International Journal of General Medicine

Dovepress
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REVIEW

The Dual Role and Therapeutic Implications of the Wnt/β-Catenin Pathway in Diabetic Kidney Disease

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Abstract: Diabetic kidney disease (DKD), a major microvascular complication of diabetes, affects 30–40% of patients and is the leading cause of end-stage renal disease. The Wnt/β-catenin signaling pathway plays a dual role in DKD pathogenesis: its moderate activation protects against hyperglycemia-induced mesangial apoptosis, while chronic overactivation exacerbates renal fibrosis, podocyte injury, and tubular dysfunction. This review synthesizes current evidence on the pathway's context-dependent mechanisms. Emerging therapeutic strategies—including small-molecule inhibitors (eg, Dickkopf-1), monoclonal antibodies, and natural compounds like curcumin and Salvia miltiorrhiza extracts—show preclinical promise in modulating Wnt/β-catenin activity. However, clinical translation faces challenges such as pathway redundancy, off-target effects, and the need for precise dosing to balance protective and injurious outcomes. Recent advances in biomarker discovery (eg, urinary β-catenin) and ongoing clinical trials highlight the pathway's potential as a therapeutic target. Future research must prioritize patient stratification, combination therapies (eg, Wnt inhibitors + RAAS blockers), and mechanistic studies to address unresolved controversies in Wnt signaling dynamics. This work underscores the therapeutic implications of targeting Wnt/β-catenin in DKD while advocating for a nuanced approach to harness its protective roles.

Keywords: Wnt/β-catenin pathway, diabetic kidney disease, therapy

Introduction

Diabetes is a group of metabolic disorders of carbohydrate metabolism in which glucose is not fully used as a source of energy and is produced excessively due to inappropriate gluconeogenesis and glycogen decomposition, leading to hyperglycemia. By 2040, it is anticipated that 642.1 million people worldwide will have diabetes mellitus due to population aging.[1] In 2019, the number of deaths caused by diabetes was 4.2 million, and 10% of adults incurred health expenses. Even worse, the percentage of diabetic adults living in developing countries is 79%, and more than 50% of these patients are not capable of receiving a diagnosis.[2]

One of the main microvascular complications of diabetes is diabetic kidney disease (DKD). DKD refers to kidney dysfunction specifically occurring in individuals with diabetes, after ruling out other potential causes of chronic kidney disease. As outlined in the current American Diabetes Association guidelines, the diagnostic criteria require either: A reduced estimated glomerular filtration rate (eGFR below 60 mL/min/1.73m²), or Elevated urinary albumin excretion (30 mg or more per gram of creatinine). Both findings must persist consistently for over three months to confirm the diagnosis.[3] Diabetic kidney disease (DKD) affects 30–40% of people with diabetes globally, with higher rates in type 1 diabetes (~40% after 20 years) and significant regional variations—accounting for 40–50% of end-stage renal disease

Received: 21 February 2025
Accepted: 21 May 2025
Published: 28 May 2025

(ESRD) cases in developed countries.[4] Key risk factors include prolonged diabetes duration (>10 years), poor glycemic control (HbA1c >7%), hypertension (present in >80% of cases), and genetic predisposition.[5] Without intervention, 20–40% of DKD patients progress to ESRD within 10–15 years, facing 10-fold higher cardiovascular mortality and triple the healthcare costs compared to non-DKD diabetics.[6,7]

Nearly 1/3 of diabetes patients have DKD. DKD usually occurs a decade after the progression of type 1 diabetes, but it may occur when type 2 diabetes is first diagnosed. DKD may result in decreased kidney function, leading to the development of ESRD or chronic kidney disease.[8] A reduced glomerular filtration rate (GFR), glomerular filtration rate, proteinuria, high blood pressure, and increasingly severe water and sodium retention—which ultimately results in renal failure—are the primary symptoms of DKD. Mesangial enlargement, podocyte damage, thickening of the basement membrane, and damage to glomerular and tubular cells are the primary pathological characteristics of DKD, which results in glomerular sclerosis and interstitial fibrosis.[9]

The characteristics of DKD include progressive decreases in renal function and structural changes within the kidney, which are driven primarily by the following mechanisms: hyperglycemia, inflammation, podocyte injury, mesangial cell dysfunction, tubular epithelial cell injury, and Wnt/β-catenin pathway dysregulation.[10–14] These mechanisms interact and contribute to the complex pathophysiology of DKD, ultimately resulting in nephropathy and, if left untreated, ESRD.

Numerous recent studies have linked diabetic kidney injury to multiple pathways.[15] This article introduces how Wnt participates in DKD and summarizes the Western scientific medicine and traditional Chinese medicine treatment of CKD related to the Wnt signaling pathway to provide a reference for new treatment methods targeting Wnt.

