Diabetic kidney disease (DKD) is a severe microvascular complication in patients with diabetes and is one of the main causes of renal failure. The current clinical treatment methods for DKD are not completely effective, and further exploration of the molecular mechanisms underlying the pathology of DKD is necessary to improve and promote the treatment strategy. Sirtuins are class III histone deacetylases, which play an important role in many biological functions, including DNA repair, apoptosis, cell cycle, oxidative stress, mitochondrial function, energy metabolism, lifespan, and aging. In the last decade, research on sirtuins and DKD has gained increasing attention, and it is important to summarize the relationship between DKD and sirtuins to increase the awareness of DKD and improve the cure rates. We have found that miRNAs, lncRNAs, compounds, or drugs that up-regulate the activity and expression of sirtuins play protective roles in renal function. Therefore, in this review, we summarize the biological functions, molecular targets, mechanisms, and signaling pathways of SIRT1–SIRT7 in DKD models. Existing research has shown that sirtuins have the potential as effective targets for the clinical treatment of DKD. This review aims to lay a solid foundation for clinical research and provide a theoretical basis to slow the development of DKD in patients.

**Keywords:** biological function, signaling pathway, diabetes kidney disease, pathological process, sirtuins

**Abbreviations:** AFSCs, Amniotic fluid stem cells; AGEs, Advanced glycation end products; BAT, Brown adipose tissue; EMT, Epithelial-mesenchymal transition; GBM, Glomerular basement membrane; GMCs, Glomerular mesangial cells; GSPB2, Grape seed procyanidin B2; HFD, High-fat diet; HG, High glucose; HGEcs, Human glomerular endothelial cells; HIC1, Hypermethylated in cancer 1; hNRP F, Heterogeneous Nuclear Ribonucleoprotein F; IRPTCs, ROS generation mediates HG stimulation of angiotensinogen expression in immortalized rat RPT cells; ISLQ, Isoliquiritigenin; KD, Knockdown; Nampt, NMN-producing enzyme nicotinamide phosphoribosyltransferase; NMN, Nicotinamide mononucleotide; OE, Overexpression; OP, A polysaccharide purified from okra; OLETF, Otsuka-Long-Evans-Tokushima-Fatty; PNS, Panax notoginseng saponins; RMCs, Renal mesangial cells; ROS, Reactive oxygen species; STZ, Streptozotocin; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; TSG, Tetrahydroxystilbene glucoside.
1 INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder with chronic microvascular and macrovascular complications. DM is one of the most problematic health issues of the 21st century due to its severe complications. DM affects approximately 451 million people worldwide and is projected to reach 693 million by 2045 (1). NAD⁺ plays a key role in redox and energy metabolism. NAD⁺ acts as a co-substrate in the deacetylation reactions of sirtuins, and the regulation of the NAD⁻/sirtuins axis is a pivotal pathway for the new therapies of metabolic diseases (2). Moreover, in different renal disease models, such as diabetic kidney disease (DKD), sirtuins have been proven to regulate anti-fibrosis and anti-oxidative stress functions, and maintain the glomerular barrier integrity (3). DKD, diabetic retinopathy, and diabetic peripheral neuropathy are the main complications of DM, among which DKD has attracted worldwide attention due to its high incidence (20%-40% in diabetic patients) and poor prognosis (4, 5). DKD is a chronic disease that leads to renal failure; the treatments for renal failure are dialysis and kidney transplantation (6). However, once the disease progresses to end-stage renal disease, the course of this disease is both uncontrollable and irreversible (7). Although many researchers have studied the molecular mechanism of DKD and attempted to improve treatment strategies, DKD remains a clinically intractable complication of DM.

Histone deacetylases (HDACs) in eukaryotes are divided into IV classes, among which the I, II, and IV groups depend on Zn²⁺, whereas class III sirtuins depend on NAD⁺ to exert catalytic activity (8). The sirtuin family is classified into SIRT1–SIRT7 based on differences in the core structural domain, all of which catalyze the deacetylation of N⁶-acyl-lysine on histone and non-histone substrates (9, 10). SIRT1, SIRT6, and SIRT7 are mainly found in the nucleus, SIRT2 is localized in the cytoplasm, and SIRT3, SIRT4, and SIRT5 are found in mitochondria, and their positions are not fixed (11). Sirtuins are involved in the regulation of various biological activities, including DNA repair, apoptosis, cell cycle, oxidative stress, metabolism, lifespan, and aging (12, 13). Based on biological regulatory functions, many studies have shown that the sirtuin family has therapeutic effects in many diseases. Sirtuins are pharmacological targets in neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease (14). Moreover, the regulation of sirtuins reveals a complex network of cellular metabolism and will provide clues for the diagnosis, treatment, and prevention of cancer (15). Additionally, as mitochondrial sirtuins affect many aspects of mitochondrial metabolism and signal transduction, targeting sirtuins may represent a potential therapeutic target to combat age-related mitochondrial recession (16). Through reviewing the literature, we found many studies on sirtuins and DKD, but a lack of systematic and detailed summaries. Therefore, in this review, we have first introduced the biological regulatory functions of SIRT1–SIRT7 in DKD animal and cell models. Subsequently, we have summarized the signaling pathways for treating DKD with various treatments, and finally, examined the differences and clinical implications of sirtuins in DKD studies.

2 SEARCH STRATEGY

Data for this review were identified by searching PubMed and Web of Science using the search terms “histone deacetylase”, “sirtuins”, “SIRT”, “diabetic nephropathy”, “diabetic kidney disease”, and “diabetic complication” for collecting articles from 2004 to 2021, with the language limited to English.

3 PATHOLOGICAL PROCESS OF DKD

The pathogenesis of DKD is multifactorial, involving structural, physiological, hemodynamic, and inflammatory processes, which ultimately lead to a decreased glomerular filtration rate (17). Hyperglycemia and hypertension are critical factors in the development of DKD (17). Proteinuria is an important factor in the development of DKD, which is directly and predictably associated with kidney damage (18). Proteinuria results from an abnormal permeability function of the glomerular filtration barrier, which consists of three layers of glomerular endothelial cells, the glomerular basement membrane (GBM), and podocytes (19). DKD is a microvascular complication of DM that develops from micro-proteinuria to massive proteinuria, ultimately leading to end-stage renal disease (18). Importantly, metabolic and hemodynamic changes in DM cause ultrastructural changes in the glomerular filtration barrier, including podocyte foot process fusion and separation, GBM thickening, reduction of endothelial cell glyocalyx, accumulation of mesangial extracellular matrix, and glomerular sclerosis, all of which are directly related to the increase in proteinuria (20).

