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Celastrol in kidney diseases: From therapeutic duality and toxicity to precision renal targeting

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ABSTRACT

Kidney disorders have become a prevalent global public health crisis, accompanied by soaring morbidity and insufficient therapeutic regimens in clinical practice. Celastrol, a biologically active pentacyclic triterpenoid isolated from *Tripterygium wilfordii*, is well documented to exert powerful anti-inflammatory, antioxidant, and anti-fibrotic bioactivities. A growing body of preclinical data confirms that celastrol yields remarkable renoprotective outcomes in a broad spectrum of renal disease models, encompassing diabetic kidney disease, IgA nephropathy, chronic kidney disease, as well as acute kidney injury. Mechanistically, celastrol alleviates renal inflammatory infiltration, oxidative stress injury, and pathological fibrotic remodeling through the synergistic regulation of pivotal signaling axes, such as PI3K/Akt/NF-κB, p38 MAPK/NF-κB, Nrf2/GPX4, and SIRT1/EZH2/Wnt/β-catenin pathways. However, a narrow therapeutic index and systemic toxicity greatly hinder its clinical translation. To address this, kidney-targeted delivery systems—including nanoparticle-based carriers (e.g., liposomes) and microneedle patches—have been developed to increase renal drug accumulation and reduce off-target toxicity. Further efforts should focus on elucidating context-dependent mechanisms, optimizing carrier design, and advancing clinical trials to fully unlock the therapeutic potential of celastrol against kidney diseases.

KEYWORDS: Celastrol; Targeted drug delivery; Efficacy enhancement; Toxicity reduction; Kidney diseases

1. Introduction

Kidney disease represents a growing global public health challenge, characterized by steadily increasing incidence, progressive pathological deterioration, and a high prevalence of multiple clinical

comorbidities[1]. Current standard therapeutic strategies, including renin-angiotensin system inhibition, blood pressure modulation, and glycemic regulation, can only partially retard the progression of renal injury[2]. Despite these available clinical interventions, the global prevalence of end-stage renal disease continues to rise. The limited therapeutic efficacy and unavoidable adverse reactions of existing treatments remain major clinical bottlenecks[3], highlighting the urgent need to explore and develop novel targeted therapeutic strategies to improve the clinical management of kidney diseases.

Celastrol, a bioactive pentacyclic triterpenoid derived from the root cortex of *Tripterygium wilfordii*, has long been used in traditional medicine to manage rheumatic and autoimmune disorders[4]. Growing evidence has revealed its wide range of pharmacological activities, including potent anti-inflammatory, antioxidant, antifibrotic, and immunomodulatory effects[5]. Notably, significant renoprotective efficacy has been demonstrated across multiple chronic kidney disease (CKD) models, including diabetic kidney disease (DKD), IgA nephropathy (IgAN), chronic renal failure, and acute kidney injury (AKI)[6,7]. At the mechanistic level, celastrol exerts its beneficial effects by coordinately regulating key signaling nodes: it suppresses NF-κB-mediated inflammatory cascades, activates Nrf2/HO-1-mediated antioxidant defenses, and

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inhibits TGF- β /Smad-dependent fibrotic pathways. These actions collectively reduce renal inflammation, oxidative damage, and interstitial fibrosis, ultimately improving renal function.

Despite these promising preclinical properties, the clinical translation of celastrol remains severely limited by inherent physicochemical and biopharmaceutical drawbacks, including a narrow therapeutic window, poor aqueous solubility, and significant systemic toxicity[8]. To overcome these challenging obstacles, extensive research has shifted to the design and development of kidney-targeted delivery systems, such as nanocarrier-based preparations, prodrug modification, and ligand-mediated active targeting strategies. These advanced methods collectively aim to achieve site-specific drug accumulation in renal lesions, improve systemic bioavailability, and significantly reduce off-target toxicity[9]. In this review, we systematically summarize the existing research on the therapeutic mechanism of celastrol in kidney diseases and the latest progress in its targeted delivery technology, with the overall goal of providing a theoretical basis for promoting its future clinical translation and therapeutic application.

The literature reviewed in this article was retrieved from PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI). Searches were performed using “celastrol” in combination with kidney disease-related keywords, including CKD, DKD, AKI, IgAN, lupus nephritis, renal fibrosis, and nephrotoxicity. Priority was given to peer-reviewed experimental studies, clinical evidence where available, and representative review articles relevant to the therapeutic mechanisms and renal toxicity of celastrol.

2. Chemical properties of celastrol

Celastrol is a friedelane-type pentacyclic triterpenoid characterized by a characteristic quinone methide moiety, isolated from the root bark of *Tripterygium wilfordii*[10]. Its molecular formula is $C_{29}H_{38}O_4$, corresponding to a molecular weight of 450.6 Da, and commercially available preparations typically achieve a purity of up to 98%[11].

Chemically, celastrol is a pentacyclic triterpenoid bearing multiple hydroxyl and carbonyl groups, which confer moderate polarity. It is readily soluble in polar organic solvents (*e.g.*, methanol and ethanol), but poorly soluble in nonpolar ones (*e.g.*, petroleum ether)[12]. Of particular structural significance is the conjugated quinone methide system embedded in the A/B rings, which acts as an electrophilic center that can undergo Michael addition with cysteine thiol groups on target proteins[13]. This intrinsic electrophilic reactivity underpins celastrol's ability to covalently bind to a wide range of protein targets, providing a structural basis for its characteristic multi-target pharmacological profile[14].

3. Molecular mechanisms underlying the renoprotective effects of celastrol

Celastrol has demonstrated robust renoprotective efficacy across diverse experimental kidney disease models, encompassing both *in vivo* and *in vitro* settings. Treatment with celastrol consistently attenuates proteinuria, preserves renal function, and significantly retards the histopathological progression of renal injury[15].

The mechanistic basis underlying these beneficial effects is inherently multifaceted, involving the coordinated regulation of several interconnected pathological processes—namely, inflammation, oxidative stress, programmed cell death, and fibrogenesis. Through hierarchical and synergistic modulation of these pathogenic cascades, celastrol orchestrates a multi-target, multi-level regulatory network that collectively underpins its renoprotective actions. The multi-level regulatory role of celastrol in kidney diseases is shown in Figure 1.

3.1. Anti-inflammatory effects

Inhibition of renal inflammation represents a core mechanism underlying the renoprotective effects of celastrol. This anti-inflammatory action operates through multilayered regulation of pivotal inflammatory signaling cascades, modulation of immune cell function, and remodeling of the local inflammatory microenvironment. Importantly, the activity of celastrol extends beyond that of a conventional broad-spectrum anti-inflammatory agent; rather, its anti-inflammatory effects exhibit marked context dependency, dynamically shaped by factors, including the nature and intensity of the inflammatory insult, as well as the regional immune milieu[16].

3.1.1. Inhibition of the NF- κ B signaling pathway

Nuclear factor- κ B (NF- κ B) is a core transcription factor that orchestrates inflammatory responses and plays a pivotal role in the onset and progression of kidney diseases[17]. In the resting state, NF- κ B dimers are sequestered in the cytoplasm by binding to I κ B inhibitory proteins. When stimulated by pro-inflammatory cytokines, oxidative stress, or pathogen-associated molecular patterns, the I κ B kinase complex becomes activated, which subsequently phosphorylates I κ B proteins and marks them for proteasome-dependent degradation. This process releases NF- κ B, which then translocates into the nucleus and promotes the transcriptional activation of pro-inflammatory mediators, including TNF- α , IL-1 β , IL-6, and MCP-1[18]. Aberrant activation of the NF- κ B pathway is closely associated with the inflammatory pathogenesis of multiple kidney diseases, including DKD[19], ischemia-reperfusion injury[20], and lupus nephritis[21]. Taken together, these findings confirm that targeted inhibition of NF- κ B signaling is a promising therapeutic

strategy for reducing renal inflammatory injury[22,23].

Celastrol effectively blocks NF- κ B p65 nuclear translocation and phosphorylation, which constitutes one of the core mechanisms underlying its anti-inflammatory activity[24]. Notably, its exact molecular mechanism of action varies greatly across different experimental contexts, exhibiting a model-dependent regulatory pattern. In high glucose-stimulated HK-2 cells, celastrol has been reported to inhibit inflammatory responses by suppressing the PI3K/Akt/NF- κ B signaling cascade[25]. In the streptozotocin (STZ)-induced DKD rat model, celastrol inhibits NF- κ B activation by blocking p38 MAPK phosphorylation[26]. Similarly, in a rat model of ischemia-reperfusion-induced AKI, the anti-inflammatory effect of celastrol is mediated by PI3K/AKT-dependent inhibition of the

NF- κ B pathway[27]. Building on this foundation, Chu *et al.* further confirmed that celastrol significantly reduces the mRNA expression of pro-inflammatory cytokines and improves tubular pathological injury in the same ischemia-reperfusion model[28]. Supplementary evidence from db/db diabetic mice has also verified the inhibitory effect of celastrol on NF- κ B signaling[29].