Pathophysiology of DKD

In DKD, chronic low-grade inflammation plays a central role through multiple interconnected pathways. Hyperglycemia triggers immune cell infiltration, with dominant M1 macrophages releasing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) via TLR4/NF-κB signaling, while impaired M2 macrophages fail to provide adequate anti-inflammatory responses.[16] T-cell dysregulation, particularly Th1/Th17 activation and Treg dysfunction, further exacerbates renal injury.[17] The NLRP3 inflammasome activation leads to IL-1β/IL-18 maturation and pyroptosis, with urinary NLRP3 levels emerging as potential biomarkers.[18] A complex cytokine network operates, where TNF-α induces podocyte apoptosis, IL-6 promotes mesangial proliferation via JAK/STAT3, and MCP-1 recruits monocytes through CCR2. Chemokine axes (CXCL12-CXCR4, CCL20-CCR6) mediate inflammatory cell homing, while pattern recognition receptors (TLRs, RAGE) amplify responses to DAMPs and AGEs.[19–21]

Fibrosis represents a pivotal pathological hallmark in DKD, driving progressive renal function decline through three interconnected mechanisms. First, sustained hyperglycemia and metabolic disturbances activate TGF-β/Smad signaling, which stimulates excessive extracellular matrix (ECM) deposition (collagen I/IV, fibronectin) by mesangial cells and fibroblasts while simultaneously inhibiting matrix degradation through upregulation of plasminogen activator inhibitor-1 (PAI-1).[22,23] Second, the Wnt/β-catenin pathway becomes dysregulated, promoting epithelial-mesenchymal transition (EMT) in tubular cells and facilitating fibroblast-to-myofibroblast differentiation through upregulation of transcription factors (Snail, Twist).[24] Third, chronic inflammation perpetuates fibrotic processes via cytokine-mediated activation of renal fibroblasts (IL-6, TNF-α) and macrophage-to-myofibroblast transition.[25,26] These pathways converge to cause glomerulosclerosis, tubular atrophy, and interstitial fibrosis.

Glomerular dysfunction constitutes a central pathological feature in DKD, manifesting through three primary mechanisms. First, podocyte injury occurs via insulin signaling impairment (downregulation of nephrin and podocin), metabolic stress-induced apoptosis (activated caspase-3), and detachment (loss of α3β1 integrin), leading to compromised slit diaphragm integrity and proteinuria. Second, mesangial cells exhibit pathological expansion through glucose-mediated TGF-β activation (Smad2/3 phosphorylation) and ECM production (collagen IV, laminin-511), while simultaneously developing contractile dysfunction due to aberrant calcium signaling.[27] Third, glomerular endothelial dysfunction arises from glycocalyx shedding (reduced heparan sulfate), diminished nitric oxide bioavailability (eNOS uncoupling), and enhanced endothelial-mesenchymal transition (EndMT) driven by Wnt/β-catenin signaling.[26,28,29] These alterations collectively impair the glomerular filtration barrier.

The Wnt/β-Catenin Pathway and DKD

Nusse was the first to discover the Wnt pathway in the late 1970s.[30] The Wnt cascade is an intercellular signaling cascade that is triggered by the secreted lipid-modified proteins of the Wnt family. Wnt signaling coordinates the developmental processes of organisms by controlling aspects such as cell fate specification, mitotic activity, and cell polarity.[31] This network is essential for tissue homeostasis, stem cell control, and embryonic development.[32]

The Wnt signaling network can be separated into the β-catenin-dependent Wnt signaling pathway and the β-catenin-independent Wnt signaling pathway.2 The primary activators of the former canonical pathway are Wnt2b, Wnt3, Wnt3a, Wnt8a, Wnt8b, Wnt9a, and Wnt10b. The latter noncanonical pathway, which can be further divided into the Wnt/Ca^{2+} signaling pathway and the Wnt/planar cell polarity pathway, is stimulated by Wnt5b and Wnt11.[33] This review focuses on β-catenin-dependent signaling pathways.

The Wnt/β-Catenin Pathway

The canonical pathway is triggered by the complex formed by Frizzled receptors, Wnt ligands, and low-density lipoprotein receptor-related proteins 5/6. This causes β-catenin to stabilize, accumulate in the cytoplasm, and then move to the cell nucleus, where it can be bound to TCF/LEF transcription factors. Then, Wnt target genes are activated. Proteins, including Axin, APC, and GSK-3β, strictly regulate this pathway to ensure its precise activation under normal physiological conditions. They create a destruction complex that targets β-catenin for degradation. For cellular homeostasis to be maintained, Wnt activation and inhibition must be balanced.[34,35]

The four components of this signaling pathway are the nuclear segment, cytoplasmic segment, membrane segment, and extracellular signal. Wnt proteins are primarily responsible for mediating extracellular signals. Wnt receptors, including Frizzled and LRP5/6, are located mainly on the cell membrane. β-catenin, dishevelled, glycogen synthase kinase-3β, AXIN, adenomatous polyposis protein, and casein kinase I are key components of the cytosolic region. Members of the TCF/LEF family, downstream target genes of β-catenin, and β-catenin, which is translocated to the nucleus, make up the majority of the nuclear portion.[36]