3.1 Relationship Between the Expression of SIRT1–SIRT7 and DKD

The important role of SIRT1 has been demonstrated by the enhanced mitochondrial damage in SIRT1 knockout mice with DM, and its role in maintaining kidney cell homeostasis under mitochondrial stress or damage (21). Moreover, in advanced glycation end products (AGE)-treated rat primary glomerular mesangial cells (GMCs), investigators found that the overexpression of SIRT1 protected against reactive oxygen species (ROS) production and fibrosis by enhancing the Keap1/Nrf2/ARE pathway (22). Additionally, under the condition of HG-induced HK-2 cells, the deacetylase activity of SIRT1 decreased and resulted in renal tubular injury induced by the SIRT1/NF-κB/microR-29/Keap1 signaling pathway (23).

Furthermore, a reduction in the NAD⁺/NADH ratio has been shown to induce a decrease in SIRT3 activity and enhance mitochondrial oxidative stress in a DKD rat model (24). Another investigator found that the overexpression of SIRT3 antagonizes apoptosis in HG-induced HK-2 cells via the AKT/FOXO1 and AKT/FOXO3a signaling pathways (25). Similarly, in a streptozotocin (STZ)-induced mouse model, high expression of SIRT3 inhibited aberrant glycolysis and prevented fibrosis via the activation of PKM2 dimer formation and HIF-1α accumulation (26). Moreover, in HG-induced endothelial cells, the overexpression of SIRT3 activated the AMPK/SIRT3 pathway to sustain redox balance and alleviate vascular inflammation (27).
A previous report indicated that the overexpression of SIRT4 reduced the inflammatory effect and restrained apoptosis and the production of ROS in HG-induced mouse podocytes via the mitochondrial pathway (28).

In HG-induced podocytes, the overexpression of SIRT6 reduced mitochondrial dysfunction and apoptosis by activating the AMPK pathway (29). Another report illustrated that overexpression of SIRT6 promoted M2 macrophage transformation and alleviated kidney injury in in vivo and in vitro DKD models by upregulating the expression of Bcl–2 and CD206, and reducing the expression of Bax and CD86 (30). Additionally, another study demonstrated that in db/db mice and AGE/HG-induced human podocytes, overexpression of SIRT6 showed anti-apoptosis and anti-inflammatory effects by inhibiting the Notch pathway (31).

Taken together, these findings indicate that the overexpression of SIRT1, SIRT3, SIRT4, and SIRT6 reduces the biological impairment of kidney function in DKD models.

### 3.2 Gene Polymorphism and Clinical Research of Sirtuins in DKD

Human gene polymorphism plays an important role in elucidating the susceptibility and tolerance of the human body to diseases and poisons, the diversity of clinical manifestations of diseases, and the response to drug therapy (32–34). Studies have shown that SIRT1 and FOXO1 play important roles in the pathogenesis of DKD. Single nucleotide polymorphisms were analyzed by including 1066 patients with type 2 diabetes (T2DM) (413 without DKD and 653 with DKD). Additionally, another study demonstrated that in db/db mice and AGE/HG-induced human podocytes, overexpression of SIRT1 showed anti-apoptosis and anti-inflammatory effects by inhibiting the Notch pathway (31).

Taken together, these findings indicate that the overexpression of SIRT1, SIRT3, SIRT4, and SIRT6 reduces the biological impairment of kidney function in DKD models.

### 5 THE ROLE OF SIRT1–SIRT7 IN SIGNALING PATHWAYS IN DKD MODELS

#### 5.1 AMPK/Sirtuins/PGC-1α Pathway

AMPK and SIRT1 are the two main energy sensors, which directly affect the activity of PGC-1α through phosphorylation and deacetylation, respectively (40). Studies have shown that impaired renal function under HG is directly related to the inactivation of the gene polymorphism and clinical studies indicate that sirtuins may represent a molecular target to explore new therapeutic approaches for DKD in the clinic.

#### 4 BIOLOGICAL EFFECTS OF SIRT1–SIRT7 IN DKD MODELS

In the cell models of DKD, injury models are mostly induced by HG or AGE, while most kidney fibrosis models are induced by TGF-β1 or HG in podocytes, mesangial cells, renal tubular cells, and some endothelial cells (Table 1). In podocyte, proximal tubular cell, and mesangial cell models, SIRT1 and SIRT3 are involved in the mechanism by which therapeutic drugs restore mitochondrial biosynthesis. In podocyte and mesangial cell models, SIRT1 and SIRT6 play significant roles in reducing abnormal mitochondrial function. Moreover, SIRT1, SIRT3, and SIRT4 are involved in the anti-oxidative stress effect in podocytes, mesangial cells, and renal tubular cells. SIRT1, SIRT3, SIRT4, SIRT6, and SIRT7 all participate in reducing the apoptosis of podocytes, mesangial cells, and renal tubular cells in DKD models. In most DKD cell models, therapies targeting SIRT1, SIRT3, SIRT4, and SIRT6 have shown anti-inflammatory effects. In DKD tubular cell models, both SIRT1- and SIRT3-targeted therapies displayed anti-fibrosis effects and suppressed epithelial-mesenchymal transition (EMT). Targeting SIRT1 also enhanced autophagy in various DKD models. By summarizing the results of previous research, we found that SIRT1, SIRT3, SIRT4, SIRT6, and SIRT7 play different biological functions in DKD cell models. Notably, SIRT1 is the most widely investigated HDAC with the most diverse biological functions (Figure 1).

Animal models are valuable for studying the pathological origins of human diseases because they allow in-depth investigation of mechanisms, which cannot be explored in clinical studies. As DKD animal models, db/db mice or rats, STZ and/or HFD-induced mice or SD/Wist rats, and some unique transgenic mouse models are often used as research objects. We summarized the research methods of SIRT1, SIRT3, SIRT4, SIRT6, and SIRT7 in different DKD animal models to understand the methods of animal models more intuitively (Tables 2–9).

