammation, and cancer [31].

To explore the role of Nov/CCN3 in obstructive renal tubular interstitial injury-related nephritis and fibrosis, Marchal et al. [32] found that compared with wild-type mice, NOV/CCN3 was highly expressed in UUO mice. Based on significantly increased NOV/CCN3 expression in renal biopsy tissues of patients with tubulointerstitial nephritis, it can be concluded that decrease of NOV/CCN3 expression may limit inflammation and renal interstitial renal fibrosis in mice with obstructive nephropathy. In addition, Shu et al. [33]found that the expression levels of sterile alpha motif and leucine zipper-containing kinase (ZAK) were correlated with the degree of renal fibrosis in Chronic kidney disease (CKD) patients. ZAK depletion effectively attenuated tubulointerstitial fibrosis (TIF) and inflammation induced by UUO (unilateral ureteral obstruction). In addition, a newly discovered ZAK small molecule inhibitor called 6p demonstrated the ability to inhibit TGF-β1-induced fibrosis in NRK52E cells in vitro. Furthermore, in vivo administration of 6p via gavage showed improvements in both the UUO and unilateral ischemia-reperfusion injury models. In conclusion, ZAK is a novel therapeutic target for TIF, and 6p may be a potential therapeutic agent for TIF. The above studies have shown that inflammation can lead to changes in renal vascular permeability and induce local renal tissue damage. At the same time, the release of excessive inflammatory mediators further aggravates the damage of normal renal tissues and promotes renal interstitial fibrosis in obstructive nephropathy.

2.3. Other

The occurrence and development of renal interstitial fibrosis in obstructive nephropathy is not only related to the above-mentioned renal tubular epithelial cell injury, tissue hypoxia, inflammation, but may also be related to the activation of related signal pathways of renal fibrosis, methylation, and exosomes, etc. The increased pressure in the renal pelvis after obstruction causes a decrease in renal blood flow, which can lead to the activation of renin-angiotensin system and the decrease of glomerular filtration rate. The activation of renin-angiotensin system can produce abundant nuclear factor-κB (NF-κB), oxygen free radicals and related factors. NF-κB can

promote the activation of macrophages to release tumor necrosis factor α (TNF-α), which in turn induces the release of apoptosis signals, leading to the apoptosis of renal tubular epithelium [34].

It is noteworthy that activated macrophages have the capability to release TGF-β1, a key transforming factor that plays a significant role in renal fibrosis. TGF-β1 is involved in various processes, including the promotion of the conversion of hematopoietic stem cells into fibroblasts, enhancement of renal fibroblast maturation, and stimulation of the transformation of renal capillary endothelial cells, renal tubular epithelial cells, and mesangial cells into mesenchymal fibroblasts [35–37]. Chen et al. [38] found that histone deacetylase 6 (HDAC6) inhibitors inhibited TGF-β1 and epidermal growth factor receptor (EGFR) signaling pathways in obstructive nephropathy to delay the development of renal fibrosis, suggesting that HDAC6 may become a potential target for the treatment of renal fibrosis. Kim et al. [39]studied the role of Akt1, one of the three subtypes of Akt, in renal fibrosis, finding that Akt1 mediated transforming growth factor 1 (TGF1)/transcriptional activator 3 (STAT3) pathway to promote kidney fibrosis in UUO mice. Yang et al. [40]found that bone marrow-derived macrophages β-catenin/foxo not only inhibited β-catenin/Tcf-mediated renal fibrosis, but also enhanced its anti-inflammatory effects, thus alleviating inflammation and renal fibrosis in UUO mice by changing transcription of bone marrow-derived macrophages. It has been found that the expression of Lysine-specific histone demethylase 1 (LSD1) is increased in UUO mouse kidneys and in cultured NRK-52E cells undergoing TGF-β1-induced epithelial-mesenchymal transition (EMT). Moreover, by activating multiple signaling pathways, LSD1 plays a key role in the regulation of renal EMT and fibrosis, so it can be used as a therapeutic target for the treatment of renal fibrosis [41]. Gwon et al. [42] found that Apamin inhibited renal inflammatory response and ECM deposition in UUO-injured mice and inhibited the activation of myofibroblasts in vivo and in vitro, So, Apamin has anti-fibrotic effects on renal fibrosis by regulating TGF-β1 classical and non-classical signaling. TGF-β1, TNF-α, NF-κB and other related factors are involved in the occurrence and development of obstructive renal fibrosis. Systematic and in-depth study of related factors can be carried out to further clarify the mechanism of renal interstitial fibers in obstructive nephropathy.