Frizzled and LRP5/6 can appear at the plasma membrane independently when Wnts are not present. APC, AXIN, CK1, and GSK3 form a "destruction complex" in the cytoplasm that phosphorylates CK1 and GSK3 to grab β-catenin and initiate the breakdown process. Consequently, GROUCHOU suppresses target gene transcription by interacting with TCF/LEF. (Figure 1)

When FZD and LRP5/6 detect Wnts, FZD loses its capacity to destroy β-catenin, and the interaction of FZD with LRP5/6 and other receptor complexes inhibits the work of the "destruction complex" that would otherwise destroy β-catenin, thus preventing β-catenin from being degraded. This causes β-catenin to accumulate in the cytoplasm and then translocate to the nucleus, where it can interact with TCF/LEF transcription factors. One of the key elements of Wnt/β-catenin pathway activation is thought to be the flow of β-catenin between the cytoplasm and nucleus.[36–40] (Figure 2)

The Controversial Dual Role of Wnt/β-Catenin Signaling in Diabetic Kidney Disease

Emerging evidence demonstrates that WNT/β-catenin signaling exhibits context-dependent duality in kidney pathophysiology. Controlled, transient activation of this pathway is essential for initiating renal repair and regeneration post-injury, whereas chronic dysregulation drives maladaptive responses, culminating in irreversible fibrotic progression.

Chronic activation of the WNT/β-catenin pathway appears to play a central role in kidney fibrosis progression. Notably, elevated canonical WNT/β-catenin signaling is consistently observed across diverse animal models of DKD and renal fibrosis, regardless of the initial injury mechanism. This consistency suggests that the injury's specific characteristics—including its nature, severity, spatiotemporal dynamics, and associated cellular interactions—critically determine whether WNT/β-catenin activation promotes adaptive repair or maladaptive remodeling. While various injuries elicit comparable WNT/β-catenin responses, the precise molecular triggers underlying WNT ligand upregulation in damaged kidneys remain largely unidentified. Elucidating these initiating mediators could enable the development of targeted therapies to modulate WNT/β-catenin signaling more precisely.[24]

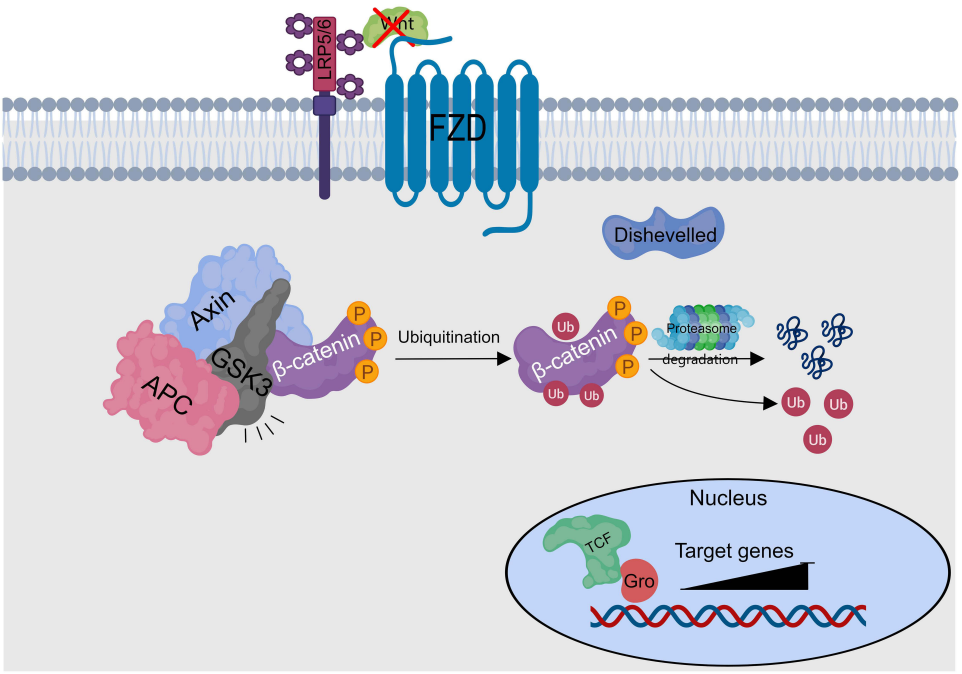

Figure 1 Wnt/β-catenin pathway: absence of the Wnt signal.Without the Wnt signal, the kinases CK1α and GSK3β phosphorylate cytosolic β-catenin, which is supported by scaffolding proteins such as AXIN and APC. β-catenin undergoes phosphorylation, which causes ubiquitylation and proteasomal breakdown. When the nucleus has low levels of β-catenin, transcriptional repressors stop activating Wnt target genes.

