



SIRT1–SIRT7 in Diabetic Kidney Disease: Biological Functions and Molecular Mechanisms

Wenxiu Qi^{1*†}, Cheng Hu^{2†}, Daqing Zhao¹ and Xiangyan Li¹

¹ Jilin Ginseng Academy, Key Laboratory of Active Substances and Biological Mechanisms of Ginseng Efficacy, Ministry of Education, Jilin Provincial Key Laboratory of Bio-Macromolecules of Chinese Medicine, Changchun University of Chinese Medicine, Changchun, China, ² College of Laboratory Medicine, Jilin Medical University, Jilin City, China

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*Correspondence:

Wenxiu Qi
qiwenxiu0517@163.com

[†]These authors have contributed
equally to this work

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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; hnRNP F, Heterogeneous Nuclear Ribonucleoprotein F; IRPTCs, ROS generation mediates HG stimulation of angiotensinogen expression in immortalized rat RPT cells; ISLQ, Isoliquiritigenin; KD, Knockdown; Namp1, 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 Zn^{2+} , 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 N^{E} -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 glycocalyx, 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* knockdown 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- κ B/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-1 α 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), and the results indicated that the *SIRT1* gene variant rs10823108 and the *FoxO1* gene variant rs17446614 may be associated with DKD in patients with T2DM (35). Another study of gene polymorphisms suggested that, among 1016 patients with T2DM (388 without DKD and 628 with DKD), the transcriptional coactivator p300 rs20551 polymorphism is associated with the development of DKD, and the SIRT1 polymorphism is related to albumin-creatinine ratio progression (36). The researchers analyzed changes in serum VASH-1 and other biomarkers in 692 patients with T2DM, and found that the UACR, VASH-1, HbA1c, ESR, CRP, VEGF, HIF-1 α , TNF- α , and TGF- β 1 levels in all patient groups were significantly higher, and the SIRT1 levels were lower compared to healthy controls. These findings indicated that serum VASH-1 may be associated with the expression of renal inflammation and fibrosis-related factors and have a potential connection with DKD (37). Another two-center, randomized study evaluated 117 patients with stage 2–4 DKD who were treated with sevelamer carbonate. The results showed that sevelamer carbonate increased anti-inflammatory defenses, including nuclear factor like-2, AGE receptor 1, and SIRT1, and decreased pro-inflammatory cytokines, such as TNF receptor 1 (38). In the latest clinical study, 313 patients with T2DM, 102 prediabetic patients, and 100 healthy volunteers were selected to study the relationship between SIRT6 and glucolipid metabolism and urinary protein. The clinical study results showed that SIRT6 increased with glucolipid metabolism and urinary protein markers, and is therefore expected to be a potential biomarker for the early prediction and diagnosis of glucolipid metabolism disorders and related nephropathy (39). The results of the above

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- β 1 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/Wistar 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.

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

5.1 AMPK/Sirtuins/PGC-1 α Pathway

AMPK and SIRT1 are the two main energy sensors, which directly affect the activity of PGC-1 α through phosphorylation and deacetylation, respectively (40). Studies have shown that impaired renal function under HG is directly related to the inactivation of the

TABLE 1 | Cellular model of diabetic nephropathy used to study SIRT1-SIRT7.

	Name	Species	Model
Podocytes		Human/Rat/Mouse	HG, AGE, ADR
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
	mRMCs (Renal mesangial cells)	Mouse	HG
	NMS2	Rat	HG
	Raw264.7	Mouse	HG
	SV40 MES 13	Mouse	\
	Renal tubule	BUMPT cells (Proximal tubule-derived cell line)	Mouse
HK-2 (Proximal tubule epithelial cell)		Human	TGF- β , HG
mProx (Proximal tubular cells)		Murine	H ₂ O ₂
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-1 α signaling pathway (41). The study results showed that CL316, 243, glycyrrhizic acid, and a polysaccharide from okra (OP) all played antioxidant roles, reduced inflammation, and improved fibrosis through activation of the AMPK/SIRT1/PGC-1 α 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-1 α 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 roflumilast 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- κ B pathway (52, 53). Additionally, in HG-induced renal tubule cells, restoration of SIRT3 expression through stanniocalcin-1 activated the AMPK/SIRT3 pathway to produce antioxidant and anti-apoptotic activities (54). Furthermore, cocoa, metformin, glycyrrhizic acid, and probucol 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-1 α pathway, thus inhibiting fibrosis and reducing