In addition to directly acting on the above signaling components, celastrol exerts additional anti-inflammatory effects by interfering with upstream activators of the NF- κ B pathway. In a rat model of IgAN and IgA1-stimulated human mesangial cells, celastrol treatment significantly inhibits the TGase-2/HMGB1 pathway, leading to downregulation of TLR4 and its adaptor protein MyD88, which in turn reduces the production of downstream inflammatory

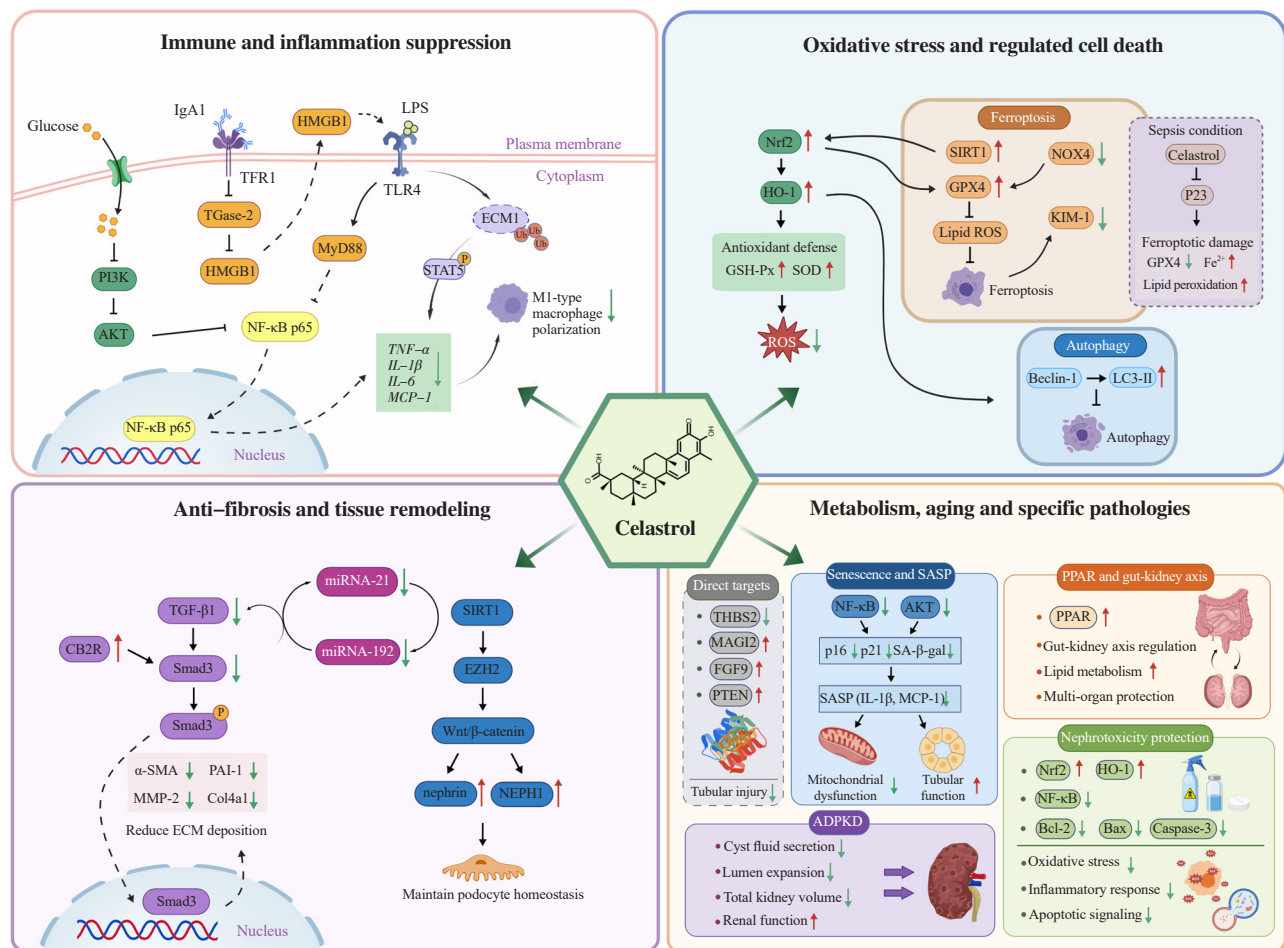


Figure 1. Molecular mechanisms of celastrol in renoprotection. PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; TGase-2: transglutaminase 2; HMGB1: high mobility group box 1; MyD88: myeloid differentiation primary response 88; NF- κ B: nuclear factor kappa B; TLR4: Toll-like receptor 4; LPS: lipopolysaccharide; ECM1: extracellular matrix protein 1; TNF- α : tumor necrosis factor-alpha; IL-1 β : interleukin-1 β ; IL-6: interleukin-6; Nrf2: nuclear factor erythroid 2-related factor 2; HO-1: heme oxygenase 1; GSH-Px: glutathione peroxidase; SOD: superoxide dismutase; SIRT1: sirtuin 1; GPX4: glutathione peroxidase 4; NOX4: NADPH oxidase 4; KIM-1: kidney injury molecule 1; P23: RNA-binding protein p23; LC3: microtubule-associated protein light chain 3; CB2R: cannabinoid receptor type 2; TGF- β : transforming growth factor-beta; Smad3: SMAD family member 3; α -SMA: α -smooth muscle actin; PAI-1: plasminogen activator inhibitor-1; MMP-2: matrix metalloproteinase-2; Col4a1: collagen type IV alpha 1 chain; EZH2: enhancer of zeste homolog 2; NEPH1: nephrin-like protein 1; THBS2: thrombospondin 2; MAGI2: membrane-associated guanylate kinase inverted 2; FGF9: fibroblast growth factor 9; PTEN: phosphatase and tensin homolog; p16: cyclin-dependent kinase inhibitor p16; p21: cyclin-dependent kinase inhibitor p21; SASP: senescence-associated secretory phenotype; PPAR: peroxisome proliferator-activated receptor; Caspase-3: cysteine-aspartic protease 3; ADPKD: autosomal dominant polycystic kidney disease.

effectors. This series of reactions effectively reduces mesangial cell proliferation and inhibits local inflammatory responses[7]. Therefore, celastrol regulates the NF- κ B pathway through a two-layer regulatory mechanism: it directly targets core signaling nodes and indirectly interferes with upstream triggers, ultimately inhibiting the expression of a variety of pro-inflammatory mediators including TNF- α , IL-1 β , IL-6, and MCP-1.

Despite the large body of evidence supporting the anti-inflammatory efficacy of celastrol, inconsistent findings have emerged under specific experimental conditions. Notably, in a high-dose lipopolysaccharide (LPS)-induced acute inflammation model, celastrol exacerbated inflammatory responses and aggravated hepatic and renal injury[30].

It should be acknowledged, however, that this finding originates from a single study. The atypical experimental conditions, particularly the severe inflammatory insult and the pretreatment dosing regimen used, may reasonably explain this discrepancy with the widely accepted consensus. Accordingly, even if celastrol does have potential pro-inflammatory effects, they appear to be highly context-dependent and require further confirmation through independent replication studies.

3.1.2. Regulation of immune cell function

In a mouse model of IgAN induced by bovine serum albumin combined with LPS, celastrol targets extracellular matrix protein 1 and promotes its ubiquitin-mediated degradation. This consequently suppresses M1 macrophage polarization, reduces the release of inflammatory mediators, and ameliorates glomerular inflammatory injury[31]. Notably, in this particular model, LPS predominantly functions as an immune adjuvant that facilitates IgA immune complex deposition, rather than serving as a direct pro-inflammatory driver. This distinction further substantiates the anti-inflammatory efficacy of celastrol in the context of chronic immune-mediated inflammation.

Beyond its direct anti-inflammatory actions, celastrol also modulates the renal immune microenvironment at a higher hierarchical level. In a model of systemic lupus erythematosus nephritis, celastrol promotes the expansion of CD4⁺Foxp3⁺ regulatory T cells (Tregs), thereby enhancing immune tolerance and dampening inflammatory responses[32]. Collectively, these observations indicate that celastrol not only curbs pro-inflammatory signaling pathways but also orchestrates a broader immunoregulatory program by reshaping the balance of local immune cell populations.

3.2. Antioxidant effects

Nuclear factor E2-related factor 2 (Nrf2) serves as a master transcription factor that governs cellular redox homeostasis. Under physiological conditions, Nrf2 remains sequestered in the cytoplasm

through association with its inhibitory partner Keap1[33]. Upon oxidative challenge, Nrf2 is released from Keap1 and translocates to the nucleus, where it drives the transcriptional activation of a set of antioxidant genes, most notably heme oxygenase-1 (HO-1), and thereby produces cytoprotective effects[34]. A growing body of evidence shows that activation of the Nrf2/HO-1 signaling axis is involved in the pathogenesis of a variety of kidney diseases, including DKD[35] and ischemia-reperfusion injury[36], and highlights its protective role in these disease contexts[37].

Activation of the Nrf2/HO-1 pathway is a key mechanism underlying the antioxidant effect of celastrol[38]. In high glucose-induced HK-2 cells and STZ-induced DKD models, celastrol upregulates HO-1 expression, which in turn reduces reactive oxygen species (ROS) levels and increases the activity of antioxidant enzymes, including glutathione peroxidase and superoxide dismutase[39]. These synergistic effects collectively reduce high glucose-induced oxidative stress and related inflammatory damage.