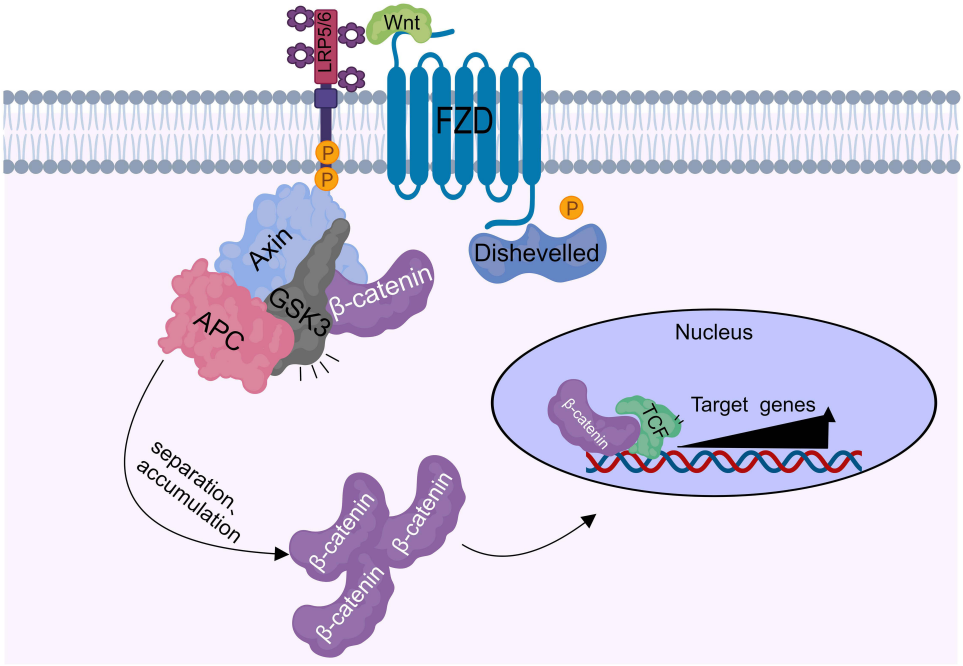

Figure 2 Wnt/β-catenin pathway-mediated Wnt signaling.Core receptors such as FZD and LRP5/6 are located on the cell surface and are bound by the extracellular Wnt signal. Subsequently, LRP5/6 undergo phosphorylation. DVL and AXIN, which function as signal transducers, are recruited into Wnt-bound receptors, which inhibits GSK3β activity. This prevents β-catenin phosphorylation and degradation, which causes accumulation in the cytoplasm before it moves into the cell nucleus. In the cell nucleus, Wnt target genes are activated through the interaction of β-catenin and TCF/LEF transcription factors.

In DKD, the Wnt/β-catenin pathway is intricate and vital. Under hyperglycemic conditions, inhibition of this pathway can cause mesangial cell apoptosis and fibrosis, thereby adversely affecting the kidneys. WNT3A stimulates renal macrophage activation and induces their differentiation into M2-type macrophages, consequently triggering TGFβ1-mediated extracellular matrix synthesis.[41] This pathological cascade is exacerbated by pattern recognition receptor (PRR) activation, which enhances β-catenin signaling, intensifies renal impairment, and aggravates inflammatory and fibrotic responses in kidney tissues.[42] Furthermore, TGFβ establishes a self-perpetuating cycle by activating non-canonical WNT pathways to promote renal fibrosis in vivo, while in proximal tubule cells, the synergistic action of TGFβ and β-catenin worsens tubular damage in DKD mouse models.[43–45] Research has indicated that renal mesangial cells are often shielded against hyperglycemia-induced apoptosis and fibrosis via pathway activation.[14] In a diabetic state, overactivation of this pathway can cause kidney damage and fibrosis, as well as podocyte injury and epithelial–mesenchymal transition of podocytes. Mesangial cells, podocytes, and renal tubular cells are among the cells involved in the pathophysiology of diabetic nephropathy that are activated by this pathway. When the pathway is activated in diabetic nephropathy, Twist and Snail expression increases, causing fibrosis and EMT development. This ultimately causes renal tubulointerstitial tissue and kidney fibrosis.[46] The signaling pathway has dual roles in DKD. A decrease in Wnt protein secretion leads to a reduction in the nuclear translocation of β-catenin, and downregulation of this pathway adversely affects the kidney, including increasing mesangial cell apoptosis and fibrous tissue accumulation in the mesangium. Overactivation of the Wnt1/β-catenin pathway caused by diabetes promotes podocyte injury and EMT, as well as kidney injury and fibrosis.[47]

The dysregulated Wnt/β-catenin pathway contributes to diabetic kidney disease (DKD)-related renal dysfunction through multifaceted mechanisms: In podocytes, chronic activation induces slit diaphragm protein (nephrin, podocin) downregulation via Snail1-mediated repression and promotes apoptosis through Bim upregulation, exacerbating albuminuria (podocyte-specific β-catenin knockout reduces albuminuria by 40% in diabetic models). Tubular epithelial cells undergo β-catenin-driven EMT via Twist1/Zeb1 upregulation and excessive extracellular matrix (ECM) production (collagen I/IV, fibronectin), correlating with rapid eGFR decline in human biopsies (3.5-fold higher nuclear β-catenin in progressive DKD). Concurrently, endothelial dysfunction arises from glycocalyx loss (MMP-9-mediated degradation), reduced nitric oxide bioavailability (eNOS uncoupling), and endothelial-mesenchymal transition (EndMT). (Figure 3) These effects are amplified by crosstalk with TGF-β/Smad, RAAS, and mTOR pathways, creating a vicious cycle of fibrosis and microvascular injury.[24,48,49]