Generally, these abnormal manifestations, such as inflammation, oxidative stress, abnormal mitochondrial function, renal fibrosis, podocyte loss and apoptosis, and impaired autophagy, are all likely to occur during the development of DKD. Meanwhile, SIRT1, SIRT3, SIRT4, SIRT6, and SIRT7 play diverse regulatory roles in these physiological processes.
TABLE 1 | Cellular model of diabetic nephropathy used to study SIRT1-SIRT7.

| Podocytes | Species | Model |
|-----------|---------|-------|
| Mesangial cells | | |
| GMcs (Glomerular mesangial cells) | Rat | HG, AGE |
| HBZY-1 | Rat | HG |
| HMcs (Human mesangial cells) | Human | TGF-β, HG |
| HRMCs (Human renal mesangial cells) | Human | HG |
| Mouse mesangial cells | Mouse | HG |
| mHMcs (Renal mesangial cells) | Mouse | HG |
| NM52 | Rat | HG |
| Raw264.7 | Mouse | HG |
| SV40 MES 13 | Mouse | |
| Renal tubule | | |
| BUMPT cells (Proximal tubule-derived cell line) | Mouse | HG |
| HK-2 (Proximal tubule epithelial cell) | Human | TGF-β, HG |
| mProx (Proximal tubular cells) | Murine | H2O2 |
| NRK-52E (Renal tubular epithelial cells) | Rat | HG, AGE |
| RPTCs (Renal proximal tubule epithelial cells) | Human | HG |
| Others | | |
| HGECs (Human glomerular endothelial cells) | Human | HG |
| HUVECs (Human umbilical vein endothelial cells) | Human | HG, AGE |
| LLC-PK1 (Renal epithelial cell line) | Porcine | HG |

AMPK/SIRT1/PGC-1α signaling pathway (41). The study results showed that CL316, 243, glycyrrhizin acid, and a polysaccharide from okra (OP) all played antioxidant roles, reduced inflammation, and improved fibrosis through activation of the AMPK/SIRT1/PGC-1α pathway in STZ and/or HFD-induced db/db DKD mouse models (42–44). Resveratrol, pro-renin receptor shRNA, and grape seed procyanidin B2 (GSPB2) regained SIRT1 expression via the AMPK/SIRT1/PGC-1α signaling axis in DKD models, thus restoring mitochondrial biosynthesis and function, reducing oxidative stress, and inhibiting apoptosis (40, 41, 45–47). In DKD animal or cell models, FGF21, metformin, salidroside, and rolflumastil increased or restored the expression level of SIRT1 and played anti-apoptotic and anti-oxidative roles by activating the AMPK/SIRT1 pathway (48–51). Moreover, catalpol and geniposide (GE) up-regulated the expression of SIRT1 in DKD models and inhibited oxidative stress and inflammation by activating the AMPK/SIRT1/NF-κB pathway (52, 53). Additionally, in HG-induced renal tubule cells, restoration of SIRT3 expression through stanniocalcin-1 activated the AMPK/SIRT1 pathway to produce antioxidant and anti-apoptotic activities (54). Furthermore, cocoa, metformin, glycyrrhizin acid, and protocul restored SIRT1 expression by activation of the AMPK/SIRT1 pathway, ultimately reducing oxidative stress, apoptosis, and enhancing autophagy in DKD models (26, 55–58). However, one particular study reported that resveratrol improved oxidative stress and enhanced mitochondrial biogenesis without altering SIRT1 expression, and is independent of the AMPK/SIRT1 pathway. The distinction is that they used H2O2-exposed proximal tubular cells as a DKD model, as opposed to HG or AGE, which are more commonly used (59). In HG-induced immortalized human mesangial cells (iHMcs), theobromine could activate SIRT1 and decrease kidney extracellular matrix (ECM) accumulation by activating the AMPK pathway (60). In BTBR ob/ob mice, honokiol protected mitochondrial health by activating mitochondrial SIRT3, which first revealed the renal protective effect of SIRT3 on diabetic glomerular disease (61). Moreover, in STZ-induced mouse models, salidroside and resveratrol restored SIRT1 expression via the SIRT1/PGC-1α pathway, thus inhibiting fibrosis and reducing mitochondrial oxidative stress, respectively (61–63). BF175, as an activator of SIRT1, increased SIRT1 activity to acetylate PGC-1α and activate PPARγ to reduce podocyte loss and oxidative stress (64). Furthermore, glucagon–like peptide–1, formononetin, and resveratrol enhanced SIRT1 expression in DKD models to attenuate apoptosis and oxidative stress by activating SIRT1 (65–67). Beyond this, in HG-induced podocytes or mesangial cells, overexpression of lncRNA SOX2OT, overexpression of lncRNA GASS, or downregulation of miR-138 increased SIRT1 expression or activity to induce autophagy, inhibit fibrosis, and decrease inflammation, respectively, by regulating the miR-9/SIRT1, miR-221/SIRT1, and miR-138/SIRT1 axes (68–70). Through the studies reported above, we conclude that AMPK/Sirtuins/PGC-1α is a crucial pathway in regulating the pathological process of DKD (Table 2).

5.2 SIRT1/p53 Pathway
SIRT1 specifically associates with and acetylates the tumor suppressor protein p53, thereby negatively regulating p53-mediated transcriptional activation. More importantly, p53 deacetylation by SIRT1 prevents DNA damage and stress-induced cell senescence and apoptosis (71, 72). A previous study has shown that in HG-induced podocytes or HK-2 cells, inhibition of miR-150-5p or miR-155-5p, which could bind to the 3’-UTR of SIRT1, promoted autophagy by targeting the SIRT1/p53 pathway (73, 74). Moreover, in DKD animal and cell models, H2S, resveratrol, and calcium dobesilate restored or enhanced SIRT1 expression to prevent apoptosis by activating the SIRT1/p53 pathway (75–77). These reports suggest that the SIRT1/p53 pathway reduces cellular stress in HG-induced cells or STZ-induced animals’ models (Table 3).