The antioxidant capacity of celastrol is further confirmed in the 5/6 nephrectomy-induced chronic renal failure model, where it upregulates the mRNA and protein expression of HMOX-1 in vascular smooth muscle cells. This leads to a decrease in ROS production and alleviates aortic calcification. The causal role of HMOX-1 in mediating these effects has been confirmed by loss-of-function studies: pharmacological inhibition or siRNA-mediated knockdown of HMOX-1 significantly reduces the antioxidant and protective effects of celastrol[40].

In the rat model of ischemia-reperfusion-induced AKI, celastrol exerts a dual protective effect by simultaneously activating the Nrf2/HO-1 antioxidant pathway and suppressing the NF- κ B inflammatory pathway *via* PI3K/AKT signaling. This coordinated activation of both antioxidant and anti-inflammatory signaling pathways plays a synergistic role in renal protection[27].

3.3. Ferroptosis inhibition

Ferroptosis is a distinct form of iron-dependent programmed cell death, characterized by the aberrant accumulation of lipid peroxides and disruption of cellular redox equilibrium[41]. In contrast to classical cell death modalities such as apoptosis, ferroptosis is accompanied by unique morphological alterations, including mitochondrial shrinkage, loss of cristae, and increased membrane density[42]. Emerging evidence has implicated ferroptosis in the initiation and progression of diverse kidney diseases[43].

3.3.1. Canonical protective mechanisms

Celastrol regulates ferroptosis in a context-dependent manner. In a cisplatin-induced AKI model, Pan *et al.* demonstrated that celastrol activates the Nrf2 signaling pathway to upregulate GPX4 expression[44]. This suppression of lipid peroxidation and ferroptosis

in renal tubular epithelial cells leads to a significant reduction in serum blood urea nitrogen and creatinine levels, alongside marked improvement in renal function. In high glucose-induced HK-2 cells and db/db mice, our group further revealed that celastrol activates the NRF2/GPX4 signaling axis through SIRT1 upregulation, thereby inhibiting ferroptosis and alleviating oxidative stress-induced injury in tubular epithelial cells[45].

Recent studies have uncovered an additional layer of regulation: celastrol reduces NOX2 expression, which in turn decreases ROS production, attenuates lipid peroxidation, and restores GPX4 expression. These coordinated effects reverse the hallmark features of ferroptosis, including iron accumulation and mitochondrial damage, and confer protection to renal tubules in early DKD[46]. Notably, the protective effects of celastrol are partially abrogated by a NOX2 agonist, further substantiating the critical regulatory role of NOX2 in this ferroptosis-related pathway.

3.3.2. Context-dependent bidirectional regulation

Notably, the regulatory effects of celastrol on ferroptosis exhibit marked context dependency. In a sepsis-associated AKI model induced by cecal ligation and puncture[47], the RNA-binding protein P23 acts as a key suppressor of ferroptosis by stabilizing *GPX4* mRNA. Under these conditions, the inhibition of P23 by celastrol disrupts this compensatory protective mechanism and, paradoxically, leads to aggravated ferroptotic injury. Collectively, these findings indicate that celastrol may exert bidirectional regulatory effects on ferroptosis, acting through distinct molecular targets depending on the specific disease context.

3.4. Autophagy activation

Autophagy activation contributes critically to the protective effects of celastrol against tubular epithelial cell injury and fibrosis[6]. In high glucose-treated HK-2 cells and two rat models of DKD, celastrol restores the HO-1-mediated autophagic pathway, as evidenced by the significant upregulation of autophagy markers including LC3 and Beclin-1, enhanced autophagosome formation, and preservation of the podocyte marker nephrin[6,39].

This autophagic response is essential for maintaining podocyte homeostasis and restraining glomerular basement membrane thickening. Importantly, these protective effects are abrogated by the autophagy inhibitor 3-methyladenine, which further confirms that autophagy is functionally required to mediate the renoprotective actions of celastrol[39,48].

3.5. Anti-fibrotic effects

Renal interstitial fibrosis is the common final pathway that leads to end-stage kidney disease in multiple types of chronic kidney

disorders. Celastrol inhibits this pathological process through multiple complementary mechanisms.

3.5.1. Modulation of the TGF- β 1/Smad pathway

In db/db diabetic mice and 5/6 nephrectomy-induced chronic renal failure models, celastrol inhibits the activation of the TGF- β 1/Smad3 signaling pathway. This effect is accompanied by reduced expression of fibrosis-related markers, including TGF- β 1, α -SMA, Col4a1, MMP-2, and PAI-1, ultimately attenuating mesangial expansion and excessive extracellular matrix deposition[29,49].

In a mouse model of lupus nephritis, celastrol similarly reduces collagen IV and fibronectin deposition, while modulating the expression of TGF- β and components of the MMP/TIMP system. These coordinated effects attenuate glomerulosclerosis[50]. Collectively, findings from different disease models confirm the renoprotective effect of celastrol, which acts by regulating extracellular matrix metabolism and inhibiting classic pro-fibrosis signaling pathways.

In addition to directly inhibiting TGF- β 1/Smad signaling, celastrol can also exert anti-fibrosis effects indirectly by regulating upstream regulators. Mechanistically, celastrol upregulates the expression of cannabinoid receptor 2 (CB2R)[51], and this effect inhibits abnormal activation of Smad3, thereby reducing renal fibrosis. The functional importance of this pathway is further supported by the finding that CB2R antagonists significantly reduce these protective effects, highlighting the key mediating role of the CB2R-Smad3 pathway in the anti-fibrosis effect of celastrol.

3.5.2. Regulation of fibrosis-associated miRNAs

In STZ-induced DKD models, celastrol downregulates a group of pro-fibrosis miRNAs, especially miR-21 and miR-192. Regulating these miRNAs and their downstream targets helps alleviate renal fibrosis[6].

3.5.3. Podocyte protection

In CKD and DKD models, celastrol preserves podocyte architecture and function by upregulating key slit diaphragm proteins, including nephrin and NEPH1. This stabilization of podocyte homeostasis indirectly slows the progression of glomerulosclerosis[49,52]. Our team has further discovered another mechanism: celastrol upregulates SIRT1, which in turn inhibits EZH2-related Wnt/ β -catenin signaling, thereby exerting a podocyte protective effect[53].

3.6. Regulation of cellular senescence and metabolism

Celastrol also modulates cellular senescence and metabolic dysfunction, contributing to renoprotection at a broader level. In a STZ-induced DKD rat model and high glucose-treated HK-2 cells, celastrol suppresses the phosphorylation of NF- κ B and AKT1. This

action significantly reduces the expression of senescence markers—including p16, p21, and senescence-associated β -galactosidase (SA- β -gal)—as well as senescence-associated secretory phenotype factors such as IL-1 β and MCP-1. Collectively, these changes alleviate mitochondrial damage and improve tubular epithelial cell function[52].

3.7. Metabolic regulation and multi-organ protection

In the field of energy metabolism regulation, Ma *et al.* demonstrated that celastrol activates heat shock factor 1 (HSF1) and upregulates PGC1 α expression in *in vivo* and *in vitro* experiments[54]. This process enhances mitochondrial function and promotes energy expenditure, ultimately improving high-fat diet-induced obesity, insulin resistance, and hepatic steatosis. The functional necessity of this axis was further confirmed by the finding that HSF1 deficiency completely eliminates these metabolic protective effects, which verifies that the HSF1-PGC1 α transcription axis is a key mechanism through which celastrol regulates energy metabolism.

Early studies have documented the multi-organ metabolic protective effects of celastrol. Kim *et al.* reported that celastrol can reduce lipid accumulation, insulin resistance, and oxidative stress in the kidney, liver, and adipose tissue of db/db mice[29]. More recently, our research group expanded this discovery. Through 16S rRNA sequencing and transcriptome analysis, we confirmed that celastrol regulates the gut-kidney axis *via* PPAR-mediated lipid metabolism[55], thereby alleviating colonic and renal injury, indicating that the gut-kidney axis is a potential mechanism underlying its metabolic regulation.

3.8. Direct protein targets and network regulation

Integration of bioinformatics analyses with experimental validation has identified potential direct protein targets of celastrol. In high glucose-induced HK-2 cells, celastrol exhibits strong binding affinity toward thrombospondin 2 (THBS2), membrane-associated guanylate kinase inverted 2 (MAGI2), and fibroblast growth factor 9 (FGF9). Through downregulation of THBS2 and upregulation of MAGI2 and FGF9, celastrol effectively attenuates renal tubular epithelial cell injury[56].

Further network pharmacology analysis has identified phosphatase and tensin homolog (PTEN) as an additional direct target of celastrol, through which celastrol exerts renoprotective effects *via* modulation of the PTEN/PI3K/AKT pathway[57]. As a central hub molecule in cellular signaling networks, PTEN plays a core role in regulating cell proliferation, inflammatory responses, and fibrosis. The identification of PTEN as a target of celastrol suggests that this compound may coordinately modulate complex signaling networks through multiple nodes. This multi-target regulatory capacity likely

underpins its pleiotropic pharmacological effects.

4. Renoprotective effects of celastrol across specific kidney diseases and injury models

Beyond the molecular mechanisms discussed above, celastrol has demonstrated therapeutic efficacy in specific kidney diseases and injury models that do not fit neatly into a single mechanistic category.