Some drugs, such as simvastatin (SIM) and spironolactone (SP), clinically increase Wnt5a protein secretion, promote β-catenin translocation to the cell nucleus, increase the inhibition of Wnt/β-catenin caused by hyperglycemia, protect against glomerular mesangial cell injury, and produce beneficial effects in patients with diabetic nephropathy.[24]

In rats with type 1 diabetes, salidroside was shown to prevent DKD by inhibiting Wnt1/β-catenin signaling.[50] However, Chong et al showed that by triggering the Wnt1/β-catenin pathway, erythropoietin (EPO) might shield endothelial cells (ECs) from high glucose exposure, indicating a protective function of Wnt1 in DKD.[51] Additionally, DKD can be prevented by blocking Wnt3a/β-catenin signaling, which is overactivated in DKD patients and animal models.[52] Furthermore, Wnt4 is intimately associated with the development of diabetes complications, particularly DKD. Restoring Wnt4 or 5a considerably reduces the fibrosis mediated by TGF-β1 in DKD because high glucose levels cause TGF-β1-mediated fibrosis in glomerular mesangial cells by blocking the canonical pathways mediated by Wnt4 and Wnt5a.[53] Wnt4- and Wnt5a-mediated canonical Wnt signaling is restored, and treatments with melatonin, simvastatin, extracts from Salvia miltiorrhiza, and liraglutide prevent mesangial cell death and ameliorate renal damage in diabetic rat.[54–56] Conversely, by blocking the canonical Wnt4 pathway, sitagliptin or soybean isoflavones have been shown to reduce renal tubulointerstitial fibrosis in DKD rats.[57,58] Studies have shown that glomerular cells are cultivated under high-glucose conditions and that the glomerular mesangium of diabetic rats exhibits modest Wnt5a expression. Thus, by reestablishing the canonical Wnt5a pathway, treatment with curcumin, exogenous superoxide dismutase (SOD), and nitric oxide (NO) donors can considerably reduce glomerular cell death and diabetic renal fibrosis.[59–61] In patients with diabetic kidney disease (DKD) and in animal models of renal fibrosis, the tubulointerstitial region of the kidney shows deletion or reduced expression of Wnt6. Moreover, Wnt6 is expressed in the renal mesenchyme of normally developing mouse embryos. Renal fibrosis is suppressed by activating the canonical Wnt6 pathway, which prevents TGF-β1 from