In addition, the development of obstructive renal fibrogenesis is also closely related to small RNA molecules, methylation, autophagy, and exosomes. Wang et al. [43]found that overexpression of MIR-155-5P promoted the expression of fibroblast-related proteins in NRK-49F murine fibroblasts and inhibited the expression of SIRT1 (Silent mating type information regulation 2 homolog-1), suggesting that MIR-155-5P may promote renal interstitial fibrosis by inhibiting SIRT1 signaling pathway, which provides a potential endogenous target for renal interstitial fibrosis. Increasing evidence suggests that circular RNA (circRNA) is a key mediator of kidney disease. CircACTR2 can activate Hippo/yes-associated protein (YAP) signaling pathway, stimulate M2 macrophage polarization and promote the development of obstructive renal fibrosis by targeting and sponging Mir-200c [44]. It is well known that TGF-β1 can induce renal epithelial-mesenchymal transition (EMT) and deposition of extracellular matrix protein to aggravate renal fibrosis. Studies have found that N6-methyladenine (m6A)-induced lncRNA transfer of related metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) can aggravate renal fibrosis through miR-145/focal adhesion kinase (FAK) pathway. MALAT1/MIR145/FAK plays an important role in TGF-β1-induced renal fibrosis. In addition, MALAT1/miR145/FAK signaling pathway is also involved in the curative effect of dihydroartemisinin on TGF-β1-induced renal fibrosis [45]. Ike et al. [46] found that hypoxia-inducible factor-α prolyl hydroxylase inhibitor FG4592 improved renal fibrosis by inducing histone H3 lysine 9(H3K9) demethylase Jumonji domain-containing 1A (JMJD1A). Hypoxia-inducible factor-1α and 2α (Hif-1α/2α) transcription factors are major regulators of the cellular response to hypoxia, which play a key role in renal fibrosis associated with acute and chronic kidney diseases.

To investigate whether exosomal microRNAs (MiRNAs) can be used as biomarkers for prenatal diagnosis of congenital hydronephrosis and assessment of fetal renal function, Xie et al. [47] discovered that the expressions of hsa-miR-300 and hsa-miR-299-5p were down-regulated in the amniotic fluid exosomes of fetuses with congenital hydronephrosis. Further investigation revealed that the target genes of hsa-miR-300 and hsa-miR-299-5p were associated with the Wnt signaling pathway. These findings suggest that reduced levels of hsa-miR-300 and hsa-miR-299-5p in fetal amniotic fluid could serve as potential biomarkers for renal fibrosis associated with congenital obstructive nephropathy. Gong et al. [48]found that Brahma-related gene 1 (BRG1) induced renal tubular senescence by inhibiting autophagy through the Wnt/β-catenin pathway, which is conducive to the development of renal fibrosis. Sang et al. [49] showed that semaphorin 3A (SEMA3A) signaling was increased in renal tubular cells and fibroblasts under UUO surgery, and SEMA3A inhibitors ameliorated UUO-induced renal fibrosis by modulating Jun N-terminal kinase (JNK) signaling, suggesting the potential of SEMA3A as inhibitor therapy in renal fibrosis. Zhang et al. [50]found that the expression of exosomal miR-26a was decreased in the kidneys and muscles of UUO mice, which can reduce protein levels of the two pro-fibrotic proteins: connective tissue growth factor (CTGF) and TGF-β1 in the kidneys of UUO mice, and limit renal fibrosis by directly inhibiting CTGF. It was also found that exosomes containing miR-26a prevented muscle atrophy by inhibiting the transcription factor forkhead box O1.