4.1. Disease-modifying effects in autosomal dominant polycystic kidney disease (ADPKD)

ADPKD is the most common inherited kidney disorder, characterized by progressive bilateral renal cyst formation. Current therapeutic options remain highly limited, underscoring the urgent need for novel intervention strategies[58]. In this context, phenotype-driven high-throughput screening has emerged as an effective strategy for identifying compounds capable of inhibiting cyst growth.

Using a recently established 3D cyst growth platform, a systematic screen of 2320 small molecules identified celastrol as a potent suppressor of cyst expansion[59]. *In vitro*, celastrol significantly reduced fluid secretion and lumen enlargement in cystic epithelial cells. These effects were further validated *in vivo*: celastrol administration in a mouse model of polycystic kidney disease delayed cyst formation, mitigated kidney enlargement, and preserved renal function. Collectively, these findings highlight the potential of celastrol, acting through distinct mechanisms, as a candidate for therapeutic intervention in ADPKD.

In a Pkd1-deficient mouse model, Chang *et al.* further confirmed the anti-cyst effects of celastrol[60]. Mechanistically, celastrol exerts protective effects by activating the AMPK signaling pathway and suppressing inflammatory responses, as evidenced by reduced TNF- α and IL-1 β expression and diminished macrophage infiltration. Of note, however, the inhibitory effect of celastrol on cyst progression was relatively modest in this study, and dose-dependent adverse effects were also observed. These findings indicate that the clinical application of celastrol will require further evaluation to achieve an optimal balance between therapeutic efficacy and safety.

4.2. Renoprotection against drug- and environmental toxicant-induced kidney injury

Beyond the disease models discussed above, celastrol has demonstrated broad nephroprotective potential against kidney injury induced by various drugs and environmental toxins. It counteracts these diverse exogenous nephrotoxic insults through coordinated

multi-target modulation of antioxidant, anti-inflammatory, and anti-apoptotic pathways.

In addition to traditional animal models, studies using human induced pluripotent stem cell-derived kidney organoids have further corroborated the renoprotective effects of celastrol. These models provide more physiologically relevant evidence that supports its clinical translation. At a low dose of 2 μ M, celastrol alleviates cisplatin-induced tubular injury by downregulating SNORD3A and HIST1H3A expression[61]. Mechanistically, celastrol pretreatment attenuates DNA damage and enhances antioxidant defense by increasing glutathione levels and the activities of glutathione reductase and catalase[62]. Celastrol also reduces tubular epithelial cell injury through inhibition of NF- κ B activation and restoration of mitochondrial function, as evidenced by improvements in mtDNA copy number, mitochondrial membrane potential, and oxidative phosphorylation activity[63].

In the context of drug-induced kidney injury, celastrol markedly reverses nephrotoxicity caused by acetaminophen overdose. This protective effect involves activation of the Nrf2/HO-1 antioxidant pathway, suppression of pro-inflammatory cytokine release, and inhibition of apoptotic markers including caspase-3 and Bax, along with upregulation of aquaporin-1 to maintain tubular water and solute transport[64]. Similarly, celastrol attenuates polymyxin-induced nephrotoxicity by activating the Nrf2/HO-1 pathway, suppressing COX-2/iNOS/TNF- α /NF- κ B-mediated inflammation, and regulating the Bcl-2/Bax/caspase-3 apoptotic axis, thereby reducing tubular epithelial cell injury and interstitial fibrosis[65]. These findings highlight the potential of celastrol as a nephroprotective adjuvant during polymyxin therapy, and more broadly, in the management of drug-induced nephrotoxicity.

Celastrol also exhibits protective effects against environmental toxins-induced kidney injury. Cypermethrin, a widely used pyrethroid insecticide, triggers a cascade of oxidative stress, inflammation, and apoptosis that culminates in renal damage. Celastrol counteracts this toxicity in a dose-dependent manner by activating the Nrf2-mediated antioxidant defense system, suppressing NF- κ B-driven inflammatory signaling, and restoring the Bcl-2/Bax balance. These coordinated actions effectively block the apoptotic cascade and preserve renal tissue structure and function[66].

The therapeutic benefits and pharmacological mechanisms of celastrol in renal disease models are summarized in Table 1.

5. Toxicity and kidney-targeted delivery systems

While celastrol exerts pronounced therapeutic effects against kidney diseases, its inherent toxicity remains a major barrier to clinical translation. Proteomic and metabolomic analyses have revealed that celastrol directly binds to key enzymes involved in metabolism and

mitochondrial function, including VDAC1 and PKM2. Binding to these targets disrupts biosynthetic processes, impairs mitochondrial function, and ultimately exacerbates renal cell apoptosis[67].

To mitigate these adverse effects, various kidney-targeted delivery systems have been developed. Zheng and colleagues designed a microneedle patch for transdermal delivery, incorporating celastrol and insulin-loaded nanoparticles. This system significantly improves transdermal drug delivery efficiency and prolongs insulin action. Importantly, it integrates blood glucose regulation with ROS scavenging, providing a novel dual-functional therapeutic strategy for DKD[68].

Wu and colleagues developed a peptide-conjugated celastrol phospholipid nanoparticle system that leverages the unique structural and pathological features of the glomerulus for targeted delivery. This system efficiently delivers celastrol to injured glomerular endothelial cells and podocytes. Consequently, it effectively suppresses inflammation, alleviates endothelial injury, and slows the progression of CKD. Notably, this targeted delivery approach concurrently reduces celastrol-associated toxicity[69]. Mechanistically, these protective effects are largely mediated by increased eNOS expression and NO production, alongside suppressed VCAM-1 expression.

Guo *et al.* constructed a celastrol-albumin nanoparticle delivery system designed for targeted delivery to mesangial cells. These nanoparticles penetrate the fenestrated glomerular endothelium and accumulate preferentially in mesangial cells. In anti-Thy1.1 nephritis rats, this targeted delivery reduces proteinuria, attenuates inflammation, and alleviates glomerular hypercellularity and excessive extracellular matrix deposition. Compared with free celastrol, the albumin nanoparticle formulation shows reduced accumulation in non-target organs and tissues, thereby minimizing systemic toxicity associated with celastrol[70].

Pang's team developed a novel nanopatform by co-encapsulating lutein and celastrol in low molecular weight chitosan micelles[71]. *In vitro*, this dual-agent micellar system reduced off-target toxicity and enhanced therapeutic efficacy against AKI, as evidenced by rapid alleviation of renal oxidative stress and stabilization of mitochondrial membrane potential. *In vivo*, the micelles inhibited activation of the NF- κ B p65 and p38 MAPK inflammatory pathways, thereby attenuating the overexpression of pro-inflammatory cytokines.

Li's group loaded celastrol into fibronectin-targeting pentapeptide-conjugated PEGylated liposomes (CREKA-Lip)[72]. *In vitro*, CREKA-Lip effectively inhibited the activation and proliferation of NRK-49F fibroblasts, a key cell type driving renal fibrogenesis. In a mouse model of unilateral ureteral obstruction, CREKA-Lip significantly reduced renal fibrosis and inflammation. Notably, compared with free celastrol, the CREKA-Lip formulation exhibited markedly lower toxicity to major organs.

Nan's group developed celastrol-loaded micelles using stearic

acid-grafted chitoooligosaccharide as a carrier[73]. These micelles increased drug accumulation in renal tubules, effectively reducing serum creatinine and urea nitrogen levels and alleviating renal tissue damage in ischemia/reperfusion-injured mice. The formulation also demonstrated an acceptable safety profile.

Xiong's team constructed a ROS-responsive celastrol nanoplatfrom, designated TCPP-Fe³⁺-Ce³⁺@Se-Se@Cyclo@Cel (TM-SeCC), designed to precisely target the kidney, improve lipid metabolism, and repair podocyte injury[74]. *In vitro*, TM-SeCC exhibited strong antioxidant activity in H₂O₂-induced podocyte inflammation, as

Table 1. The therapeutic benefits and pharmacological mechanisms of celastrol in renal disease models.