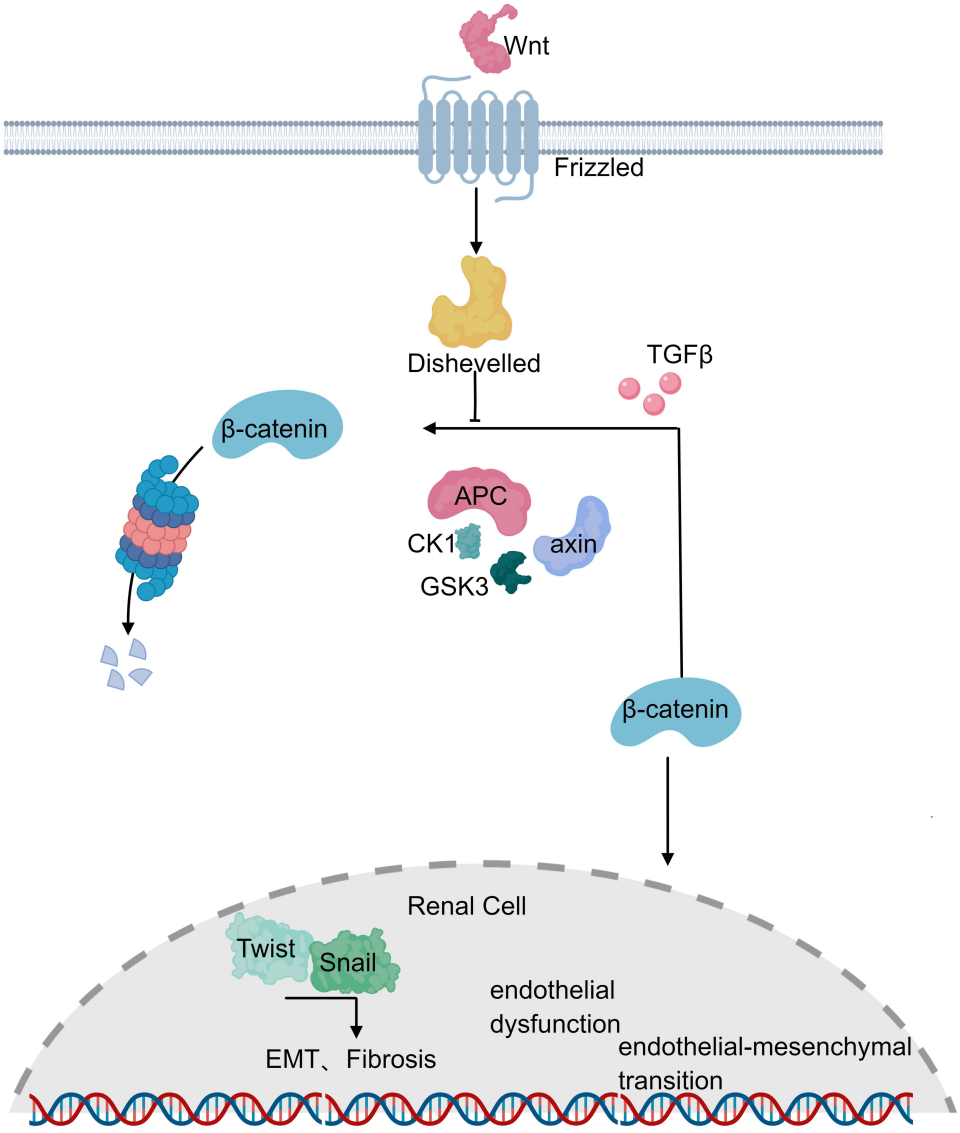

Figure 3 Wnt/β-catenin pathway and DKD.In diabetic nephropathy, overactivation of Wnt pathway can cause kidney damage, fibrosis, and epithelial–mesenchymal transition of podocytes. Twist and Snail expression increases, causing fibrosis, endothelial dysfunction, and EMT development. TGFβ and β-catenin worsen the damage.
Abbreviations: APC, Adenomatous Polyposis Coli is abbreviated as; AXIN, Axis Inhibition Protein is abbreviated as; CK1α, Casein Kinase 1 Alpha is abbreviated as; DVL, Dishevelled is abbreviated as; FZD, Frizzled is abbreviated as; GSK3β, Glycogen Synthase Kinase 3 Beta is abbreviated as; LEF, Lymphoid Enhancer-Binding Factor is abbreviated as; Low-Density LRP, Lipoprotein Receptor-Related Protein is generally abbreviated as; TCF, T-Cell Factor is abbreviated as.

activating the NF-κB pathway.[62] ATF3 levels are elevated in the glomeruli of proteinuric patients, and podocyte destruction is the outcome of the activation of the ATF3/NFAT axis during DKD development. Wnt6 has been found to be a target of this axis and is elevated in podocytes overexpressing ATF3, indicating that Wnt6 may worsen podocyte loss and damage.[63]

Therapeutic Implications of the Wnt/β-Catenin Pathway in DKD

As previously stated, DKD and the disruption of Wnt signaling pathways are closely related. For the treatment of DKD, suitable therapeutic strategies that target Wnt signaling pathways are therefore appealing.

Western Scientific Medicine

Preclinical research has shown promise for a number of drugs that imitate the Wnt/β-catenin signaling cascade. Wnt signaling can reverse the neurodegeneration and behavioral abnormalities caused by beta-amyloid fibrils, suggesting

potential therapeutic applications in DKD.[64] Indirubin-3'-monoxime, 5-aminoimidazole-4-carboxamide ribonucleotide, tosendanin, kirenol, genistein, 13 m indole derivatives, and arctigenin are a few possible Wnt activators.[65] Curcumin is a potentially useful natural substance that controls a variety of intracellular processes, pathways, and crucial enzymes. Curcumin was reported by Cheng Ho et al to reduce the buildup of the extracellular matrix in DKD by reducing the downregulation of Wnt/β-catenin signaling and reducing diabetes-mediated superoxide production.[59]

The canonical Wnt signaling system has been shown to be a target for illnesses such as DKD through the inhibition of Wnt and β-catenin. The Dickkopf, Klotho, and Sclerostin/SOST families are Wnt antagonists. According to reports, Dickkopf-1, a Wnt inhibitor, controls the remodeling of different tissue types. Changes in the way Wnt inhibitors work can be seen as creative strategies to lessen tissue deterioration.[66] By attaching to LRP5/6, these molecules counteract Wnt signaling and prevent FZD-LRP6 dimerization.[67]

Chen et al reported that Klotho derived peptide 6, a peptide that functions similarly to the protein Klotho, inhibits canonical Wnt/β-catenin signaling as a small molecule by binding directly to natural Wnt ligands.[68] Curcumin is a potentially useful natural substance that controls a variety of intracellular processes, pathways, and crucial enzymes. By restoring the downregulation of Wnt/β-catenin signaling, Cheng Ho et al reported that curcumin reduces the formation of the extracellular matrix in DKD.[59] In diabetic nephropathy, sitagliptin may block the tubulointerstitial Wnt/β-catenin signaling cascade and preserve the kidneys by reducing renal tubulointerstitial fibrosis and transdifferentiation.[57] Liraglutide improves renal damage in DKD by increasing Wnt/β-catenin signaling and inhibiting the synthesis of extracellular matrix proteins.[54]