Studies have shown that increased renal fibrosis is associated with prolonged UUO days, and exosome secretion is significantly increased in UUO kidneys and TGF-β1-stimulated NRK-52E cells. Exosomal miR-21 from renal tubular epithelial cells may active fibroblasts in obstructed kidneys via the miR-21/PTEN/Akt pathway, thus accelerating the development of renal fibrosis [51]. Zhang et al. [52] found that Liproxstatin-1(Lip-1) alleviated renal fibrosis by inhibiting ferroptosis in renal tubular epithelial cells, specifically, Lip-1 reduced peripheral fibroblasts by inhibiting the paracrine secretion of pro-fibrotic factors in HK2 cells. Lip-1 may be used as a therapeutic approach for UUO-induced renal fibrosis. Yoon et al. [53] conducted an ultrasound examination on a rabbit model of obstructive urinary tract disease. The study revealed that obstructive urinary tract disease induced alterations in kidney elasticity and blood perfusion. These changes contributed to renal fibrosis and increased stiffness in the renal cortex, as well as delayed and reduced perfusion in the renal cortex. These findings suggest that the extent of renal fibrosis in obstructive nephropathy can potentially be assessed through ultrasound examination. The above studies have shown that the activation of related signal pathways, methylation, and exosomes are all involved in the occurrence of obstructive renal fibrosis, suggesting that there are complex and diverse mechanisms affecting the occurrence of obstructive renal fibrosis. See Table 1 for details.

3. Treatment of renal interstitial fibrosis in obstructive nephropathy

3.1. Gene therapy

TGF-β1 is a key cytokine promoting renal fibrosis, which plays an important role in the occurrence and development of renal fibrosis. At present, there are numerous studies in which TGF-β1 is taken as the key point of the gene pathway. Through in-depth study of TGF-β1 and related genes, the studies aim to explore feasible therapeutic approaches and theoretical basis for the treatment of renal fibrosis. Cui et al. [54] found that a member of the G protein-coupled receptors family (GPR87) played a key role in treatment of renal fibrosis by accelerating glycolysis and mitochondrial damage, suggesting that targeting GPR87 may represent a new therapeutic strategy for patients with CKD. Li et al. [55] used methylated RNA immunoprecipitation sequencing in the kidney of UUO mice to draw a genome-wide N-methyladenosine (mA) map, finding that mA levels were decreased in a time-dependent manner within 1 week, reaching the lowest level on the 7th day. There were a total of 823 differential methylation transcriptions in 507 genes. Demethylated mRNA selectively acted on multiple pathways including TGF-β1, suggesting that mA modification played an important role in obstructive renal interstitial fibrosis, which is expected to become a target for treatment of renal fibrosis. Xi et al. [56] found that miR-155 levels were significantly increased in UUO mouse kidney tissue and HK-2 renal epithelial cells treated with TGF-β1, while knockdown of miR-155 could target at the upstream molecule phosphodiesterase3A (PDE3A) to inhibit the activation of TGF-β1/Smad1/Smad signals, thereby reducing renal fibrosis, which suggests that inhibition of miR-155 may be a new treatment method to prevent fibrotic kidney disease. Liu et al. [57]found that hypochlorite modified albumins (HOCl-alb) promoted tubular cells apoptosis and renal interstitial fibrosis through the damage of renal tubular interstitial mitochondria in mice with obstructive nephropathy and the protective effect of antioxidant peptides. It suggests that mitochondrial dysfunction may aggravate renal interstitial fibrosis, based on which a new method may be proposed for the treatment of obstructive renal fibrosis. Jung et al. [58]found that interleukin 10 (IL-10, a potent anti-inflammatory cytokine) could prevent ureteral obstruction-induced renal fibrosis by inhibiting endoplasmic reticulum stress and apoptosis. The research improves understanding of the cellular mechanisms that lead to fibrosis and could help develop new treatments. In addition, it has been shown that let-7i-5p is a Smad3-dependent microRNA that promotes renal fibrosis in mice with unilateral ureteral obstruction, and let-7i-5p may be a promising gene therapeutic target for the treatment of renal

Table 1
The mechanism of renal interstitial fibrosis in obstructive nephropathy.