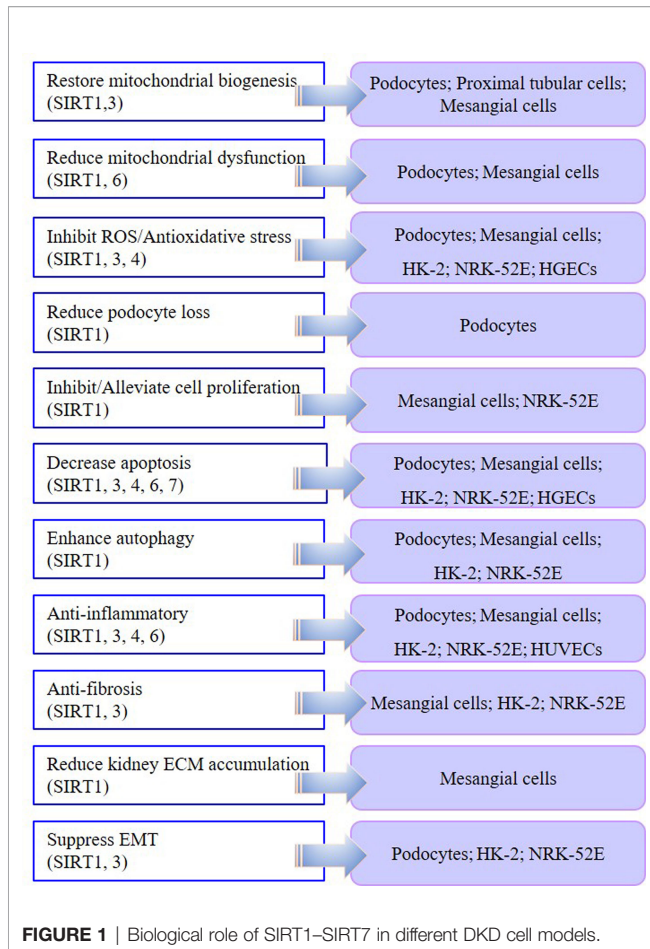
mitochondrial oxidative stress, respectively (61–63). BF175, as an activator of SIRT1, increased SIRT1 activity to acetylate PGC-1 α and activate PPAR γ to reduce podocyte loss and oxidative stress (64). Furthermore, glucagon-like peptide-1, formononetin, and resveratrol enhanced SIRT1 expression in 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 GAS5, 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-1 α 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- κ B-Related Pathway

Previous studies have demonstrated that the ability of SIRT1 deacetylation is critical to control the function of the transcription factor NF- κ B, as SIRT1 modulates various biological responses by deacetylating NF- κ B, including



inflammation and autophagy (78, 79). In DKD models, isoliquiritigenin (ISLQ), baicalin, astragaloside IV, ligustilide, nicotinamide mononucleotide (NMN), and Tangshen formula have been shown to increase or activate SIRT1 through the SIRT1/NF- κ B signaling pathway to improve inflammation, decrease apoptosis, and enhance autophagy (80–86). Moreover, in STZ-induced mouse models, BF175 decreased albuminuria and glomerular disease *via* the transcription factor NF- κ B and p53 pathways (87). Additionally, panax notoginseng saponins (PNS) and baicalin have been found to up-regulate SIRT1 to inhibit inflammation, reactivate autophagy, and alleviate fibrosis *via* the NF- κ B and TGF- β pathways in DKD models (88, 89). Furthermore, in HG-induced HK-2 cells, Na₂S₄ has been shown to directly sulfhydrylate two conserved domains of SIRT1, leading to dephosphorylation and deacetylation of NF- κ B and STAT3, which improves oxidative stress, apoptosis, and the inflammatory response (90). Thus, SIRT1 also has a protective effect on renal function by regulating downstream of NF- κ B in DKD (Table 4).