5.3 SIRT1/NF-κB-Related Pathway
Previous studies have demonstrated that the ability of SIRT1 deacetylation is critical to control the function of the transcription factor NF-κB, as SIRT1 modulates various biological responses by deacetylating NF-κB, including...
in most chronic kidney diseases, and the inhibition of TGF-β is a key regulator of cell homeostasis (111). It has been reported that formononetin, resveratrol, and polydatin up-regulate the expression of SIRT1 to anti-oxidative stress and fibrosis by activating the Nrf2/ARE pathway in HG/AGE-induced GMCs (112–114). Investigators have also found that SRT2104 (SIRT1 activators) protect against oxidative stress, inflammation, and fibrosis via the SIRT1/p53/Nrf2 pathway in DKD models (115).

5.4 Sirtuins and the TGF-β1/Smad3 Pathway

TGF-β superfamily members are critical in regulating fibrosis in most chronic kidney diseases, and the inhibition of TGF-β1 or its downstream signaling (e.g. Smad) has been shown to decrease renal fibrosis (91–94). It has also been reported that the reduction of miR-34a-5p targets the 3’UTR of SIRT1, which inhibits fibrosis by regulating TGF-β1 signaling in HG-induced HK-2 cells (95). Moreover, in AGE stimulated NRK-52E cells, oligo-fucoidan has been shown to improve renal fibrosis via restraint of the pro-fibrosis process caused by TGF-β1 activation (96). Additionally, tetrahydroxystilbene glucoside (TSG) restored SIRT1 expression to alleviate oxidative stress by targeting SIRT1 and TGF-β1 signaling both in vivo and in vitro (97). Moreover, the inhibition of miRNA–135a–5p increased SIRT1 expression and inhibited fibrosis by targeting the TGF-β1/Smad3 pathway in TGF-β1-induced HK-2 and HMC cells (98). As a unique example, FOXO3a binds to the SIRT6 promoter and promoted SIRT6 expression to reduce EMT and fibrosis through FOXO3a-mediated SIRT6/Smad3 pathway in DKD models (99). The above summary highlights the vital function of the TGF-β1/Smad3 pathway in the regulation of renal fibrosis by sirtuins in DKD (Table 5).

5.5 PI3K/AKT/FOXO Pathway

The PI3K/AKT pathway plays a crucial role in cell physiology, which participates in glucose homeostasis, lipid metabolism, protein synthesis, and cell proliferation and survival (100, 101). FOXO1 and FOXO3a, as important substrates of AKT, are regulated by the PI3K/AKT pathway (102). Researchers have found that resveratrol restored SIRT1 expression to attenuate oxidative stress damage in STZ-induced rat models through the SIRT1/FOXO3α or SIRT1/FOXO1 pathway (103–105). Moreover, the inhibition of miRNA–135a–5p targeting the SIRT1 promoter and promoted SIRT6 expression to reduce oxidative stress damage in STZ-induced rat models through the SIRT1/FOXO3α or SIRT1/FOXO1 pathway (106–107). Moreover, in STZ- and HFD-induced mouse models, purinergic receptor (P2Y2R) deficiency enhanced autophagy and the expression of SIRT1 by AKT/FoxO3α and SIRT1 signaling pathways (108). Additionally, pyrroloquinoline quinine increased the expression of SIRT3 to antagonize oxidative stress and apoptosis in HG-induced HK-2 cells via the PI3K/AKT/FOXO3α signaling pathway (109). Moreover, it has been reported that progranulin (PGRN) restored both SIRT1 and SIRT3 to maintain mitochondrial biogenesis and mitophagy via SIRT1/PGC-1α/FoxO1 signaling in HG-treated podocytes (110). These findings suggest that the PI3K/AKT/FOXO pathway performs important biological functions in improving DKD by targeting sirtuins (Table 6).