Year/Country	Related pathways	Key factor	Study Objective	Author
2019/China	CTGF/TGF-β1	Exogenous miR-26a	Exogenous miR-26a suppresses muscle wasting and renal fibrosis in obstructive kidney disease	Zhang et al. [50]
2022/USA	EMT	LSD1	Regulate renal EMT	Zhang et al. [41]
2021/China	GPX4/ ferroptosis	Lip-1	Liprostatin-1 inhibits renal tubular epithelial cell ferroptosis and alleviates renal fibrosis	Zhang et al. [52]
2022/Japan	H3K9/JMJD1A	FG4592	FG4592 ameliorated renal fibrosis by inducing H3K9 demethylase JMJD1A	Ike et al. [46]
2021/Japan	JNK	SEMA3A	SEMA3A inhibitor ameliorates renal fibrosis through the regulation of JNK signaling	Sang et al. [49]
2022/China	miR-200c/YAP	circACTR2	Promotes obstructive renal fibrosis	Fu et al. [44]
2021/China	miR-21/PTEN/ Akt	Exogenous miR-21	Exosomal miR-21 from tubular cells contributes to renal fibrosis by activating fibroblasts via targeting PTEN in obstructed kidneys	Zhao et al. [51]
2020/China	MALAT1/ MIR145/FAK	m6A	m6A methylation Promotes obstructive renal fibrosis	Liu et al. [45]
2020/South Korea	NA	Ultrasonography	Ultrasonography can determine the degree of renal fibrosis in obstructive nephropathy	Yoon et al. [53]
2021/China	SIRT1	MIR-155-5P	MIR-155-5P inhibits SIRT1 signaling pathway and promotes obstructive renal fibrosis	Wang et al. [43]
2020/China	TGF-β1/EGFR	HDAC6	HDAC6 delays renal fibrosis by inhibiting TGF-β1 and EGFR signaling pathways	Chen et al. [38]
2020/Republic of Korea	TGF1/STAT3	Akt1	Akt1 promotes renal fibrosis in UUO mice through TGF1/STAT3 pathway	Kim et al. [39]
2021/Republic of Korea	TGF-β1	Apamin	Inhibits myofibroblast activation	Gwon et al. [42]
2019/China	β-catenin/Tcf	β-catenin/foxo	β-catenin/FoxO changes the transcription of bone marrow-derived macrophages to reduce renal fibrosis	Yang et al. [40]
2017/China	Wnt	hsa-miR-300/hsa-miR-299-5p	Biomarkers of renal fibrosis associated with congenital obstructive nephropathy	Xie et al. [47]
2021/China	Wnt/β-catenin	BRG1	BRG1 promotes tubular senescence and renal fibrosis through Wnt/ β-catenin/autophagy axis	Gong et al. [48]

Abbreviations EGFR: epidermal growth factor receptor; HDAC6: histone deacetylase 6; TGF1: transforming growth factor 1; STAT3: transcriptional activator 3; LSD1: Lysine-specific histone demethylase 1; SIRT1: Silent mating type information regulation 2 homolog- 1; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; FAK: focal adhesion kinase; m6A: N6-methyladenine; H3K9: histone H3 lysine; JMJD1A: Jumonji domain-containing 1a; BRG1: Brahma-related gene 1; SEMA3A: semaphorin 3 A; CTGF: connective tissue growth factor; Lip-1: Liproxstatin-1.

fibrosis associated with CKD (chronic kidney disease) [59]. Li et al. [60] found that mesenchymal stem cells reduced renal fibrosis through exosomes derived from mirNA-122a and inhibitd autophagy, and the export of mirNA-122a by mesenchymal stem cell-derived exosomes represents a new strategy to reduce obstructive renal fibrosis. The above-mentioned scholars' studies have shown that there are diverse gene therapy targets in treatment of obstructive renal fibrosis. The role of related target genes should be further studied to provide a theoretical basis for the treatment of obstructive renal fibrosis. See Table 2 for details.