5.4 Sirtuins and the TGF- β /Smad3 Pathway

TGF- β superfamily members are critical in regulating fibrosis in most chronic kidney diseases, and the inhibition of TGF- β 1

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- β 1 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- β 1 activation (96). Additionally, tetrahydroxystilbene glucoside (TSG) restored SIRT1 expression to alleviate oxidative stress by targeting SIRT1 and TGF- β 1 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- β 1/Smad3 pathway in TGF- β 1-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- β 1/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/FOXO3a or SIRT1/FOXO1 pathway (103–105). Furthermore, fucoxanthin and angiotensin 1–7 restored SIRT1 expression in response to antioxidative stress *via* the AKT/SIRT1/FOXO3a and SIRT1/FOXO1/ATGL signaling pathways in DKD models, separately (106, 107). Moreover, in STZ- and HFD-induced mouse models, purinergic receptor (P2Y2R) deficiency enhanced autophagy and the expression of SIRT1 by AKT/FOXO3a 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/FOXO3a signaling pathway (109). Moreover, it has been reported that progranulin (PGRN) restored both SIRT1 and SIRT3 to maintain mitochondrial biogenesis and autophagy *via* SIRT1/PGC-1 α /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).

TABLE 2 | DKD studies on AMPK/sirtuins/PGC-1 α pathway.

Reference	Drug/Target	Sirtuins	Model	Mechanism of protection	Pathway
(21)	SIRT1 Deficiency	SIRT1 Knockdown	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-1 α signaling pathway
(41)	Resveratrol	Restore SIRT1 expression	db/db mice HG-induced NMS2 mesangial cells	Anti-apoptosis and oxidative stress	AMPK/SIRT1/PGC-1 α axis
(42)	OP	Increase expression of SIRT1	HFD and STZ-induced mice	Suppress apoptosis and oxidative stress	Activate AMPK/SIRT1/PGC-1 α 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-1 α signaling pathway
(44)	Glycyrrhizic acid	Restore SIRT1	Male diabetic db/db mouse	Inhibit ROS	Activate AMPK/SIRT1/PGC-1 signaling
(45)	Resveratrol	Restore SIRT1 expression	db/db diabetic mouse HG-induced HGECs	Inhibit oxidative stress and apoptosis	By activating the AMPK/SIRT1/PGC-1 α axis
(46)	GSPB2	Restore SIRT1 expression	HG-induced podocyte	Reduce mitochondrial dysfunction and apoptosis	Via the AMPK/SIRT1/PGC-1 α axis
(47)	Grape seed procyanidin B2 (GSPB2)	Restore SIRT1 expression	High-dose glucosamine rat mesangial cells	Ameliorate mitochondrial dysfunction and inhibit apoptosis	The activation of the AMPK/SIRT1/PGC-1 α 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 male rat as T1DM model HG-induced rat mesangial cells	Anti-apoptosis and oxidative stress	Activate AMPK/SIRT1 signaling pathway
(51)	Roflumilast	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- κ B pathway
(53)	Geniposide (GE)	Up-regulate protein expression of SIRT1	HFD/STZ-induced mice HG-induced podocyte model	Antioxidative stress, anti-inflammatory	APMK/SIRT1/NF- κ B pathway
(54)	Stanniocalcin-1	Restore SIRT3 protein expression	Male C57BL/6J db/db mice, HG-treated BUMPT cells	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	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)