Disease	Model	Treatment regimen	Results	Mechanisms	Ref
DKD	STZ-induced SD rats	1.5 mg/kg/day, <i>i.g.</i> , for 7 weeks	Blood glucose↓, 24 h urine albumin↓, BUN↓, Scr↓, LC3II↑, p62↓	Downregulated miRNA-192-5p and miRNA-21-5p, activated autophagy, inhibited PI3K/p-AKT/NF-κB/mTOR, as well as attenuated oxidative stress and fibrosis	[6]
	High glucose-exposed HK-2	20, 50, and 100 nM for 24 h	Cell viability↑, ROS↓, TNF-α↓, IL-6↓, MCP-1↓	Inhibited PI3K/Akt/NF-κB signaling pathway	[25]
	STZ-induced SD rats	50 and 100 μg/kg/day, <i>i.g.</i> , for 4 weeks	BUN↓, Scr↓, proteinuria↓, renal tissue injury↓	Inhibited MAPK/NF-κB pathway	[26]
	db/db mice	1 mg/kg/day, <i>i.g.</i> , for 2 weeks	Insulin resistance↓, glomerulosclerosis↓, TNF-α↓, IL-6↓, MCP-1↓	Inhibited NF-κB activation	[29]
	High glucose-exposed MPC	1.5 μM for 5 h (pretreatment)	Podocyte injury↓, inflammation↓, insulin resistance↓, HO-1↑, LC3II↑	Restored HO-1-mediated autophagy pathway and inhibited NF-κB activation	[39]
	db/db mice	0.25, 0.5, and 1 mg/kg/day, <i>i.g.</i> , for 8 weeks	Ferroptosis↓, renal injury↓, GPX4↑, SIRT1↑, NRF2↑	Regulation of the SIRT1/NRF2/GPX4 pathway	[45]
	STZ-induced C57BL/6 mice	1 mg/kg/day, <i>i.g.</i> , for 4 weeks	Renal tubular epithelial cell injury↓, GPX4↑, KIM-1↓, NOX2↓	Regulated NOX2 and inhibited ferroptosis	[46]
	STZ-induced SD rats	0.5 and 1.5 mg/kg/day, <i>i.g.</i> , for 4 weeks	Early DN progression↓, TGF-β1↓, α-SMA↓, Col IV↓	Inhibited PI3K/AKT pathway	[48]
	STZ-induced SD rats; high glucose-exposed HK-2	<i>In vivo</i> : 0.5 mg/kg/day, <i>i.p.</i> , for 21 days; <i>In vitro</i> : 50, 250, and 500 nM for 48 h	Renal tubular epithelial cell senescence↓, p16↓, p21↓, SASP↓, DKD progression↓	Inhibited senescence-associated secretory phenotype	[52]
	db/db mice; high glucose-exposed MPC	<i>In vivo</i> : 1 mg/kg/day, <i>i.g.</i> , for 10 weeks; <i>In vitro</i> : 100 nM for 36 h	Renal injury↓, SIRT1↑, EZH2↓, Wnt/β-catenin↓	Upregulated SIRT1 and inhibited EZH2-mediated Wnt/β-catenin signaling	[53]
	db/db mice	1 mg/kg/day, <i>i.g.</i> , for 8 weeks	Renal function↑, metabolic disorders↓, PPAR signaling↑	Modulated the gut-kidney axis and activated PPAR signaling pathway	[55]
AKI	Swiss albino rats (I/R)	2 mg/kg/day, <i>i.g.</i> , for 1 week (before surgery)	Renal tissue injury↓, BUN/Scr↓, MDA↓, SOD↑	Activated Nrf2/HO-1, PI3K/AKT; inhibited NF-κB and ERK phosphorylation	[27]
	SD rats (I/R)	4 and 6 mg/kg, <i>i.p.</i> , for 30 min (before surgery)	Renal function↑, MDA↓, SOD↑	Inhibited inflammatory response and attenuated renal tubular necrosis	[28]
	C57BL/6 mice (I/R); HK-2 cells (hypoxia/reoxygenation)	<i>In vivo</i> : 1 mg/kg/day, <i>i.p.</i> , for 3 days (before cisplatin); <i>In vitro</i> : 10 nM for 24 h	Renal tubular necrosis↓, BUN/Scr↓, MDA↓, GSH↑	Activated Nrf2/GPX4 pathway and inhibited ferroptosis	[44]
	Human iPSC-derived kidney organoids	1 and 2 μM for 48 h	Kidney organoid injury↓, LDH↓, apoptosis↓, SNORD3A↓	Downregulated SNORD3A level and attenuated DNA damage and apoptosis	[61]
	Cisplatin-induced NRK-52E	50, 100, and 500 nM for 24 h (pretreatment)	Renal tubular injury↓, BUN/Scr↓, SOD/CAT↑, MDA↓	Inhibited oxidative stress and attenuated lipid peroxidation	[62]
	Cisplatin-treated C57BL/6 mice and HK-2	<i>In vivo</i> : 1 and 2 mg/kg/day, <i>i.p.</i> , for 24 h (before cisplatin); <i>In vitro</i> : 25 and 50 nM for 2 h (pretreatment)	BUN/Scr↓, TUNEL↓, Drp1↓, OPA1↑	Inhibited NF-κB, improved mitochondrial function, and attenuated inflammation	[63]
	Colistin-treated Wistar rats	0.5 and 1 mg/kg/day, <i>i.p.</i> , for 6 days	Renal function↑, MDA↓, SOD↑, CAT↑, Nrf-2↑, HO-1↑, TNF-α↓, COX-2↓, iNOS↓, NF-κB↓, Bax↓, caspase-3↓, Bcl-2↑	Activated Nrf-2/HO-1 antioxidant pathway, inhibited NF-κB-mediated inflammation, and suppressed mitochondrial apoptosis pathway	[65]
	Balb/c mice subjected to CLP; HK-2 exposed to LPS and TNF-α	<i>In vivo</i> : 1 mg/kg, <i>i.p.</i> , for 1 h (before surgery); <i>In vitro</i> : 1 μM for 1 h (pretreatment)	Renal tubular injury↓, BUN/Scr↓, TNF-α↓, IL-6↓	Upregulated co-chaperone P23, stabilized GPX4 protein, as well as inhibited ferroptosis and inflammation	[47]

Table 1. The therapeutic benefits and pharmacological mechanisms of celastrol in renal disease models (continued).

Disease	Model	Treatment regimen	Results	Mechanisms	Ref
IgAN	LPS and CCl ₄ -treated SD rats; aIgA1-induced HMCs	<i>In vivo</i> : 0.5 and 1 mg/kg/day, <i>i.g.</i> , for 8 weeks; <i>In vitro</i> : 300 nM for 24 h (pretreatment)	Renal IgA deposition↓, mesangial cell proliferation↓, proteinuria↓, BUN↓, Scr↓	Targeted TGase-2/HMGB1 signaling pathway and attenuated inflammation	[7]
	LPS and CCl ₄ -treated C57BL/6 mice; LPS-stimulated RAW 264.7	<i>In vivo</i> : 1 mg/kg/day, <i>i.g.</i> , for 21 days; <i>In vitro</i> : 0.5 μM for 24 h	M1 polarization↓, renal tissue injury↓	Downregulated ECM1 and inhibited macrophage pro-inflammatory activation	[31]
	LPS and CCl ₄ -treated C57BL/6 mice; aIgA1-induced HMCs	<i>In vivo</i> : 1 mg/kg/day, <i>i.p.</i> , for 21 days; <i>In vitro</i> : 75 nM for 48 h	PCNA↓, Cyclin D1↓, renal tissue injury↓	Targeted PTEN and inhibited PI3K/AKT pathway	[57]
LN	C57BL/6 mice	1 and 3 mg/kg/day, <i>i.v.</i> , for 8 weeks	Proteinuria↓, anti-dsDNA antibody↓, BUN/Scr↓, IgG/C3 deposition↓	Induced CD4 ⁺ Foxp3 ⁺ regulatory T cell (Treg) differentiation and inhibited autoimmune response	[32]
	BW F1 female mice	3 and 6 mg/kg/week, <i>i.p.</i> , for 20 weeks (3 times/week)	Proteinuria↓, anti-dsDNA antibodies↓, FN↓, Col IV↓, TIMP-1/-2↓, TGF-β1↓, MMP-1/-2↑, glomerulosclerosis↓	Upregulated MMP-1/-2, downregulated TGF-β1/TIMP-1/-2, and suppressed B cell autoantibodies	[50]
CKD	SD rats subjected to 5/6 nephrectomy	1 mg/kg/day, <i>i.p.</i> , for 3 weeks	Renal injury↓, MDA↓, SOD↑, aortic calcification↓	Upregulated HMOX-1 and inhibited oxidative stress	[40]
	SD rats subjected to 5/6 nephrectomy	3 mg/kg/day, <i>i.p.</i> , for 8 weeks	α-SMA↓, FN↓, Col IV↓, E-cadherin↑, Vimentin↓	Inhibited TGF-β1/Smad3 pathway and suppressed EMT	[49]
	UUO-induced BALB/c mice; TGF-β1-stimulated HK-2 cells	<i>In vivo</i> : 1 mg/kg/day, <i>i.p.</i> , for 7 days; <i>In vitro</i> : 200 and 500 nM for 1 h (pretreatment)	α-SMA↓, FN↓, Col I↓, TGF-β1↓	Upregulated CB2 receptor expression and inhibited TGF-β1/Smad signaling	[51]

STZ: streptozotocin; HK-2: human kidney-2 cell line; *i.g.*: intragastric administration; *i.p.*: intraperitoneal injection; *i.v.*: intravenous injection; BUN: blood urea nitrogen; Scr: serum creatinine; mTOR: mammalian target of rapamycin; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1; MPC: mouse podocyte cell; I/R: ischemia/reperfusion; MDA: malondialdehyde; LDH: lactate dehydrogenase; SNORD3A: small nucleolar RNA C/D box 3A; CAT: catalase; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; Drp1: dynamin-related protein 1; OPA1: optic atrophy 1 (mitochondrial inner membrane fusion protein); COX-2: cyclooxygenase-2; iNOS: inducible nitric oxide synthase; Bax: Bcl-2-associated X protein; LPS: lipopolysaccharide; aIgA1: aberrantly glycosylated IgA1; CCl₄: carbon tetrachloride; HMCs: human mesangial cells; PCNA: proliferating cell nuclear antigen; LN: lupus nephritis; FN: fibronectin; TIMP-1: tissue inhibitor of metalloproteinase-1; E-cadherin: epithelial cadherin; iPSC: induced pluripotent stem cell; CLP: cecal ligation and puncture; EMT: epithelial-mesenchymal transition; UUO: unilateral ureteral obstruction; SA-AKI: sepsis-associated acute kidney injury; IgAN: IgA nephropathy.