5.6 Keap1/Nrf2/ARE Pathway

Dysregulation of Nrf2 transcriptional activity has been described in the pathogenesis of various diseases, and the Nrf2/Keap1 axis is a key regulator of cell homeostasis (111). It has been reported that formononetin, resveratrol, and polydatin up-regulate the expression of SIRT1 to anti-oxidative stress and fibrosis by activating the Nrf2/ARE pathway in HG/AGE-induced GMCs (112–114). Investigators have also found that SRT2104 (SIRT1 activators) protect against oxidative stress, inflammation, and fibrosis via the SIRT1/p53/Nrf2 pathway in DKD models (115).
| Reference | Drug/Target | Sirtuins | Model | Mechanism of protection | Pathway |
|-----------|-------------|----------|-------|-------------------------|---------|
| (21)      | SIRT1       | SIRT1    | SIRT1RNAi transgenic mouse STZ-induced mouse ADR-induced nephropathy murine podocytes | Enhance mitochondrial damage | SIRT1 signaling |
| (27)      | SIRT3 OE    | SIRT3    | HG-induced HUVEC | Sustain redox balance and alleviate vascular inflammation | Increased SIRT3-activated AMPK pathway |
| (29)      | SIRT6 OE    | Up-regulate SIRT6 | STZ induced male C57BL/6 mice HG-induced podocyte | Attenuate mitochondrial dysfunction and apoptosis | Activate AMPK pathway |
| (40)      | Pro-renin receptor shRNA | Restore SIRT1 | STZ C57BL/6 mouse HG-mouse renal mesangial cells (mRMCs) | Restore mitochondrial biogenesis and function | AMPK/SIRT1/PGC-1α signaling pathway |
| (41)      | Resveratrol | Restore SIRT1 expression | db/db diabetics | Anti-apoptosis and oxidative stress | AMPK/SIRT1/PGC-1α axis |
| (42)      | OP | Increase expression of SIRT1 | HFD and STZ-induced mice | Suppress apoptosis and oxidative stress | Activate AMPK/SIRT1/PGC-1α signaling axis |
| (43)      | CL316,243 | Reverse the decrease of SIRT1 | STZ and HFD treated mouse | Improve renal fibrosis, inflammation, and oxidative stress, and enhance BAT activity | AMPK/SIRT1/PGC-1α signaling pathway |
| (44)      | Glycyrrhizin | Restore SIRT1 | Male diabetic db/db | Inhibit ROS | Activate AMPK/SIRT1/PGC-1 signaling |
| (45)      | Resveratrol | Restore SIRT1 expression | db/db diabetic mice | Inhibit oxidative stress and apoptosis | By activating the AMPK/SIRT1/PGC-1α axis |
| (46)      | GSPB2 | Restore SIRT1 expression | HG-induced HGECs | Reduce mitochondrial dysfunction and apoptosis | Via the AMPK/SIRT1/PGC-1α axis |
| (47)      | Grape seed procyanidin B2 (GSPB2) | Restore SIRT1 expression | High-dose glucosamine | Ameliorate mitochondrial dysfunction and inhibit apoptosis | The activation of the AMPK/SIRT1/PGC-1α axis |
| (48)      | FGF21 | Increase SIRT1 levels | OVE26 transgenic mouse as a T1DM nephropathy model | Anti-apoptosis, antioxidative stress, anti-inflammatory | AMPK/SIRT1 pathway |
| (49)      | Metformin | Increase SIRT1 protein expression | HG-induced primary rat podocytes | Improve the insulin resistance | Dependent on AMPK and SIRT1 activity |
| (50)      | Salidroside | Restore SIRT1 expression | STZ-induced Wistar rat as T1DM model | Anti-apoptosis and oxidative stress | Activate AMPK/SIRT1 signaling pathway |
| (51)      | Rolflumilast | Restore SIRT1 expression | STZ-induced SD rat | Anti-apoptosis | AMPK/SIRT1 pathway |
| (52)      | Catalpol | Increase SIRT1 level | HFD/STZ-induced mice, HG-induced podocyte model | Inhibit oxidative stress and inflammation accompanied with pyroptosis | Activate AMPK/SIRT1/NF-κB pathway |
| (53)      | Geniposide (GE) | Up-regulate protein expression of SIRT1 | Male C57BL6J db/db mice, HG-treated BUMPT cells | Antioxidative stress, anti-inflammatory | AMPK/SIRT1/NF-κB pathway |
| (54)      | Stannioclacin-1 | Restore SIRT3 protein expression | HG-induced podocyte model | Antioxidant and anti-apoptotic activities | AMPK/SIRT3 pathway |
| (55)      | Metformin | Restore SIRT1 | HFD and low dose STZ rats HG-induced RMCs | Alleviate oxidative stress and enhance autophagy | AMPK/SIRT1/FOXO1 pathway |
| (56)      | Cocoa | Restore SIRT1 | Zucker diabetic fatty (ZDF) rats in diabetic | Antioxidant, stimulate autophagy and suppress apoptosis | Activation of stress related key proteins (ERK/MAPKs and NOX-4), cytoprotective-related proteins (AMPK, SIRT1 and mTOR), autophagy and apoptosis pathways |

(Continued)
Moreover, in HG-induced NRK-52E cells, ISLQ treatment reduced inflammation and oxidative stress by inhibiting MAPK activation and the induction of Nrf2 signaling (116). These findings demonstrate that SIRT1 regulates the transcription factor Nrf2 in DKD models (Table 7).

### 5.7 STAT and HIF-1α-Related Pathway

It has been reported that connexin 43, LincRNA 1700020i14Rik, and silencing of miR-217 restrain inflammation and fibrosis in both in vivo and in vitro DKD models through SIRT1/HIF-1α signaling (117–119). Additionally, in AGE-induced human
podocytes, PYR as an AGE inhibitor, restored SIRT1 expression to reduce kidney injury by decreasing p65 and STAT3 acetylation (120). In one study in HFD-diet DM rats, EX-527, as a SIRT1 inhibitor, reduced SIRT1 expression and increased SIRT3 expression to lessen fibrosis and inflammation by blocking the phosphorylation of EGFR and PDGFR, blocking STAT3 signaling (121). In another study, glucagon-like peptide-1 decreased SIRT1 expression to improve the inflammatory changes in db/db mice by inhibiting JAK/STAT signaling (122). Thus, STAT and HIF-1α-related pathways reduce negative effects in DKD models by targeting sirtuins (Table 8).

5.8 Other Pathways Involved in the Regulation of Sirtuins in DKD

5.8.1 Pathways Associated With SIRT1 in DKD

Researchers have shown that both 1α, 25-Dihydroxyvitamin D3 and puerarin activate and increase SIRT1 expression to achieve anti-oxidative effects by suppressing NOX4 expression in DKD models (123, 124). Carnosine upregulated SIRT1 expression

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### Table 3: DKD studies on SIRT1/p53 pathway.

| Reference | Drug/Target | Sirtuins | Model | Mechanism of protection | Pathway |
|-----------|-------------|----------|-------|--------------------------|---------|
| (73)      | Inhibition  | SIRT1    | HG-induced HK-2 | Promote autophagy | A signaling loop p53/miR-155-5p/SIRT1 |
|           | mIR-155-5p  |          |       |                          |         |
| (74)      | Silencing   | SIRT1    | HG-induced podocyte injury | Activate AMPK-dependent autophagy | Targeting SIRT1/p53/AMPK pathway |
| mIR-150-5p|             |          |       |                          |         |
| (75)      | Resveratrol | SIRT1    | STZ-induced diabetic nephropathy in mice | Suppress oxidative stress and apoptosis | SIRT1, SOD, caspase-3, p53, MDA |
| H2S       |             |          | STZ-induced male rat | Inhibit apoptosis | SIRT1/p53 axis |
| (76)      | Calcium     | SIRT1    | Renal interstitial fibrosis induced by unilateral ureteral obstruction (UOO) mouse model | Suppress EMT progression and promote anti-apoptotic | Via activating the SIRT1/p53 signaling pathway |
| dobesilate|             |          | HUVECs |                          |         |

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### Table 4: DKD studies on SIRT1/NF-κB related pathway.