TABLE 2 | Continued

Reference	Drug/Target	Sirtuins	Model	Mechanism of protection	Pathway
(57)	Probucol	Restore SIRT1 expression	STZ-induced mouse HG-induced HK-2	Attenuate oxidative stress and fibrosis	Suppress p66Shc expression via the AMPK/SIRT1/Ach3 pathway
(58)	Glycyrrhizic acid	Restore SIRT1 expression	HG-induced NRK-52E	Anti-cell proliferation and oxidative stress	Increase AMPK, SIRT1 and Mn-SOD expression
(59)	Resveratrol	No change on SIRT1 expression	Male db/db mouse H ₂ O ₂ exposed murine proximal tubular cells (mProx)	Improve oxidative stress and enhance mitochondrial biogenesis	Via AMPK/SIRT1-independent pathway
(60)	Theobromine	SIRT1 activation	STZ-induced male spontaneously hypertensive rats HG-induced iHMCs	Reduce kidney ECM accumulation	AMPK activation
(61)	Honokiol	Activation of SIRT3	BTBR ob/ob mice with T2DM	Preserve mitochondrial wellness	Through the activation of SOD2 and the restoration of PGC-1 α expression
(62)	Resveratrol	Restore SIRT1 expression	STZ induced CD-1 mouse HG-induced mouse podocytes	Attenuate mitochondrial oxidative stress	Via SIRT1/PGC-1 α pathway
(63)	Salidroside	Restore SIRT1 expression	STZ induced male C57BL/6J mouse	Inhibit fibrosis	SIRT1/PGC-1 α axis
(64)	BF175 (SIRT1 agonist)	Increase SIRT1 activity	OVE26 mouse HG induced human podocytes	Reduce podocyte loss and oxidative stress	Deacetylation of PGC-1 α and activation of PPAR γ
(65)	Formononetin	Increase SIRT1 expression	HFD and low dose of STZ induced rat	Anti-oxidative stress	Increase SIRT1 expression
(66)	Glucagon-like peptide-1	Restore SIRT1	HG-induced mouse podocytes	Reduce apoptosis, ROS, and proinflammatory cytokine	Activation of SIRT1
(67)	Resveratrol	Enhance SIRT1 expression	STZ-induced T2DM rat HG-induced NRK-52E cells	Suppress apoptosis through promoting autophagy activity	SIRT1 activation
(68)	lncRNA GAS5 OE	Enhance the expression level of SIRT1	HG induced mesangial cells (RAW264.7)	Inhibit cell proliferation and fibrosis	By sponging miR-221 and modulating SIRT1 expression
(69)	lncRNA SOX2OT OE	Increase SIRT1 expression	HG-induced human podocytes cells (HPCs)	Induce autophagy	miR-9/SIRT1 axis
(70)	Downregulation of miR-138	Bind the 3'-UTR of SIRT1	HG-induced mice podocytes db/db mice kidney tissues	Anti-inflammatory	The regulatory axis of miR-138/SIRT1/p38/TTP
(142)	Olmесartan	Restore SIRT1 expression	db/db mouse HG-induced podocytes	Inhibit podocyte apoptosis	Through inhibiting angiotensin II/p38/SIRT1
(143)	Selenium nanoparticles	Up-regulate SIRT1	STZ induced SD male rat	Anti-oxidative stress and lower apoptosis	Activate HSP-70/SIRT1 axis
(144)	hnRNP F OE	Increase SIRT1 expression	db/db hnRNP F-Tg mouse HG-induced rat IRPTCs	Against oxidative stress, tubulointerstitial fibrosis, and RPTC apoptosis	Via stimulation of SIRT1 expression and signaling
(145)	KD miR-133b and miR-199b	Upregulate SIRT1	Old male OLETF rat (spontaneous T2DM) TGF- β 1-treated HK-2	Attenuate EMT and renal fibrosis	By targeting SIRT1
(146)	Inhibiting PARP1	Upregulate the expression of SIRT1	db/db mice HG-induces mesangial cells	Decrease kidney ECM accumulation	AMPK/PGC-1 α signaling pathway

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-1 α -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-1 α signaling (117–119). Additionally, in AGE-induced human

TABLE 3 | DKD studies on SIRT1/p53 pathway.

Reference	Drug/Target	Sirtuins	Model	Mechanism of protection	Pathway
(73)	Inhibition miR-155-5p	Binding to the SIRT1 3'UTR region	HG-induced HK-2	Promote autophagy	A signaling loop p53/miR-155-5p/SIRT1
(74)	Silencing of miR-150-5p	Targeted the 3'-UTR of SIRT1	HG-induced podocyte injury	Activate AMPK-dependent autophagy	Targeting SIRT1/p53/AMPK Pathway
(75)	H ₂ S	Upregulate SIRT1	STZ induced male rat	Suppress oxidative stress and apoptosis	SIRT1, SOD, caspase-3, p53, MDA
(76)	Resveratrol	Restore SIRT1 expression	STZ-induced Wistar rat	Inhibit apoptosis	SIRT1/p53 axis
(77)	Calcium dobesilate	Enhance SIRT1 signaling	HG-induced HK-2 Renal interstitial fibrosis induced by unilateral ureteral obstruction (UUO) mouse model HUVECs	Suppress EMT progression and promote anti-apoptotic	Via activating the SIRT1/p53 signaling pathway