Table 2. Summary of kidney-targeted celastrol delivery systems.

Category	Formulation	Efficacy	Ref
Nanoparticle delivery	Microneedle patch integrating celastrol and insulin-loaded nanoparticles	Enhances transdermal delivery and prolongs insulin action, enabling synergistic glycemic control and ROS clearance	[68]
	Peptide-conjugated celastrol-phospholipid nanoparticles	Targets glomerular endothelium and podocytes to suppress inflammation, alleviate endothelial injury, and minimize systemic toxicity	[69]
	Celastrol-albumin nanoparticles	Achieves preferential mesangial accumulation, thereby reducing proteinuria and off-target toxicity	[70]
	ROS-responsive targeted nanozyme platform	Enables precise renal targeting and prolonged retention, improving lipid metabolism, thereby reducing podocyte injury	[74]
Micelle systems	Low-molecular-weight chitosan micelles co-loaded with lutein and celastrol	Reduces off-target toxicity while stabilizing mitochondrial membrane potential and inhibiting pro-inflammatory pathways	[71]
	Stearic acid-grafted chitoooligosaccharide micelles	Increases renal tubular accumulation, thereby improving renal function and safety in I/R injury models	[73]
Liposome modification technology	Fibronectin-targeting pentapeptide-conjugated PEGylated liposomes	Inhibits fibroblast activation and proliferation, thereby significantly reducing renal fibrosis and systemic toxicity	[72]

confirmed by a significant reduction in intracellular ROS levels. It also inhibited differentiation of 3T3-L1 preadipocytes and demonstrated favorable hemocompatibility. In DKD mice, TM-SeCC achieved precise renal targeting, prolonged renal retention, and high biocompatibility, effectively reducing proteinuria and

reversing disease progression. Mechanistically, these therapeutic effects are attributed to improved lipid metabolism and restoration of podocyte function. The kidney-targeted celastrol delivery systems are summarized in Table 2.

Beyond physical encapsulation-based delivery strategies, chemical

modification represents another important approach to reduce the toxicity of celastrol. Hu *et al.* conjugated celastrol to glucosamine to generate the celastrol-glucosamine conjugate[75]. In a renal ischemia-reperfusion injury model, this derivative retained renoprotective efficacy while significantly reducing systemic toxicity. Together with delivery systems, such structural modification strategies offer complementary avenues for improving the safety and clinical translation potential of celastrol.

6. Conclusion

Celastrol, a bioactive compound derived from traditional medicinal plants, exhibits remarkable therapeutic potential across a broad spectrum of kidney disease models, owing to its multi-target and multi-pathway pharmacological properties. Accumulating evidence has demonstrated that celastrol exerts potent anti-inflammatory, antioxidant, and anti-fibrotic effects, while also modulating autophagy, cellular senescence, and ferroptosis. These actions are primarily mediated through coordinated regulation of key signaling pathways, including NF- κ B, PI3K/Akt, Nrf2/HO-1, SIRT1, and TGF- β /Smad. Through these interconnected mechanisms, celastrol preserves renal function and attenuates pathological damage in diverse conditions, ranging from DKD and IgAN to CKD, AKI, and ADPKD.

Notably, celastrol also confers protection against nephrotoxicity induced by various drugs, including cisplatin, acetaminophen, and polymyxin, as well as environmental toxins. This underscores its potential as a broad-spectrum renoprotective agent and offers new opportunities for toxicity mitigation in combination therapies.

Despite these promising findings, the clinical translation of celastrol is hindered by its intrinsic hepatotoxicity, nephrotoxicity, and systemic adverse effects, which are likely associated with mitochondrial dysfunction and metabolic disturbances. To address these limitations, significant progress has been made in the development of kidney-targeted delivery systems. Emerging strategies encompass glomerulus-targeted platforms (*e.g.*, peptide-conjugated lipid nanoparticles), microenvironment-responsive systems (*e.g.*, ROS-responsive nanoplatfoms), biomimetic carriers (*e.g.*, albumin-based nanoparticles), and innovative administration approaches (*e.g.*, microneedle-mediated transdermal delivery). In preclinical studies, these systems have demonstrated the ability to achieve precise renal accumulation, enhance therapeutic efficacy, and reduce off-target toxicity, collectively providing compelling proof of concept for the “efficacy enhancement and toxicity reduction” paradigm.

Looking forward, several critical challenges must be addressed to facilitate the successful clinical translation of celastrol. First, the precise molecular targets and regulatory networks of celastrol in the

complex human physiological context require further elucidation, particularly with respect to disease-specific mechanisms and potential context-dependent effects. Second, the long-term biosafety, scalability, and clinical feasibility of current delivery systems must be rigorously evaluated. Third, the potential synergistic effects between celastrol and existing standard-of-care therapies warrant systematic investigation to optimize therapeutic regimens.

Although this review summarizes the current understanding of celastrol in kidney diseases, several limitations should be acknowledged. First, the available evidence is predominantly derived from preclinical studies, while clinical evidence remains limited. Second, differences in experimental models, celastrol dosages, treatment duration, and outcome measures may affect the comparability of findings across studies. Third, the literature search was restricted to English-language publications and to the databases we consulted. This may have introduced language and publication bias. Finally, emerging studies published after the completion of the literature search could not be included. Ongoing and future research will be important to update and refine the conclusions presented here.

In conclusion, celastrol represents a promising direction for innovative drug development for kidney diseases. However, its successful clinical application will depend largely on advances in safe and efficient targeted delivery technologies. Future efforts should focus on elucidating its precise molecular mechanisms across different renal pathologies, while also optimizing delivery systems to ensure long-term safety and clinical translatability. Collectively, these endeavors will help facilitate the translation of this natural compound into effective therapies for patients with kidney diseases.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Authors' contributions

YNC contributed to data curation and resources and prepared the original draft. MDL and TJX performed the investigation,

visualization, and formal analysis. YWT contributed to data curation, manuscript review and editing. JWC performed the investigation and validation. FW conceived and designed the study, as well as contributed to the methodology, manuscript review and editing, and funding acquisition. All authors contributed to and approved the final version of the manuscript.