| Reference | Drug/Target | Sirtuins | Model | Mechanism of protection | Pathway |
|-----------|-------------|----------|-------|--------------------------|---------|
| (23)      | -- --       | SIRT1    | STZ-induced Wistar rat | Inhibit renal tubular injury | SIRT1/NF-κB/microR-29/Keap1 signal pathway |
|           |             |          | HG-induced HK-2 |                          |         |
| (80)      | Baicalin    | SIRT1    | HG-induced podocyte | Decrease apoptosis of high glucose induced podocyte | SIRT1/NF-κB signaling pathway |
|           |             |          |       |                          |         |
| (81)      | ISLQ        | SIRT1    | Male rat by STZ | Antioxidant, anti-inflammatory, and reduce collagen accumulation | Normalize the SIRT1/NF-κB balance, control NLRP3 expression |
|           |             |          |       |                          |         |
| (82)      | Astragaloside IV | SIRT1 | Polygenic KK-Ay mice | Inhibit EMT and enhance autophagy | SIRT1/NF-κB pathway |
|           |             | expression | models HG induced podocyte |                    |         |
| (83)      | Tangshen formula | SIRT1 | STZ-HFD induced SD rat | Improve inflammation | Through SIRT1/NF-κB pathway |
|           |             | expression |       |                          |         |
| (84)      | NMN         | SIRT1    | STZ induced SD male | Alleviate inflammatory–fibrosis | Nampt/NF-κB p65 and SIRT1 signaling pathway |
|           |             | expression | rat |                          |         |
| (85)      | Astragaloside IV | SIRT1 | HG induced HB2Y-1 mouse | Enhance autophagy | SIRT1/NF-κB pathway |
|           |             | expression | Mesangial cell (SV40 MES 13) |                          |         |
| (86)      | Ligustilide | SIRT1    | STZ combined with a HFD rat | Attenuate podocyte injury | Suppressing the SIRT1/NF-κB signaling pathways |
|           | protein expression |          |       |                          |         |
| (87)      | BF175       | SIRT1    | STZ mice | Reduce albuminuria and glomerular disease | NF-κB and p53 signaling pathways |
|           |             | expression |       |                          |         |
| (88)      | Baicalin    | SIRT1    | STZ rats | Inhibit inflammation, inhibit extracellular matrix accumulation, regulate cell proliferation, reactivate autophagy, alleviate renal fibrosis | NF-κB signaling pathway, TGF-β/Smad3 pathway, IGF-1/IGF-1R/p38 MAPK pathway |
|           |             | expression |       |                          |         |
| (89)      | PNS         | SIRT1    | Alloxan-induced SD rat | Inhibit inflammation and antioxidant | Through decreasing the NF-κB-mediated induction of inflammatory cytokines and TGF-β1 |
|           |             | protein expression | HG-induced RMCs |                          |         |
| (90)      | Na₂S₄       | SIRT1    | HG-induced HK-2 cells | Restrain the overproduction of inflammation cytokine and ROS | Suppressing phosphorylation and acetylation of p65 NF-κB and STAT3 |

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### TABLE 5 | DKD studied on sirtuins and TGF-β1/Smad3 pathway.

| Reference | Drug/Target | Sirtuins | Model | Mechanism of protection | Pathway |
|-----------|-------------|----------|-------|-------------------------|---------|
| (95)      | Reduce miR-34a-5p | SIRT1 | Targeting the 3' UTR of SIRT1 | HG-induced HK-2 | Inhibit fibrosis | TGF-β1 signaling |
| (96)      | Oligo-Fucoidan | SIRT1 | Restore SIRT1 expression | AGE stimulated NRK-52E cells | Improve kidney disease caused by excessive fibrosis | Suppress the HMGB1/RAGE/NTF-κB/TGF-β1/TGF-β1/TGF-β1/RN pathway and HIF-1α activation |
| (97)      | TSG | SIRT1 | Restore SIRT1 expression | STZ-induced SD rat | Alleviate oxidative stress | SIRT1 and TGF-β1 pathway |
| (98)      | Inhibition of miRNA-135a-5p | SIRT1 | Target SIRT1 3' UTR expression | TGF-β1-induced HK-2 and HMCs | Inhibit renal fibrosis | Target SIRT1 and inactivating Smad3 signaling |
| (99)      | FOXO3a | SIRT1 | Bind to the SIRT6 promoter and promote SIRT6 expression | db/db T2DM mouse | Reduce EMT and fibrosis | FOXO3a-mediated SIRT6/Smad3 signaling pathways |

### TABLE 6 | DKD studied on PI3K/AKT/FOXO3 pathway.

| Reference | Drug/Target | Sirtuins | Model | Mechanism of protection | Pathway |
|-----------|-------------|----------|-------|-------------------------|---------|
| (25)      | SIRT3 OE | SIRT3 | HFD/STZ induced CS7BL/6 mouse | Inhibit apoptosis | AKT/FoxO signaling pathway |
| (103)     | Resveratrol and rosuvastatin | SIRT1 | Restore SIRT1 mRNA expression | STZ-induced Wistar rat | Antagonize high glucose-induced apoptosis | AKT/FoxO signaling pathway |
| (104)     | Resveratrol | SIRT1 | Restore SIRT1 expression | STZ-induced Wistar rat | Attenuate oxidative stress damage | AKT/FoxO signaling pathway |
| (105)     | Resveratrol | SIRT1 | Restore SIRT1 expression | STZ-induced SD rat | Reduce oxidative stress damage | AKT/FoxO signaling pathway |
| (106)     | Fucoxanthin | SIRT1 | Restore SIRT1 expression | GMCS cultured in HG | Anti-oxidative stress and anti-fibrosis | AKT/FoxO signaling pathway |
| (107)     | Angiotensin 1–7 | SIRT1 | Increase SIRT1 expression | db/db mouse T2DM model | Anti-oxidative stress and anti-fibrosis | AKT/FoxO signaling pathway |
| (108)     | P2Y2R deficiency | SIRT1 | Increased SIRT1 expression | HFD and STZ mouse | Reduce oxidative stress, inflammation, and lipotoxicity | AKT/FoxO signaling pathway |
| (109)     | Pyrroloquinoline quinone | SIRT1 | Uregulate SIRT3 expression | HG-induced HK-2 | Anti-oxidative stress and anti-fibrosis | AKT/FoxO signaling pathway |
| (110)     | PGRN | SIRT1 | Restore SIRT1 and SIRT3 expression | STZ-induced mice and patients with DKD, HG-treated podocytes | Maintain mitochondrial biogenesis and mitophagy | Via PGRN/SIRT1/PGC-1α/FOXO1 signaling |
| (111)     | Reduce LncRNA MALAT1 | SIRT1 | Restore SIRT1 expression | HG induced HK-2 | Renal protective effect | MALAT1/FoxO signaling |