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	Via SIRT1/NF-κB/microR-29/Keap1 signal pathway
(80)	Baicalin	Increase the expression of SIRT1	HG-induced podocyte	Decrease apoptosis of high glucose induced podocyte	SIRT1/NF-κB signaling pathway
(81)	ISLQ	Restore SIRT1	Male rat by STZ	Antioxidant, anti-inflammatory, and reduce collagen accumulation	Normalize the SIRT1/NF-κB balance, control NLRP3 expression
(82)	Astragaloside IV	Increase SIRT1 expression	Polygenic KK-Ay mice models	Inhibit EMT and enhance autophagy	SIRT1/NF-κB pathway
(83)	Tangshen formula	Activate SIRT1	STZ+HFD induced SD rat	Improve inflammation	Through SIRT1/NF-κB pathway
(84)	NMN	Restore SIRT1 expression	STZ induced SD male rat	Alleviate inflammatory-fibrosis	Nampt/NF-κB p65 and SIRT1 signaling pathway
(85)	Astragaloside IV	Restore SIRT1 expression	HG induced HBZY-1 HFD-induced KK-Ay mouse	Enhance autophagy	SIRT1/NF-κB pathway
(86)	Ligustilide	Promote SIRT1 protein expression	Mesangial cell (SV40 MES 13) STZ combined with a HFD rat	Attenuate podocyte injury	Suppressing the SIRT1/NF-κB signaling pathways
(87)	BF175	Increase SIRT1	STZ mice	Reduce albuminuria and glomerular disease	NF-κB and p53 signaling pathways
(88)	Baicalin	Enhance level of 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
(89)	PNS	Up-regulate SIRT1	Alloxan-induced SD rat	Inhibit inflammation and antioxidant	Through decreasing the NF-κB-mediated induction of inflammatory cytokines and TGF-β1
(90)	Na ₂ S ₄	Sulfhydrating SIRT1	HG-induced HK-2 cells STZ mice	Restrain the overproduction of inflammation cytokine and ROS	Suppressing phosphorylation and acetylation of p65 NF-κB and STAT3

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-1 α -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 1 α , 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

TABLE 5 | DKD studied on sirtuins and TGF- β 1/Smad3 pathway.

Reference	Drug/Target	Sirtuins	Model	Mechanism of protection	Pathway
(95)	Reduce miR-34a-5p	Targeting the 3'UTR of SIRT1	HFD/STZ induced C57BL/6 mouse HG induced HK-2	Inhibit fibrosis	TGF- β 1 signaling
(96)	Oligo-Fucoidan	Restore SIRT1 expression	AGE stimulated NRK-52E cells STZ and nicotinamide combined with a HFD mouse	Improve kidney disease caused by excessive fibrosis	Suppress the HMGB1/RAGE/NF- κ B/TGF- β 1/TGF- β 1R/FN pathway and HIF-1 α activation
(97)	TSG	Restore SIRT1 expression	STZ-induced SD rat HG-induced HBZY-1	Alleviate oxidative stress	SIRT1 and TGF- β 1 pathway
(98)	Inhibition of miRNA-135a-5p	Target SIRT1 3'UTR	TGF- β -induced HK-2 and HMCs	Inhibit renal fibrosis	Target SIRT1 and inactivating Smad3 signaling
(99)	FOXO3a	Bind to the SIRT6 promoter and promote SIRT6 expression	db/db T2DM mouse HG-induced HK-2	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	HG-induced HK-2	Antagonize high glucose-induced apoptosis	AKT/FoxO signaling pathway
(103)	Resveratrol and rosuvastatin	Restore SIRT1 mRNA expression	STZ-induced Wistar rat	Attenuate oxidative stress damage	Through increasing FOXO1/SIRT1 dependent antioxidant defenses
(104)	Resveratrol	Restore SIRT1 expression	STZ-induced Wistar rat HG-induced HK-2	Reduce oxidative stress damage	SIRT1/FOXO3a pathway
(105)	Resveratrol	Restore SIRT1 expression	STZ-induced SD rat	Anti-oxidative stress	SIRT1/FOXO1 pathway
(106)	Fucoanthin	Restore SIRT1	GMCs cultured in HG	Antioxidative stress and anti-fibrosis	AKT/SIRT1/FOXO3a signaling
(107)	Angiotensin 1-7	Increase SIRT1 expression	db/db mouse T2DM model	Reduce oxidative stress, inflammation, and lipotoxicity	SIRT1/FOXO1/ATGL pathway
(108)	P2Y2R deficiency	Increased SIRT1 expression	HFD and STZ mouse	Enhance autophagy response	AKT/FOXO3a and SIRT1 signaling pathways
(109)	Pyroloquinoline quinine	Upregulate SIRT3 expression	HG-induced HK-2	Anti-oxidative stress and apoptosis	PI3K/AKT/FOXO3a pathway
(110)	PGRN	Restore SIRT1 and SIRT3	STZ-induced mice and patients with DKD, HG-treated podocytes	Maintain mitochondrial biogenesis and mitophagy	Via PGRN/SIRT1/PGC-1 α /FOXO1 signaling
(147)	Reduce LncRNA MALAT1	Restore SIRT1 expression	HG induced HK-2	Renal protective effect	MALAT1/FOXO1/SIRT1 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	Reverse the downregulation of SIRT1 protein expression and deacetylase activity	AGEs-induced GMCs	Anti-oxidative stress and fibrosis	Activation of SIRT1/Nrf2/ARE pathway
(113)	Formononetin	Up-regulated the expression of SIRT1	GMCs exposed to HG	Antioxidative stress, prevent the progression of renal fibrosis	Nrf2/ARE signaling pathway
(114)	Resveratrol (SIRT1 activator)	Restore SIRT1 expression	STZ-induced SD rat AGEs-induced SD rat primary GMCs	Antioxidative and fibrosis	By activating the Nrf2/ARE pathway
(115)	SRT2104	Enhance SIRT1 expression and activity	STZ induced C57BL/6 mouse	Protection against the oxidative stress, inflammation, fibrosis	SIRT1/p53/Nrf2 pathway
(116)	ISLQ	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