Traditional Chinese Medicine

Effective treatments for DKD are also available in traditional Chinese medicine. By controlling the Wnt/β-catenin pathway, Tripterygium and its extracts may be able to efficiently lower urine protein and safeguard renal function.[69] Celastrol is the primary active ingredient of Tripterygium. Yuewen Tang et al reported that celastrol inhibited Wnt/β-catenin signaling to attenuate DKD.[70] The Radix Astragali is a Chinese herbal medicine in the Leguminosae family. Clinical practice and experimental research have confirmed that the Astragalus genus and its extracts can treat DKD by regulating the Wnt/β-catenin pathway.[71] Astragaloside IV has anti-inflammatory, antioxidative, and antiepithelial–mesenchymal transition properties. According to Enyu Wang et al, it can also inhibit the pathway, which ultimately reduces kidney damage caused by high glucose.[72] The traditional Chinese plant Erigeron breviscapus is the source of the natural flavonoid combination known as breviscapine. Scutellarin is a constituent of breviscapine. Bangrui Huang et al reported that scutellarin improves DKD by regulating the Wnt/β-catenin pathway.[73] One of the primary traditional Chinese medications used in clinical settings to treat diabetes and its consequences is Cornus officinalis. According to Cheng-Guo Ju et al, digesting Cornus officinalis may reduce renal damage in DKD rats by preventing the pathway from being activated, controlling the structural makeup of intestinal microbes, and ultimately contributing to renal protection.[74] A natural herbal remedy, Salvia miltiorrhiza, has several bioactivities, including anti-inflammatory, anti-tumor, anticerebral ischemia, and antioxidant properties. Xiang Xiang et al reported that Wnt4 and β-catenin were more highly expressed in the renal tissue of DKD mice and in cells enriched with high glucose. Salvia miltiorrhiza therapy significantly decreased the expression of these proteins. Extracts from the stems and leaves of Salvia miltiorrhiza can also reduce the expression of β-catenin and Wnt4. These findings demonstrate that Salvia miltiorrhiza and its stems and leaves can protect rats from early DKD by blocking these pathways.[56] Tanshinone IIA is an effective component of Salvia miltiorrhiza Bge. It also ameliorates tubulointerstitial fibrosis by regulating the Wnt/β-catenin pathway in rats with DKD.[75] Panax notoginseng is a medicinal and edible herb used for fitness in China. Ling Xie et al reported that Panax notoginseng improves albuminuria and podocyte EMT in diabetic mice by inhibiting the Wnt pathway.[76] The traditional Chinese medicine Qishen Yiqi Dropping Pills (QYDP) is composed of various herbs used in medicine, including Astragalus Membranaceus, Salviae Miltiorrhizae, Panax notoginseng, and Dalbergia odorifera. Qian Zhang et al demonstrated that QYDP protects the kidneys by blocking the Wnt/β-catenin signaling pathway in diabetic rats.[77] The mulberry leaf is the dried leaf of the deciduous Morus alba L. tree, which belongs to the Moraceae family. Tao Ji et al discovered that a mixture of mulberry leaf active ingredients may help alleviate kidney damage by regulating blood sugar and cholesterol levels and inhibiting the pathway.[78] A diterpenoid obtained from Rabdosia rubescens, oridonin, possesses

Table 1 Traditional Chinese Medicine Treats DKD Through Wnt/β-Catenin Signaling Pathways

Traditional Chinese Medicine	Model	Intervention	Function	Role in Wnt/β-catenin	Reference
Celastrol	db/db mice	Celastro gavage 1 mg/kg/d	Lower inflammatory cytokine	Inhibit	[45]
Astragaloside IV	SD rats, high-fat diet for 6 weeks, STZ (30 mg/kg)	40 mg/kg or 80 mg/kg of AS-IV through daily intragastric administration	Restrains EMT	Inhibit	[47]
Scutellarin	C57BL/6J male mice, 60 mg/kg STZ intraperitoneal injection	Scutellarin, 10 or 40 mg/kg/day	Ameliorates renal fibrosis and podocyte injury	Inhibit	[48]
Cornus officinalis	SD rats, f high-sugar and high-fat diet for 6 weeks, STZ (35 mg/kg)	Cornus officinalis, 281.25 mg/kg/d	Reduces 24-h urinary albumin, reduce renal pathological damage	Inhibit Wnt4, β-catenin	[49]
Salvia miltiorrhiza	SD rats, f high-sugar and high-fat diet for 3 weeks, STZ (30 mg/kg)	Salvia miltiorrhiza, low dose and high dose	Improves the renal injury and regulation of abnormal glycolipid metabolism.	Inhibit Wnt4, β-catenin	[31]
Tanshinone IIA	SD rats, 1% STZ, 60 mg/kg	Tanshinone IIA, 10.8 mg/kg, intraperitoneal injection	Ameliorates renal fibrosis	Inhibit	[50]
Panax notoginseng	SD rats, STZ, 55 mg/kg	Panax notoginseng, 0.4 g/kg/d	Ameliorates albuminuria and podocyte EMT	Inhibit Wnt1, β-catenin	[51]
Qishen Yiqi dripping pill	SD rats, STZ, 60 mg/kg	Qishen Yiqi dripping pill, 150 mg/kg/d or 300 mg/kg/d	Attenuates kidney function and renal fibrosis	Inhibit Wnt1, β-catenin	[52]
Mulberry leaf	SD rats, f high-sugar and high-fat diet for 3 weeks, STZ (30 mg/kg)	Mulberry leaf, 200 mg/kg, intraperitoneal injection,21 days	Controls blood glucose and lipid	Inhibit Wnt2, Wnt4, β-catenin	[53]
Oridonin	SD rats, high-fat diet for 4 weeks, STZ (35 mg/kg)	Oridonin, 10 mg/kg/d, 10 weeks	Ameliorates renal fibrosis	Inhibit Wnt4, β-catenin	[54]