3.2. Drug therapy

3.2.1. TGF-β1 related pathway drug therapy

TGF-β1 is recognized as a key cytokine in the formation of renal fibrosis. In recent years, drugs for the treatment of renal fibrosis with TGF-β1 as the therapeutic target constantly emerge, including NF-κB inhibitors, TGF-β1 antisense oligos, and TGF-β1 antibodies. Wang et al. [7] found that baicalin could alleviate renal interstitial fibrosis in UUO mice by inhibiting the TGF-β/Smad signaling pathway, suggesting that baicalin could be a potential therapeutic option for the treatment of renal interstitial fibrosis (RIF). You et al. [61] discovered a new small-molecule Petchiether A (PetA) from Ganoderma lucidum. As a potential inhibitor of TGF-β1-induced Smad3 phosphorylation, it can reduce macrophage infiltration, inhibit the expression of pro-inflammatory cytokines (interleukin-1β and TNF-α) and reduce the deposition of extracellular matrix (α-smooth muscle actin, type I collagen and fibronectin) to prevent the kidney inflammation and fibrosis of UUO mice. In addition, it was found that PetA inhibited the activity of Smad3 response promoter in a dose-dependent manner, indicating that PetA inhibited the expression of genes downstream of the TGF-β1/Smad3 signaling pathway. Kim et al. [62]found that tamoxifen (TAM), a selective estrogen receptor modulator (SERM), inhibited sarcoma (Src) and PI3K/Akt/mTOR signaling pathways to resist renal interstitial fibrosis. In addition, it can also reduce renal fibrosis by regulating TGF-β1/Smad3 signal.

As a sweetener, steviol glycosides are widely used in foods, demonstrating many beneficial biological effects such as anti-diabetes, lowering blood pressure, and kidney protection. Shen et al. [63]found that steviol glycosides can increase the expression of peroxisome proliferator-activated receptor γ (PPARγ) and Smad7 protein in UUO mice kidney, lower the expression of NF-κB, STAT3, p-STAT3, TGF-β1, Smad2/3 and p-Smad2/3 proteins, thereby antagonizing obstructive renal interstitial fibrosis, which provides a new potential application of steviol glycosides in the prevention and treatment of renal fibrosis. Indian scholar Ram et al. [37] found that Biochanin A (BCA), as A isoflavone, has A variety of pharmacological activities, which can inhibit the TGF-β1/Smad2/3 and nuclear factor-k-gene binding (Nf-Kb/NLRP3) signaling axis to reduce renal interstitial fibrosis and inflammation caused by unilateral ureteral obstruction in mice. The Recombinant Purinergic Receptor P2Y(P2Y12) inhibitor clopidogrel attenuates renal fibrosis by inhibiting the transition of macrophages to myofibroblasts via the TGF-β/Smad3 signaling pathway [64]. Capsaicin attenuates renal fibrosis by inhibiting TGF-β1-Smad2/3 signaling pathway, delaying myofibroblast activation and protecting renal tubular epithelial cell phenotype changes [65], Corni Fructus alleviates renal fibrosis by inhibiting oxidative stress in UUO and modulating the TGF-β1/Smad pathway [66]. Similarly, Nootkatone can also exert anti-fibrotic effects in a mouse model of unilateral ureteral obstruction by regulating the Tgf-β/Smad signaling pathway [67]. Apamin inhibits renal fibrosis via suppressing TGF-β1 and STAT3 signaling in vivo and in vitro [42]. The above studies show that related drugs play a role in anti-renal fibrosis through TGF-β related pathways, and more and more drugs will be developed and applied in the treatment of obstructive renal fibrosis. See Table 3 for details.

3.2.2. Drug therapy of renal fibrosis via other pathways

For the drug treatment of obstructive renal fibrosis, it is not only necessary to develop and apply drugs based on TGF-β pathway, but

Table 2
Gene therapy in renal interstitial fibrosis of obstructive nephropathy.