### TABLE 7 | DKD studied on Keap1/Nrf2/ARE pathway.

| Reference | Drug/Target | Sirtuins | Model | Mechanism of protection | Pathway |
|-----------|-------------|----------|-------|-------------------------|---------|
| (22)      | SIRT1 OE | SIRT1 | AGES-treated rat primary GMCS | Inhibit ROS production and anti-fibrosis | Enhanced the activity of Keap1/Nrf2/ARE pathway |
| (112)     | Polydatin | SIRT1 | Reverse the downregulation of SIRT1 protein expression and deacetylase activity | Anti-oxidative stress and fibrosis | Activation of SIRT1/Nrf2/ARE pathway |
| (113)     | Formononetin | SIRT1 | Up-regulated the expression of SIRT1 | Antioxidative stress, prevent the progression of renal fibrosis | Nrf2/ARE signaling pathway |
| (114)     | Resveratrol (SIRT1 activator) | SIRT1 | Restore SIRT1 expression | STZ-induced SD rat | Antioxidative and fibrosis | By activating the Nrf2/ARE pathway |
| (115)     | SRT2104 | SIRT1 | Enhance SIRT1 expression and activity | STZ-induced C57BL/6 mouse | Protection against the oxidative stress, inflammation, fibrosis | SIRT1/p53/Nrf2 pathway |
| (116)     | ISLQ | SIRT1 | SIRT1 binds to ISL directly | STZ-induced T1DM HG-induced NRK-52E cells | Reduce inflammation and oxidative stress | Inhibition of MAPK activation, and the induction of Nrf2 signaling |
to decrease glycative and liperoxidative stress in HG-induced podocytes via the Hsp70/HO-1 pathway. Another report showed that anserine revealed anti-oxidant and glycative stress in HG-induced HK-2 cells via the Hsp70/HO-1 defense system, but did not affect SIRT1 expression (125, 126). Several other studies have shown that aerobic exercise training, inhibition of HIC1, INT-767 (FXR/TGR5 dual agonist), and SGLT2 restored SIRT1 expression under DKD animal and cell models, which improve mitochondrial function, reduce ROS, anti-inflammation, and prevent glucose entry (127).

These results suggest that SIRT1 largely exhibits anti-inflammatory effects through different signaling pathways in DKD models.

### 5.8.2 Pathways Associated With SIRT3 in DKD

Apigenin (CD38 inhibitor) and emaprilat (SGLT2 inhibitor) have been shown to increase SIRT3 levels in HG-induced HK-2 cells to relieve mitochondrial oxidative stress and restore aberrant functions; this is mediated by restoring the NAD+/NADH ratio and inhibiting glucose uptake into the proximal tubules, respectively (131, 132). Liraglutide (glucagon-like peptide-1 agonist) has also been shown to increase SIRT3 expression to prevent the activation of mitochondrial apoptosis by activating the ERK–Yap signaling pathway in HG-induced HRMCs (133). It has been reported that INT-777 (TGR5 agonist) increased the activity of both SIRT1 and SIRT3 to improve mitochondrial biogenesis, and reduce oxidative stress and fibrosis via the TGR5 pathway in db/db diabetic mice (134). Moreover, in the C57BL/KsJ db/db mouse model, the overexpression of SIRT3 reduced apoptosis and fibrosis through modulation of mitophagy (135). It can be seen from the above results that high expression of SIRT3 reduced mitochondrial stress response, including oxidative stress and apoptosis.

### 5.8.3 Pathways Associated With SIRT6 in DKD

SIRT6-knockout male mice have been shown to exhibit an enhanced fibrotic phenotype, which was controlled by the Namp-SIRT6 axis to regulate extracellular matrix remodeling, and the authors found that SIRT1 is not the controller of SIRT6 expression (136). The results of this article show that SIRT6 plays an important regulatory role in ECM remodeling.

### 5.8.4 Pathways Associated With SIRT7 in DKD

In HG-treated podocytes, the increase in SIRT7 has been shown to inhibit podocyte apoptosis, while the suppression of microRNA-20b promotes SIRT7 expression to decrease apoptosis (137) (Table 9). This research demonstrated that increasing the expression of SIRT7 reduced the occurrence of apoptosis in podocytes.

### 5.9 Summary of SIRT1–SIRT7

SIRT1 was the first sirtuin discovered in mammals, and remains the most extensively and deeply studied so far (138). Resveratrol is the most recognized and studied activator of SIRT1 (139). SIRT1 has been extensively studied in DKD models, including podocytes, mesangial cells, and tubular cells. SIRT2 is the only cytoplasmic sirtuin, but its role in treating DKD has not been reported yet so far, nor has that of SIRT5. SIRT3 is normally located in the mitochondria, but under cellular stress, it can translocate into the nucleus (140). Some studies have reported that increased expression of SIRT3 is beneficial to DKD, mainly through AMPK or PI3K pathways (25, 27, 54, 109, 110). However, we found one article that reported that the overexpression of SIRT4 reduced inflammatory effects, and inhibited ROS production and apoptosis in HG-induced podocytes (28). SIRT6 is a nuclear HDAC that plays an important role in the pathological processes of inflammation, aging, cancer, and neurodegenerative diseases (141). However, only a few studies on SIRT6 have been reported, mainly in podocyte and tubular cell models of DKD. Additionally, the catalytic activity of SIRT7 is weak, and a previous report indicated that the suppression of microRNA-20b increased SIRT7 expression and reduced HG-induced podocyte apoptosis (137) (Figure 2).