TABLE 8 | DKD studied on STAT and HIF-1 α pathway.

Reference	Drug/Target	Sirtuins	Model	Mechanism of protection	Pathway
(26)	SIRT3 high expression	SIRT3	STZ-induced mice model (fibrotic model: CD-1, less fibrotic model: C57Bl6)	Inhibit aberrant glycolysis and combat fibrosis	By activation of PKM2 dimer formation and HIF-1 α accumulation
(117)	Silencing of miR-217	Restore SIRT1 expression	HG-induced RMCs	Restrain inflammation and fibrosis	Through SIRT1/HIF-1 α signaling pathway
(118)	LincRNA 170002014Rik	SIRT1	C57BL/KsJ db/db mouse	Alleviate cell proliferation and fibrosis	miR-34a-5p/SIRT1/HIF-1 α signaling
(119)	Connexin 43	Increase SIRT1 levels	HG induced mouse mesangial cells db/db mice HG-induced NRK-52E cells	Inhibit the EMT progress and renal tubulointerstitial fibrosis	SIRT1/HIF-1 α signaling pathway
(120)	PYR	Restore SIRT1 expression	db/db mouse AGE-induced human podocytes	Reduce kidney injury	Reduced p65 and STAT3 acetylation
(121)	EX-527	Reduce SIRT1 expression, increase SIRT3 expression	HFD-induced diabetic rats	Anti-fibrosis and anti-inflammation	Block the phosphorylation level of EGFR and PDGFR, blockade of STAT3 signaling
(122)	Glucagon-like peptide-1	Decrease SIRT1 expression	db/db mouse AGEs and HG induced HUVECs	Improve the inflammatory changes	Inhibit the JAK/STAT pathway

to decrease glycativ and lipoperoxidative stress in HG-induced podocytes *via* the Hsp70/HO-1 pathway. Another report showed that anserine revealed anti-oxidant and glycativ 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 (127–130). These results suggest that SIRT1 largely exhibits anti-inflammatory and anti-oxidant effects through different signaling pathways in DKD models.