Genes	Key Pathways	Study Objective	Status of Therapies	Author
HOCl-alb	Damage of renal tubulointerstitial mitochondria and the protective effect of antioxidant peptides	Mitochondrial dysfunction may aggravate renal interstitial fibrosis	Pre-clinical study	Liu [57] et al.
GPR87	Glycolysis and mitochondrial damage	Targeting GPR87 may represent a new therapeutic strategy for CKD patients	Pre-clinical study	Cui et al. [54]
IL10	Inhibition of endoplasmic reticulum stress and apoptosis	Interleukin-10 Protects against Ureteral Obstruction-Induced Kidney Fibrosis by Suppressing Endoplasmic Reticulum Stress and Apoptosis	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Jung et al. [58]
miRNA-122a	Inhibition of autophagy can reduce renal fibrosis	Mesenchymal Stem Cells Alleviate Renal Fibrosis and Inhibit Autophagy via Exosome Transfer of miRNA-122a	Pre-clinical study	Li et al. [60]
mA	Multiple pathways including TGF-β1	mA modification plays an important role in renal interstitial fibrosis in obstructive nephropathy	Pre-clinical study	Li et al. [55]
miR-155	PDE3A/TGF-β1/Smad1/Smad	Mir-155 may be a novel therapeutic approach for the prevention of fibrotic kidney disease	Pre-clinical study	Xi et al. [56]
let-7i-5p	Smad3	Let-7i-5p may be a promising gene target for the treatment of renal fibrosis associated with CKD	Pre-clinical study	Peng et al. [59]

Abbreviations: GPR87: G protein-coupled receptors family; mA: N-methyladenosine; PDE3A: phosphodiesterase3A; IL-10:Interleukin-10.

Table 3
TGF-β1 related pathway drug therapy in renal interstitial fibrosis of obstructive nephropathy.

Year/Country	Drug	Key Pathways or Genes	Study Objective	Status of Drug	Author
2021/ Republic of Korea	Apamin	TGF-β1/Smad2/3, STAT3	Apamin has anti-fibrotic effects on renal fibrosis by regulating classical and non-classical TGF-β1 signaling	Pre-clinical study	Gwon et al. [42]
2022/China	Baicalin	TGF-β/Smad	Inhibition of fibrosis and inflammation improves RIF in UUO mice	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Wang et al. [7]
2022/India	Biochanin A	TGF-β1/Smad2/3, NF-kB/NLRP3	Biochanin A has a therapeutic benefit against renal fibrosis	Pre-clinical study	Ram et al. [37]
2022/China	Clopidogrel	P2Y12, TGF-β/Smad3, MMT	a new and effective anti-fibrotic drug for CKD	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Chen et al. [64]
2022/China	Capsaicin	TGF-β1-Smad2/3	Delays myofibroblast activation and protects phenotypic changes in renal tubular epithelial cells	Pre-clinical study	Liu et al. [65]
2022/ Republic of Korea	Corni Fructus	TGF- β/Smad	nhibition of oxidative stress in UUO to modulate the TGF-β1/Smad pathway to alleviate renal fibrosis	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Lee et al. [66]
2021/India	Nootkatone	TGF- β/Smad	NTK might be a budding therapeutic candidate for renal fibrosis	Pre-clinical study	Gairola et al. [67]
2019/China	Petchiether A	TGF-β/Smad3 and NF-κB	Selective inhibition of TGF-β/Smad3 signaling to prevent kidney inflammation and fibrosis	Clinical trails	You et al. [61]
2020/China	Stevioside	NF-κB, STAT3, p-STAT3, TGF-β1, Smad2/3	A new potential application in the prevention and treatment of renal fibrosis	Clinical trails	Shen et al. [63]
2019/ Republic of Korea	Tamoxifen	Src,PI3K/Akt/ mTOR, TGF-β1/ Smad3	Tamoxifen is a new therapeutic option for the prevention and treatment of renal fibrosis	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Kim et al. [62]

Abbreviations RIF: renal interstitial fibrosis; MMT:macrophage-to-myofibroblast transition. NTK: Nootkatone.

also necessary to develop and apply renal fibrosis drugs based on other pathways.. Wang et al. [68]found that curcumin inhibited renal tubular epithelial cell-mesenchymal transition by inhibiting TLR4/NF-κB and PI3K/AKT pathways, thereby inhibiting renal interstitial fibrosis and inflammation, which suggests the potential application value of curcumin in the treatment of renal interstitial fibrosis. Chang et al. [3] found that protocatechuic aldehyde (PCA), as a natural product, could reduce TGF-β1-induced fibrosis and EMT in vitro and in vivo (UUO rat model). Li et al. [69] isolated coumarin nodakenin from the roots of Angelica sinensis and found it can effectively counteract the fibrosis caused by UUO by down-regulating the expression of Snail1. Nodakenin can prevent the infiltration of inflammatory cells, reduce the pro-inflammatory cells, downgrade the activation of macrophages and reduce the abnormal deposition of extracellular matrix at the injured site. Shenkang injection liquid, as Chinese patent medicine, was found to reduce tubulointerstitial fibrosis in obstructive nephropathy by targeting pericyte-myofibroblast transition (PMT), suggesting that targeting PMT can provide a new strategy for treatment of obstructive nephropathy [70]. Chen et al. [71]found that Withaferin A had a protective effect on chronic kidney disease. This may be because Withaferin A can alleviate apoptosis, inflammation and fibrosis related to endoplasmic reticulum stress in the kidney of UUO mice, suggesting that Withaferin A may become a potential drug for the treatment of chronic kidney disease.