### 6 CONCLUSIONS AND PERSPECTIVES

Many researchers are working to investigate the etiology of DKD and explore new treatment methods. In our conventional view,
Table 9: DKD studied on other pathways.

| Reference | Drug/Target | Sirtuins | Model | Mechanism of protection | Pathway |
|-----------|-------------|---------|-------|--------------------------|---------|
| (24) | SIRT3 | Reduction of SIRT3 activity | ZDF rat T2DM model | Enhance mitochondrial oxidative stress | CD38 OE, intracellular NAD+/NADH ratio |
| (28) | SIRT4 OE | SIRT4 | HG-induced HK-2 | Attenuate inflammatory response, prevent apoptosis and ROS production | Inhibit apoptosis via the mitochondrial pathway |
| (30) | SIRT6 OE | Increase SIRT6 expression | STZ rats mouse podocyte MPC-5 | Promote M2 macrophage transformation, alleviate renal injury | Upregulate the expression of Bcl-2 and CD206, and decrease expression of Bax and CD66 |
| (31) | SIRT6 OE | Increase SIRT6 expression | STZ-induced C57BL/6 mouse, db/db mouse | Anti-apoptosis and inflammation by increasing autophagic flux | Through inhibition of the Notch pathway |
| (123) | 1α,25-Dihydroxyvitamin D3 | Activating SIRT1 expression | ZDF rats | Antioxidant | PARP1/SIRT1/NOX4 pathway |
| (124) | Puerarin | Increase SIRT1 expression | STZ-induced eNOS-null C57BL/6 male mouse | Anti-oxidative | Through the suppression of NOX4 expression |
| (125) | Carnosine | Upregulation of SIRT1 | HG-induced podocyte | Reduce glycative and liperoxidative stress. | Hsp70, SIRT1, Trx, γ-GCS, HO-1 |
| (126) | Anserine | No effect on SIRT1 | db/db mouse | Anti-oxidant and glycative stress | Hsp70/HO-1 defense system |
| (127) | Inhibition of HIC1 | Rescue SIRT1 expression | HG-induced HK-2 | Reduce ROS accumulation | Target the HIC1/EZH2/DMR1 axis |
| (128) | INT-767 | Restore SIRT1 expression | STZ-induced DBA/2J mouse, db/db mice with T2DM | Prevent inflammation, oxidative stress, and tubulointerstitial fibrosis | Induce mitochondrial biogenesis pathway, prevents activation of fibrotic signaling pathways |
| (129) | SGLT2 inhibition | Restore SIRT1 | Male C57BL/6 db/db mouse | Prevent intracellular glucose entry from the apical side into the proximal tubular cells | GLUT2/importin-α1/HNF-1α pathway |
| (130) | Aerobic exercise training | Restore SIRT1 expression | STZ induced C57BL/6 mouse T1DM | Improve mitochondrial function | MMP, ATP, superoxide production |
| (131) | Apigenin | Increase SIRT3 activity | Male diabetic fatty rats | Relieve mitochondrial oxidative stress | Restore the intracellular NAD+/NADH ratio and SIRT3 activity |
| (132) | Empagliflozin | Restore SIRT3 expression levels | STZ mice | Suppress the EMT, with restoration of all aberrant functions | Inhibiting glucose uptake into the proximal tubule |
| (133) | Liraglutide | Upregulate SIRT3 expression | HG induced HRMCs | Prevent activation of mitochondrial apoptosis | Activate ERK/Yap signaling pathway |
| (134) | INT-777 | Increase activity of SIRT1 and SIRT3 | db/db diabetic mouse | Increase mitochondrial biogenesis, decrease oxidative stress and fibrosis | TGR5 signaling |
| (135) | AFSCs transplantation | SIRT3 OE in AFSCs | C57BL/6 mice | Reduce apoptosis and fibrosis | By modulation of mitophagy |
| (136) | Nampt | | STZ induced male mouse HK-2 | Reduce fibrogenic extracellular matrix remodeling | Nampt/SIRT6 axis |
| (137) | Suppression of microRNA-20b | SIRT7 OE | HG-induced podocyte | Inhibit the podocyte apoptosis | By targeting SIRT7 |
| (148) | AGEs-RAGE system | Down-regulate SIRT1 | AGEs-induced GM6 | Diabetic renal fibrosis | Through the ubiquitin-proteasome pathway |
| (149) | Resveratrol | Restore SIRT1 expression | STZ-induced SD rat as a T1DM model HG-induced mouse podocytes | Modulate angiogenesis, reduce GBM thickness and fibrosis | Via modulating the angiogenic factors |

Sirtuins are a class of HDACs involved in the regulation of longevity and maintaining the stability of nucleosomes by balancing with histone acetylases (13). However, in addition to deacetylate histones, we discovered that sirtuins also regulate many transcription factors, including FOXO1, FOXO3a, STAT3, Smad2/3, NF-κB, p53, and Nrf-2. These transcription factors are involved in regulating many biological processes, including autophagy, oxidative stress, apoptosis, inflammation, EMT, and fibrosis (Figure 3). We found that in DKD studies, the high expression of SIRT1–SIRT7 alleviated or reduced kidney injury through different mechanisms or molecular pathways, of which SIRT1 is the most widely explored. However, an
exception was found in db/db mice, which showed that treatment with glucagon-like peptide-1 reduced SIRT1 expression, while in HUVEC cells, glucagon-like peptide-1 had no significant effect on the SIRT1 expression level. The authors explained that the in vivo results were due to a reduced inflammatory environment that did not stimulate SIRT1, while the in vitro results were due to SIRT1 only participating in transcriptional responses (122). Resveratrol is a recognized activator of SIRT1, but in db/db mice, treatment with resveratrol failed to cause changes in SIRT1 expression, and it still improved oxidative stress and enhanced mitochondrial biogenesis in the AMPK/SIRT1-independent pathway (59). Furthermore, the expression of SIRT1, SIRT2, SIRT3, and SIRT6 was higher than SIRT4, SIRT5, and SIRT7 in the kidney; therefore, the study of SIRT1, SIRT2, SIRT3, and SIRT6 in DKD models is both reasonable and credible (136).
In light of the above, to better illuminate the roles of SIRT1–SIRT7 in DKD and the research progress, we have summarized in vitro and in vivo models of DKD (Figure 3). Our aim is that this review will serve as a valuable reference for future studies of sirtuins and DKD, and provide a theoretical foundation for delaying the pathological process of DKD in the clinic.

AUTHOR CONTRIBUTIONS
WQ and CH contributed to designing and writing the manuscript. DZ and XL approved the submitted version. All authors contributed to the article and approved the submitted version.

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