References

- [1] Francis A, Harhay MN, Ong ACM, Tummalapalli SL, Ortiz A, Fogo AB, et al. Chronic kidney disease and the global public health agenda: An international consensus. *Nat Rev Nephrol* 2024; **20**(7): 473-485.
- [2] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024; **105**(4S): S117-S314.
- [3] Bhadange R, Gaikwad AB. Repurposing the familiar: Future treatment options against chronic kidney disease. *J Pharm Pharmacol* 2025; **77**(6): 715-728.
- [4] Lv QW, Zhang W, Shi Q, Zheng WJ, Li X, Chen H, et al. Comparison of *Tripterygium wilfordii* Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): A randomised, controlled clinical trial. *Ann Rheum Dis* 2015; **74**(6): 1078-1086.
- [5] Shi J, Li J, Xu Z, Chen L, Luo R, Zhang C, et al. Celastrol: A review of useful strategies overcoming its limitation in anticancer application. *Front Pharmacol* 2020; **11**. doi: 10.3389/fphar.2020.558741.
- [6] Al-Tantawy SM, Eraky SM, Eissa LA. Novel therapeutic target for diabetic kidney disease through downregulation of miRNA-192-5p and miRNA-21-5p by celastrol: Implication of autophagy, oxidative stress, and fibrosis. *Naunyn Schmiedebergs Arch Pharmacol* 2025; **398**(6): 6915-6928.
- [7] Wu Y, Chen R, Deng D, Wu W, Wang X. Celastrol modulates damage of renal tissues in immunoglobulin A nephropathy via targeting TGase-2/HMGB1 signaling pathway. *BMC Nephrol* 2025; **26**(1): 209. doi: 10.1186/s12882-025-04139-7.
- [8] Song J, He GN, Dai L. A comprehensive review on celastrol, triptolide and triptonide: Insights on their pharmacological activity, toxicity, combination therapy, new dosage form and novel drug delivery routes. *Biomed Pharmacother* 2023; **162**. doi: 10.1016/j.biopha.2023.114705.
- [9] He P, Sun J, Tan J, Shi YN, Zhang CJ, Zhu N, et al. From physicochemical constraints to clinical prospects of celastrol: Challenges and nano delivery strategies. *Int J Nanomedicine* 2025; **20**: 10907-10931.
- [10] Yadav P, Jaswal V, Sharma A, Kashyap D, Tuli HS, Garg VK, et al. Celastrol as a pentacyclic triterpenoid with chemopreventive properties. *Pharm Pat Anal* 2018; **7**(4): 155-167.
- [11] Lyu Y, Xu SW, Chen L. Study on extraction technology of celastrol from root bark of *Tripterygium wilfordii*. *Anhui Sci Technol* 2011; (9): 38-39.
- [12] Zhang KL, Tian CK, Wang SS, Wu ZB. Research progress on extraction, isolation and pharmacological activity of celastrol. *Shandong Chem Ind* 2024; **53**(8): 129-131, 135.
- [13] Liu YL, Lindert S, Zhu W, Wang K, McCammon JA, Oldfield E. Taxodione and arenarone inhibit farnesyl diphosphate synthase by binding to the isopentenyl diphosphate site. *Proc Natl Acad Sci U S A* 2014; **111**(25): E2530-E2539.
- [14] Liu J, Lee J, Salazar Hernandez MA, Mazitschek R, Ozcan U. Treatment of obesity with celastrol. *Cell* 2015; **161**(5): 999-1011.
- [15] Zhao PD, Guo YY, Ren XG, Zhang JW, Zhai WS. Mechanism of *Tripterygium wilfordii* and its active components in treating diabetic kidney disease: A review. *Chin J Exp Tradit Med Form* 2026; **32**(7): 352-362.
- [16] Zhang K, Jordan PM, Pace S, Hofstetter RK, Werner M, Chen X, et al. Modulation of inflammation-related lipid mediator pathways by celastrol during human macrophage polarization. *J Inflamm Res* 2022; **15**: 3285-3304.
- [17] Hayden MS, Ghosh S. NF- κ B in immunobiology. *Cell Res* 2011; **21**(2): 223-244.
- [18] Liu T, Zhang L, Joo D, Sun SC. NF- κ B signaling in inflammation. *Signal Transduct Target Ther* 2017; **2**. doi: 10.1038/sigtrans.2017.23.
- [19] Li X, Zhao S, Xie J, Li M, Tong S, Ma J, et al. Targeting the NF- κ B p65-MMP28 axis: Wogonoside as a novel therapeutic agent for attenuating podocyte injury in diabetic nephropathy. *Phytomedicine* 2025; **138**. doi: 10.1016/j.phymed.2025.156406.
- [20] Wu Z, Tan W, Wang C, Lin L, Tian E, Huo B, et al. TAX1BP1 regulates the apoptosis of renal tubular epithelial cells in ischemia/reperfusion injury via the NF- κ B/PMAIP1 signaling pathway. *Inflamm Res* 2025; **74**(1). doi: 10.1007/s00011-024-01976-4.
- [21] Huang HX, Li WW. Research progress on the mechanism of renal resident cells in lupus nephritis based on NF- κ B signaling. *Chin J Integr Tradit West Med Pediatr* 2025; **17**(5): 397-401.
- [22] Yang R, Feng X, Zhang J, Chen T, Wang W, Liu Y, et al. Peptide FK2 attenuates inflammation and pro-fibrotic cellular transitions via targeting the IKK β /NF- κ B/TGF- β 1 axis in renal fibrosis. *Eur J Pharmacol* 2026; **1015**. doi: 10.1016/j.ejphar.2026.178567.
- [23] Shen S, Wang X, Li Z, Zhuang J, Zhang K. Dihydroquercetin/taxifolin inhibits METTL3/m6A/PIM2 expression by suppressing RIPK2 phosphorylation-mediated NF- κ B p65 signaling pathway to alleviate renal ischemia-reperfusion injury in mice. *Kidney Dis (Basel)* 2025; **11**(1): 543-559.
- [24] Sethi G, Ahn KS, Pandey MK, Aggarwal BB. Celastrol, a novel triterpene, potentiates TNF-induced apoptosis and suppresses invasion of tumor cells by inhibiting NF- κ B-regulated gene products and TAK1-mediated NF- κ B activation. *Blood* 2007; **109**(7): 2727-2735.
- [25] Wang X, Abu Bakar MH, Kassim MA, Shariff KA, Mohamad Rosdi MN. Renoprotective mechanisms of celastrol in high glucose-mediated HK-2 cell injury through inhibition of the PI3K/Akt/NF- κ B signalling pathway. *Biochem Biophys Rep* 2025; **41**. doi: 10.1016/j.bbrep.2025.101928.
- [26] Zhang M, Chen Y, Yang MJ, Fan XR, Xie H, Zhang L, et al. Celastrol

- attenuates renal injury in diabetic rats *via* MAPK/NF- κ B pathway. *Phytother Res* 2019; **33**(4): 1191-1198.
- [27]Younis NS, Ghanim AMH. The protective role of celastrol in renal ischemia-reperfusion injury by activating Nrf2/HO-1, PI3K/AKT signaling pathways, modulating NF- κ B signaling pathways, and inhibiting ERK phosphorylation. *Cell Biochem Biophys* 2022; **80**(1): 191-202.
- [28]Chu C, He W, Kuang Y, Ren K, Gou X. Celastrol protects kidney against ischemia-reperfusion-induced injury in rats. *J Surg Res* 2014; **186**(1): 398-407.
- [29]Kim JE, Lee MH, Nam DH, Song HK, Kang YS, Lee JE, et al. Celastrol, an NF- κ B inhibitor, improves insulin resistance and attenuates renal injury in db/db mice. *PLoS One* 2013; **8**(4). doi: 10.1371/journal.pone.0062068.
- [30]Wu M, Chen W, Yu X, Ding D, Zhang W, Hua H, et al. Celastrol aggravates LPS-induced inflammation and injuries of liver and kidney in mice. *Am J Transl Res* 2018; **10**(7): 2078-2086.
- [31]Zhao J, Liu H, Chen Q, Xia M, Wan L, Yu W, et al. Mechanistic study of celastrol-mediated inhibition of proinflammatory activation of macrophages in IgA nephropathy *via* down-regulating ECM1. *Int J Biol Sci* 2024; **20**(14): 5731-5746.
- [32]Xiang G, Shi K, Wang J. Celastrol alleviates murine lupus nephritis *via* inducing CD4⁺Foxp3⁺ regulatory T cells. *Folia Histochem Cytobiol* 2022; **60**(3): 237-246.
- [33]Zhong M. Research progress on Nrf2-Keap1 antioxidant system. *Chin J Public Health* 2006; **22**(3): 360-362.
- [34]Baird L, Llères D, Swift S, Dinkova-Kostova AT. Regulatory flexibility in the Nrf2-mediated stress response is conferred by conformational cycling of the Keap1-Nrf2 protein complex. *Proc Natl Acad Sci U S A* 2013; **110**(38): 15259-15264.
- [35]Wilmes A, Crean D, Aydin S, Pfaller W, Jennings P, Leonard MO. Identification and dissection of the Nrf2 mediated oxidative stress pathway in human renal proximal tubule toxicity. *Toxicol In Vitro* 2011; **25**(3): 613-622.
- [36]Li T, Wang H, Chang B, Lu H, Yang R, Zhang H, et al. Grape seed proanthocyanidin extract inhibits ferroptosis by activating Nrf2/HO-1 and protects against diabetic kidney disease. *PLoS One* 2025; **20**(12). doi: 10.1371/journal.pone.0336472.
- [37]Luo Q, Zhu Z, Wan L. Exploring the protective effect and regulatory mechanism of plumbagin on renal ischemia-reperfusion injury based on the Nrf-2/HO-1 signaling pathway. *Transplant Proc* 2025; **57**(6): 1180-1186.
- [38]Qing TL, Yan L, Wang SK, Dai XY, Ren LJ, Zhang JQZ, et al. Celastrol alleviates oxidative stress induced by multi-walled carbon nanotubes through the Keap1/Nrf2/HO-1 signaling pathway. *Ecotoxicol Environ Saf* 2023; **252**. doi: 10.1016/j.ecoenv.2023.114623.
- [39]Zhan X, Yan C, Chen Y, Wei X, Xiao J, Deng L, et al. Celastrol antagonizes high glucose-evoked podocyte injury, inflammation and insulin resistance by restoring the HO-1-mediated autophagy pathway. *Mol Immunol* 2018; **104**: 61-68.
- [40]Yang X, Chen A, Liang Q, Dong Q, Fu M, Liu X, et al. Up-regulation of heme oxygenase-1 by celastrol alleviates oxidative stress and vascular calcification in chronic kidney disease. *Free Radic Biol Med* 2021; **172**: 530-540.
- [41]Duo K, Feng X, Tian X, Wang F, Zhao Y, Yu J, et al. Ferroptosis inhibitors: Mechanisms of action and therapeutic potential. *Cell Mol Life Sci* 2025; **82**(1). doi: 10.1007/s00018-025-05958-5.
- [42]Kinowaki Y, Taguchi T, Onishi I, Kirimura S, Kitagawa M, Yamamoto K. Overview of ferroptosis and synthetic lethality strategies. *Int J Mol Sci* 2021; **22**(17). doi: 10.3390/ijms22179271.
- [43]Wang W, Chen J, Zhan L, Zou H, Wang L, Guo M, et al. Iron and ferroptosis in kidney disease: Molecular and metabolic mechanisms. *Front Immunol* 2025; **16**. doi: 10.3389/fimmu.2025.1531577.
- [44]Pan M, Wang Z, Wang Y, Jiang X, Fan Y, Gong F, et al. Celastrol alleviated acute kidney injury by inhibition of ferroptosis through Nrf2/GPX4 pathway. *Biomed Pharmacother* 2023; **166**. doi: 10.1016/j.biopha.2023.115333.
- [45]Tang YW, Xu TJ, Cao JW, Jiang MY, Yang RC, Wan F. Celastrol mitigates diabetic kidney disease by inhibiting ferroptosis *via* the SIRT1/NRF2/GPX4 pathway. *Diabetol Metab Syndr* 2026; **18**(1): 55. doi: 10.1186/s13098-026-02085-4.
- [46]Ma D, Dai T, Wang D, Zhang J, Zeng C, Dai S, et al. Celastrol protects against renal tubular injury in early diabetic kidney disease through modulation of NOX2 and ferroptosis. *Int Immunopharmacol* 2026; **177**. doi: 10.1016/j.intimp.2026.116533.
- [47]Luo M, Xu Q, Sun Y, He N, Wen Z, Wang Z, et al. Co-chaperone P23 inhibits ferroptosis in sepsis-associated acute kidney injury by regulating GPX4 stability. *Shock* 2025; **64**(2): 254-264.
- [48]Nie Y, Fu C, Zhang H, Zhang M, Xie H, Tong X, et al. Celastrol slows the progression of early diabetic nephropathy in rats *via* the PI3K/AKT pathway. *BMC Complement Med Ther* 2020; **20**(1): 321. doi: 10.1186/s12906-020-03050-y.
- [49]Tang YW, Yang RC, Wan F, Tang XL, Zhang HQ, Lin Y. Celastrol attenuates renal injury in 5/6 nephrectomized rats *via* inhibiting epithelial-mesenchymal transition and transforming growth factor- β 1/Smad3 pathway. *Exp Biol Med (Maywood)* 2022; **247**(21): 1947-1955.
- [50]Xu C, Wu Z. The effect of tripterine in prevention of glomerulosclerosis in lupus nephritis mice. *Zhonghua Nei Ke Za Zhi* 2002; **41**(5): 317-321.
- [51]Tang M, Cao X, Zhang K, Li Y, Zheng QY, Li GQ, et al. Celastrol alleviates renal fibrosis by upregulating cannabinoid receptor 2 expression. *Cell Death Dis* 2018; **9**(6): 601.
- [52]Zhang Y, Sun Z, Meng W, Lei S, Sun J, Tang Y, et al. Celastrol attenuates diabetic kidney disease progression by repressing senescence of renal tubular epithelial cells. *Front Aging* 2025; **6**. doi: 10.3389/fragi.2025.1657947.
- [53]Tang Y, Wan F, Tang X, Lin Y, Zhang H, Cao J, et al. Celastrol attenuates diabetic nephropathy by upregulating SIRT1-mediated inhibition of EZH2-related Wnt/ β -catenin signaling. *Int Immunopharmacol* 2023; **122**.