Relaxin inhibit renal fibrosis and epithelial-mesenchymal transition by downregulating the Wnt/β-catenin signaling pathway [72]. Rhein significantly improved renal interstitial fibrosis in UUO rats by regulating SHH-Gli1-Snail signaling pathway [73]. Chrysophanol effectively improved renal fibrosis by inhibiting NKD2/NF-κB pathway [74]. Tongluo Yishen decoction exerted renal protection by inhibiting NLRP3-mediated pyroptosis [75]. Shenkang injection alleviated renal fibrosis by inhibiting EMT and modulating Wnt/β-Catenin pathway [76]. Icariin reduced renal fibrosis by inhibiting the Notch2/Hes-1 pathway in vivo and in vitro [77], Oral hydrogen-rich water may reduce oxidative stress and prevent interstitial fibrosis in UUO kidneys via a klotho mechanism [78]. Dihydroartemisinin inhibited renal fibrosis in UUO mice by reversing increased Klotho and inhibiting DNA methyltransferase 1 (79). Dapagliflozin attenuated renal fibrosis by inhibiting RIP1-RIP3-MLKL signaling pathway-mediated necroinflammation in unilateral ureteral obstruction [79]. Nesfatin-1 (NES-1) ameliorated UUO-induced renal fibrosis, which may be associated with the inhibition of neutrophil infiltration, thereby ameliorating oxidative stress and inflammation [80]. Dual soluble epoxide hydrolase inhibitor-PPAR-γ agonist (RB394) alleviated renal fibrosis by reducing renal inflammation, oxidative stress, tubular injury and vascular injury [81]. Tamoxifen attenuated renal fibrosis in human kidney slices and rats subjected to unilateral ureteral obstruction [82]. Cyclophilin inhibitor (GS-642362) effectively inhibited acute kidney injury and renal fibrosis [83]. Nifuroxazide suppressed UUO-induced renal fibrosis in rats via inhibiting STAT-3/NF-κB signaling, oxidative stress and inflammation [84]. The above studies show that with the deepening of the research on obstructive renal fibrosis, more and more drugs have been used for the treatment of obstructive renal fibrosis, among which traditional Chinese medicine drugs are a major force. This suggests that there may be some anti-obstructive renal fibrosis components in natural drugs, which needs to be revealed by further in-depth research. See Table 4 for details.

The above studies show that most of the drugs exerting anti-renal fibrosis effects through TGF-β pathway or other pathways are

Table 4
Drug therapy for other pathways of renal interstitial fibrosis in obstructive nephropathy.