Abbreviations: DKD, Diabetic kidney disease; ESRD, End-stage renal disease; PKC, Protein Kinase C; RAAS, Renin-Angiotensin-Aldosterone System; Fzd, Frizzled; LRP5/6, lipoprotein receptor-related proteins 5/6; APC, adenomatous polyposis coli; GSK-3β, glycogen synthase kinase 3β; CK1, casein kinase I; EMT, epithelial-mesenchymal transition; TGF-β1, transforming growth factor-β1.

a variety of pharmacological properties, including antifibrotic, antitumor, anti-inflammatory, immunoregulatory, and antioxidant activities. Jushuang Li et al reported that oridonin alleviates fibrosis in DKD by inhibiting signaling pathways.[79] (Table 1)

WNT–β-Catenin as a Therapeutic Target

Therapeutic modulation of the WNT/β-catenin pathway is gaining traction as a potential treatment approach for both acute and chronic kidney injury, along with related systemic complications. Multiple investigational compounds targeting distinct nodes of this signaling cascade are currently under development. While clinical applications of WNT/β-catenin-directed therapies have thus far been primarily explored in oncology, emerging evidence suggests that agents selectively modulating specific pathway components—rather than broadly inhibiting WNT signaling—may offer superior efficacy with reduced off-target effects.[80] To date, romosozumab, a humanized monoclonal antibody against sclerostin, represents the only clinically approved WNT pathway modulator. Phase II trial data demonstrated its dual anabolic and anti-resorptive effects in postmenopausal osteoporosis, significantly increasing bone mineral density while reducing bone turnover markers. Subsequent large-scale studies further established romosozumab's clinical superiority over established therapies, showing greater vertebral fracture risk reduction versus denosumab (RANKL inhibition) and more pronounced

hip bone density improvements compared to either teriparatide (PTH analog) or bisphosphonate monotherapy in high-risk populations.[81–84]

In addition to the WNT/β-catenin pathway, two other evolutionarily conserved developmental signaling cascades—Notch and Hedgehog (HH)—are reactivated during kidney injury.[85] Emerging evidence suggests a hierarchical relationship among these pathways: HH signaling potentially functions upstream of WNT/β-catenin activation, while WNT/β-catenin and Notch pathways may engage in reciprocal positive feedback regulation.[86] Deciphering these intricate cross-pathway interactions could reveal novel nodal points for therapeutic intervention, particularly key molecules that orchestrate their crosstalk.

Conclusion

The Wnt/β-catenin pathway plays a pivotal yet complex role in the pathogenesis of diabetic kidney disease (DKD), exhibiting context-dependent duality that influences both renal protection and injury. This review synthesizes key findings on the pathway's dual mechanisms: moderate activation mitigates hyperglycemia-induced mesangial apoptosis, while chronic overactivation exacerbates renal fibrosis, podocyte injury, and tubular dysfunction. Emerging therapeutic strategies—ranging from small-molecule inhibitors (eg, Dickkopf-1) to natural compounds like curcumin and Salvia miltiorrhiza extracts—demonstrate preclinical potential in modulating Wnt/β-catenin signaling. However, clinical translation faces challenges, including pathway redundancy, off-target effects, and the need for precise dosing to balance protective and detrimental outcomes.

Future research should prioritize: Mechanistic clarity: Resolving controversies in Wnt signaling dynamics across DKD stages. Therapeutic precision: Developing targeted interventions (eg, combination therapies with RAAS blockers) and biomarker-guided patient stratification. Translational gaps: Addressing safety and efficacy in human trials to bridge preclinical promise with clinical application. By elucidating the Wnt/β-catenin pathway's nuanced roles and advancing tailored therapies, this review underscores its potential as a transformative target for DKD treatment, while advocating for a balanced approach to harness its protective effects without exacerbating renal injury.

Acknowledgments

Nothing to acknowledge.

Funding

The survey was funded by the Department of Science and Technology of Xinjiang Uygur Autonomous Region (Tianshan Innovation Team, 2022TSYCTD0014). Xinjiang Medical University Student Innovation Training Program (202310760018). The funder had no role in the design, data collection, data analysis, and reporting of this study.

Disclosure

The authors report no conflicts of interest in this work.

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