- doi: 10.1016/j.intimp.2023.110584.
- [54] Ma X, Xu L, Alberobello AT, Gavrilova O, Bagattin A, Skarulis M, et al. Celastrol protects against obesity and metabolic dysfunction through activation of a HSF1-PGC1 α transcriptional axis. *Cell Metab* 2015; **22**(4): 695-708.
- [55] Tang YW, Cao JW, Lu MD, Yang RC, Wan F. Celastrol, a bioactive compound from *Tripterygium wilfordii*, exerts renoprotective effects by modulating the gut-kidney axis and PPAR signaling in a mouse model of diabetic kidney disease. *Asian Pac J Trop Biomed* 2025; **15**(9): 353-364.
- [56] Wang X, Abu Bakar MH, Kassim MA, Shariff KA, An L, Qin Y. Celastrol protects against diabetic nephropathy by modulating immune-related pathways: A bioinformatics and experimental validation. *Am J Transl Res* 2025; **17**(4): 2467-2483.
- [57] Zhao J, Liu H, Xia M, Chen Q, Wan L, Leng B, et al. Network pharmacology and experimental validation to explore that celastrol targeting PTEN is the potential mechanism of *Tripterygium wilfordii* (Lév.) Hutch against IgA nephropathy. *Drug Des Devel Ther* 2023; **17**: 887-900.
- [58] Shao G, Zhu S, Yang B. Applications of herbal medicine to treat autosomal dominant polycystic kidney disease. *Front Pharmacol* 2021; **12**. doi: 10.3389/fphar.2021.629848.
- [59] Booi TH, Leonhard WN, Bange H, Yan K, Fokkelman M, Plugge AJ, et al. *In vitro* 3D phenotypic drug screen identifies celastrol as an effective *in vivo* inhibitor of polycystic kidney disease. *J Mol Cell Biol* 2020; **12**(8): 644-653.
- [60] Chang MY, Hsieh CY, Lin CY, Chen TD, Yang HY, Chen KH, et al. Effect of celastrol on the progression of polycystic kidney disease in a Pkd1-deficient mouse model. *Life Sci* 2018; **212**: 70-79.
- [61] Shen C, Wang Q, Ye X, Zhou Y, Xing H, Pan C, et al. Celastrol reduces cisplatin-induced nephrotoxicity by downregulating SNORD3A level in kidney organoids derived from human iPSCs. *Front Pharmacol* 2025; **16**. doi: 10.3389/fphar.2025.1464525
- [62] Boran T, Gunaydin A, Jannuzzi AT, Ozcagli E, Alpertunga B. Celastrol pretreatment as a therapeutic option against cisplatin-induced nephrotoxicity. *Toxicol Res (Camb)* 2019; **8**(5): 723-730.
- [63] Yu X, Meng X, Xu M, Zhang X, Zhang Y, Ding G, et al. Celastrol ameliorates cisplatin nephrotoxicity by inhibiting NF- κ B and improving mitochondrial function. *EBioMedicine* 2018; **36**: 266-280.
- [64] Ibrahim MM, Osman A, Helal AI, Faheem AM, El-Kattan MAE, Ibrahim I, et al. Celastrol mitigates acetaminophen-induced nephrotoxicity in rats *via* targeting renal oxidative stress, inflammation, apoptosis with enhancement in aquaporin 1 level. *Rep Biochem Mol Biol* 2024; **13**(2): 204-217.
- [65] Nasrullah MZ, Fahmy UA, Abdel-Naim AB, Babekir EY, Alhothaly AH, Elmesilhy AM, et al. Celastrol mitigates colistin-induced renal toxicity in rats *via* modulating Nrf-2/HO-1 and NF- κ B signaling pathways. *J Biochem Mol Toxicol* 2025; **39**(12). doi: 10.1002/jbt.70641.
- [66] Albrakati A. Nrf2-mediated mechanistic pathways of celastrol nephroprotection: Disrupting the oxidative-inflammatory-apoptotic axis in cypermethrin toxicity. *Front Pharmacol* 2025; **16**. doi: 10.3389/fphar.2025.1670444.
- [67] Liu X, Zhang Q, Wang P, Peng X, An Y, Chen J, et al. Dissection of targeting molecular mechanisms of celastrol-induced nephrotoxicity *via* a combined deconvolution strategy of chemoproteomics and metabolomics. *Int J Biol Sci* 2024; **20**(12): 4601-4617.
- [68] Zheng Y, Ma Y, He P, Yan L, Cao H, Shao F. Phycocyanin/hyaluronic acid microneedle patches loaded with celastrol nanoparticles for synergistic treatment of diabetic nephropathy. *ACS Biomater Sci Eng* 2025; **11**(1): 371-382.
- [69] Wu Q, Wang J, Wang Y, Xiang L, Tan Y, Feng J, et al. Targeted delivery of celastrol to glomerular endothelium and podocytes for chronic kidney disease treatment. *Nano Res* 2022; **15**(4): 3556-3568.
- [70] Guo L, Luo S, Du Z, Zhou M, Li P, Fu Y, et al. Targeted delivery of celastrol to mesangial cells is effective against mesangioproliferative glomerulonephritis. *Nat Commun* 2017; **8**(1): 878. doi: 10.1038/s41467-017-00834-8.
- [71] Pang M, Duan S, Zhao M, Jiao Q, Bai Y, Yu L, et al. Co-delivery of celastrol and lutein with pH sensitive nano micelles for treating acute kidney injury. *Toxicol Appl Pharmacol* 2022; **450**. doi: 10.1016/j.taap.2022.116155.
- [72] Li R, Li Y, Zhang J, Liu Q, Wu T, Zhou J, et al. Targeted delivery of celastrol to renal interstitial myofibroblasts using fibronectin-binding liposomes attenuates renal fibrosis and reduces systemic toxicity. *J Control Release* 2020; **320**: 32-44.
- [73] Nan S, Che Y, Gong T, Zhang Z, Fu Y. Renal-targeted drug delivery by chitosan oligosaccharide micelles with HSA-enriched protein corona for the treatment of ischemia/reperfusion-induced acute kidney injury. *ACS Appl Mater Interfaces* 2024; **36**(37): 49913-49925.
- [74] Xiong X, Feng X, Wei W, Zhu Y, Li M, Sun K. Celastrol-loaded targeted antioxidative nanozyme for improving lipid metabolism and the renal microenvironment in diabetic nephropathy. *ACS Appl Mater Interfaces* 2025; **17**(35): 49272-49285.
- [75] Hu X, Jia M, Fu Y, Zhang P, Zhang Z, Lin Q. Novel low-toxic derivative of celastrol maintains protective effect against acute renal injury. *ACS Omega* 2018; **3**(3): 2652-2660.

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