Year/Country	Drug	Key Pathways or Genes	Study Objective	Status of Drug	Author
2020/China	Curcumin	TLR4/NF-κB and PI3K/AKT	Inhibition of epithelial-mesenchymal transition to alleviate renal interstitial fibrosis in obstructive nephropathy	On the market	Wang et al. [68]
2022/China	Chrysophanol	NKD2/NF-κB	Inhibition of NKD2/NF-κB pathway effectively improves renal fibrosis	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Gu et al. [74]
2022/China	Dihydroartemisinin	DNMT1, Klotho	Targeting DNMT1 to reverse Klotho inhibits renal fibrosis	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Zhou et al. [85]
2022/China	Dapagliflozin	Wnt3 α/β -catenin/ GSK-3,RIP1-RIP3-MLKL	Necroinflammation to improve β signaling in renal fibrotic UUO	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Xuan et al. [79]
2020/Australia	GS-642362	NA	Gs-642362 can effectively inhibit obstructive renal fibrosis	Pre-clinical study	Leong et al. [83]
2022/Japan	Hydrogen-rich water	Klotho	Reduces oxidative stress and prevents interstitial fibrosis in UUO kidneys	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Mizutani et al. [78]
2022/China	Icariin	Notch2/Hes-1	Attenuates renal fibrosis by inhibiting Notch2/Hes-1 pathway in vivo and in vitro	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Zhang et al. [77]
2022/Turkey	Nesfatin-1	Neutrophil infiltration	NES-1 may have a regulatory role in protecting the kidneys against obstruction-induced renal injury	Pre-clinical study	Tezcan et al. [80]
2020/China	Nodakenin	Snail1	Prevents inflammatory cell infiltration, reduces pro-inflammatory cytokine levels, reduces activation of macrophages, and reduces abnormal deposition of extracellular matrix at the site of injury	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Li et al. [69]
2021/Egypt	Nifuroxazide	STAT-3/NF-κB	NIF treatment suppressed interstitial fibrosis in UUO renal tissues	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Hassan et al. [84]
2022/China	PCA	EMT	Reduces TGF-β1-induced fibrosis and EMT in vitro and in vivo	Pre-clinical study	Chang et al. [3]
2022/China	Relaxin	Wn t/β-catenin	Down-regulation of Wnt/β-catenin signaling pathway inhibits renal fibrosis and EMT	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Chen et al. [72]
2022/China	Rhein	SHH-Gli1-Snail	Rhein improves renal interstitial fibrosis in UUO rats by inhibiting SHH-Gli1-Snail signaling pathway.	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Luo et al. [73]
2020/USA	RB394	Attenuate renal inflammation, oxidative stress,	RB394 demonstrates exciting potential as a therapeutic for renal fibrosis	Pre-clinical study	Stavniichuk et al. [81]
2022/China	ShenKang Injection	Wnt/β - Catenin	Regulation of the Wnt/β-catenin pathway and EMT inhibition to mediate renal fibrosis	On the market	Wei et al. [76]
2019/China	Shenkang injection	PMT, PDGFR/VEGFR	Targeting PMT could provide new strategies for ON treatment	On the market	Liu et al. [70]
2022/China	Tongluo Yishen	NLRP3, Pyroptosis	Inhibition of NLRP3-mediated pyroptosis exerts renal protection	On the market	Jia et al. [75]
2021/Denmark	Tamoxifen	NA	Tamoxifen is effective in preventing and treating obstructive renal fibrosis	Drug was already on the market but still in pre clinical study of obstructive nephropathy	Tingskov et al. [82]
2020/China	Withaferin A	NA	Attenuates ER stress-related apoptosis, inflammation, and fibrosis in CKD kidneys	Pre-clinical study	Chen et al. [71]

Abbreviations PCA: Protocatechuic aldehyde; EMT: Epithelial-mesenchymal transition; PMT: pericyte-myofibroblast transition; PDGFR: platelet-derived growth factor receptor; VEGFR: vascular endothelial growth factor receptor; ON: obstructive nephropathy; DNMT1: DNA methyltransferase 1. NIF: Nifuroxazide.

currently in the stage of animal experiments. However, there are few effective drugs that can be used to delay the development of human renal tubulointerstitial fibrosis (TIF), which indicates that there is still a long way to fully realize the clinical application of drug therapy for TIF, and a large number of clinical trials are needed for verification.

4. Conclusion and prospect

Obstructive renal fibrosis is characterized by complex occurrence and development process, which may be related to renal tubular epithelial cell injury, hypoxic microenvironment of renal tissue, inflammatory cell infiltration, release of inflammatory mediators, release of renal fibrotic growth factors, activation of related signal pathways, etc. At present, with the application of single-cell sequencing technology, inflammation chip technology, gene chip technology, proteomics, epigenetics research, etc., the mechanism of obstructive renal fibrosis will be elucidated more clearly and completely, and gene or drug-based therapy will be applied more maturely and effectively. It is expected that large-scale clinical trials can ultimately improve the treatment effect of obstructive renal fibrosis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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