5.8.2 Pathways Associated With SIRT3 in DKD

Apigenin (CD38 inhibitor) and empagliflozin (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 Nampt-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 mouse podocytes	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 CD86
(31)	SIRT6 OE	Increase SIRT6 expression	STZ-induced C57BL/6 mouse, db/db mouse AGE/HG induced human podocytes	Anti-apoptosis and -inflammation by increasing autophagic flux	Through inhibition of the Notch pathway
(123)	1 α ,25-Dihydroxyvitamin D3	Activate SIRT1	ZDF rats	Antioxidant	PARP1/SIRT1/ NOX4 pathway
(124)	Puerarin	Increase SIRT1 expression	STZ-induced eNOS-null C57BL/6 male mouse HG-induced murine podocytes	Anti-oxidative	Through the suppression of NOX4 expression
(125)	Carnosine	Upregulation of SIRT1	HG-induced podocyte	Reduce glycativ and lipoperoxidative stress.	Hsp70, SIRT1, Trx, γ -GCS, HO-1
(126)	Anserine	No effect on SIRT1	db/db mouse HG-induced HK-2	Anti-oxidant and glycativ stress	Hsp70/HO-1 defense system
(127)	Inhibition of HIC1	Rescue SIRT1 expression	HG-induced HK-2	Reduce ROS accumulation	Target the HIC1/EZH2/DNMT1 axis
(128)	INT-767	Restore SIRT1 expression	STZ-induced DBA/2J mouse, db/db mice with T2DM	Prevent inflammation, oxidative stress, endoplasmic reticulum stress, and tubulointerstitial fibrosis	Induce mitochondrial biogenesis pathway, prevents activation of pofibrotic signaling pathways
(129)	SGLT2 inhibition	Restore SIRT1	Male C57BL/6 db/db mouse HG-cultured porcine LLC-PK1 cells	Prevent intracellular glucose entry from the apical side into the proximal tubular cells	GLUT2/importin- α 1/HNF-1 α 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 HG-induced HK-2 cells	Relieve mitochondrial oxidative stress	Restore the intracellular NAD ⁺ /NADH ratio and SIRT3 activity
(132)	Empagliflozin	Restore SIRT3 levels	STZ mice HG-induced HK-2	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/KsJ db/db mouse	Reduce apoptosis and fibrosis	By modulation of mitophagy
(136)	Nampt	SIRT6	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 GMCs	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- κ B, 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

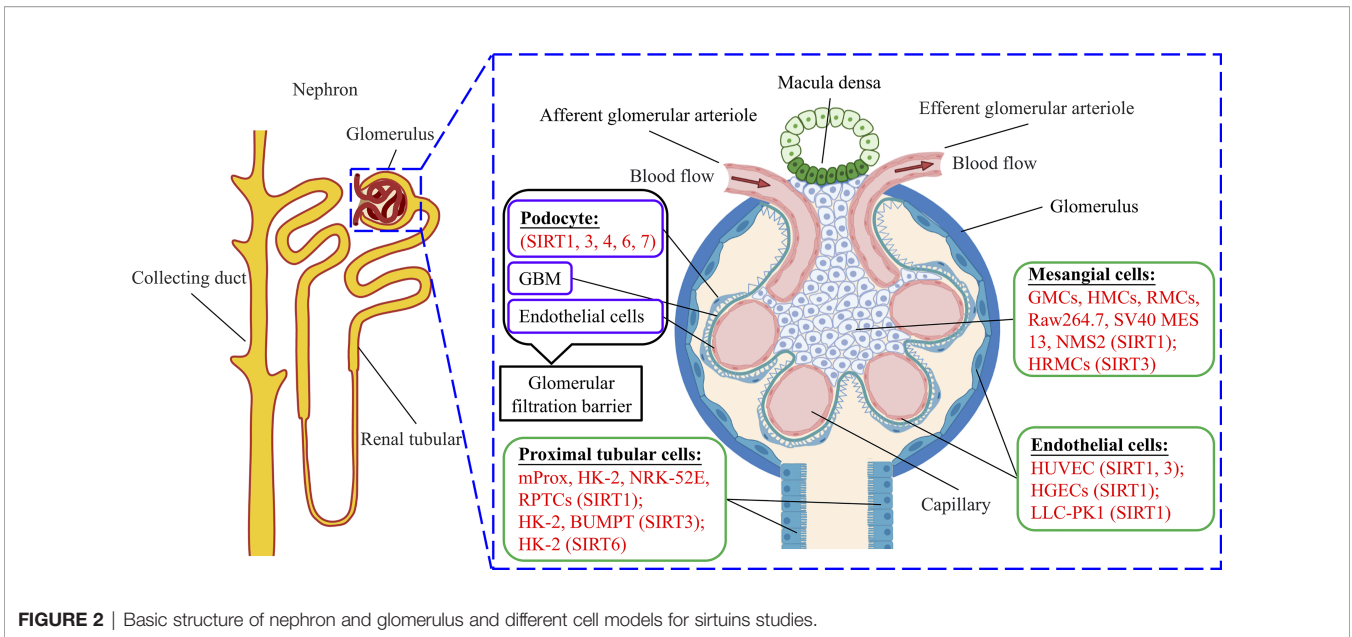


FIGURE 2 | Basic structure of nephron and glomerulus and different cell models for sirtuins studies.

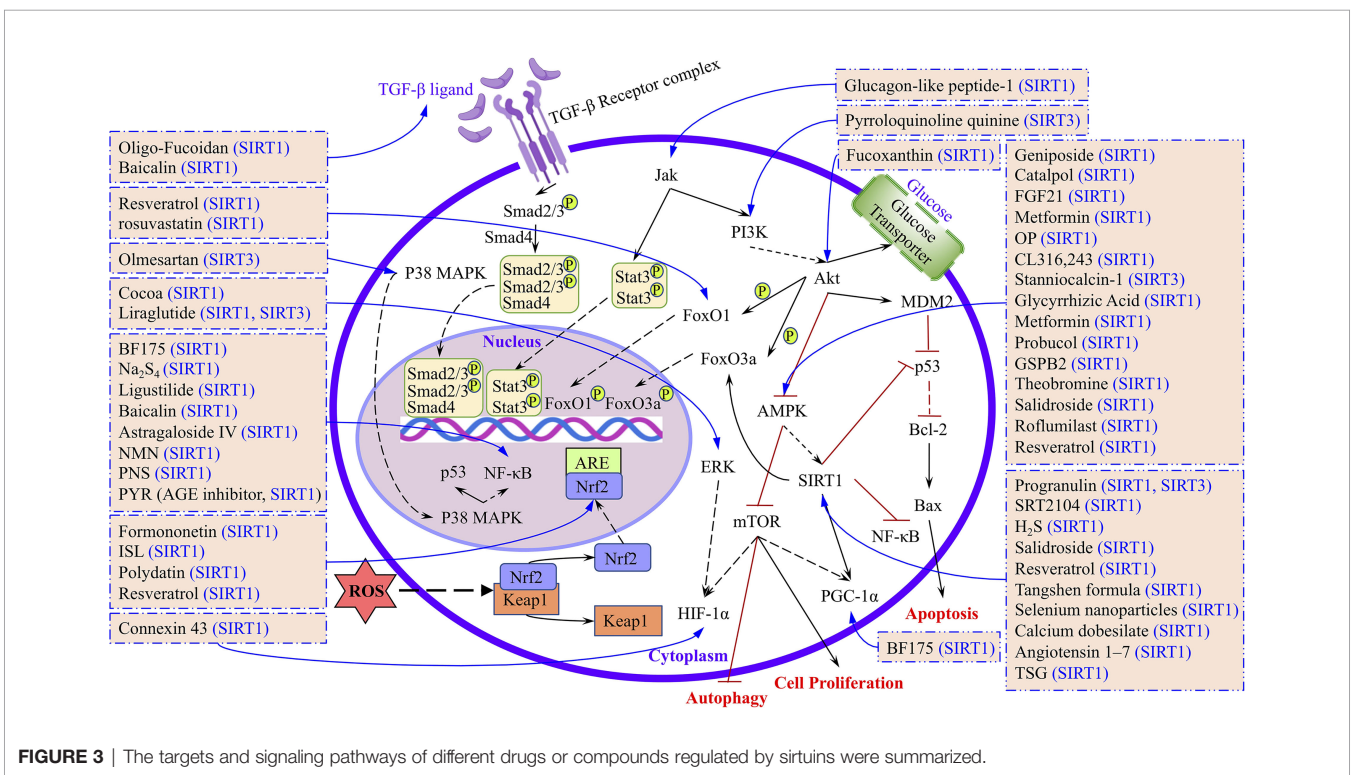


FIGURE 3 | The targets and signaling pathways of different drugs or compounds regulated by sirtuins were summarized.

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 the therapeutics, targets, and signaling pathways involved in *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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