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REVIEW

Programmed Cell Death in Diabetic Kidney Disease: Mechanisms and Therapeutic Targeting

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Abstract: The escalating incidence and mortality of diabetic kidney disease (DKD) underscore the critical need to elucidate its pathogenesis. Programmed cell death (PCD) plays a dual role in maintaining physiological homeostasis and driving pathological processes in DKD. Accumulating evidence demonstrates that apoptosis, autophagy, pyroptosis, and ferroptosis contribute directly or indirectly to DKD progression via distinct gene-regulated signaling pathways. Recently identified PCD modes (eg, necroptosis, parthanatos) remain poorly characterized in DKD, with emerging evidence suggesting crosstalk between different PCD pathways. This review synthesizes current knowledge on PCD-mediated DKD pathogenesis and PCD-targeted therapies, while highlighting research limitations (eg, unclear PCD interactions, translational gaps). We propose that dissecting the multifaceted roles of PCD in DKD will deepen mechanistic understanding and accelerate the development of novel therapeutics, offering significant scientific and clinical benefits.

Keywords: diabetic kidney disease, programmed cell death, apoptosis, autophagy, pyroptosis, ferroptosis

Introduction

Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD) and a major microvascular complication of diabetes.[1] According to IDF data, the global diabetic population has reached 643 million and is projected to rise to 853 million by 2050, equivalent to one-eighth of the world's population.[2] Between 20% and 40% of diabetic patients develop DKD, associated with significantly increased morbidity and mortalityreflected in a 10-fold higher incidence of kidney failure compared to non-diabetics.[3] By exploring mechanisms to identify novel therapeutic approaches for DKD, targeting programmed cell death (PCD) pathways offers a promising strategy to prevent, treat, or accelerate recovery by limiting renal parenchymal cell loss and inflammation.

Cell death, a fundamental process in physiological homeostasis and pathological states,[4,5] is classified as accidental (ACD) or regulated (RCD).[6] RCD, a genetically controlled suicide mechanism initiated upon failed adaptation to stress,[7] is crucial for development and tissue renewal.[8] Under pathological conditions like DKD, dysregulated RCD (synonymous with PCD) contributes to organ dysfunction.[6,9–12]

More than a dozen distinct PCD modes exist, each defined by specific molecular pathways and functional consequences.[13] While evolved to protect organisms,[14] aberrant PCD drives pathology. This review synthesizes current knowledge on both established PCD pathways (apoptosis, autophagy, pyroptosis, ferroptosis) and emerging forms (eg, necroptosis, parthanatos, alkaliptosis, oxeiptosis)[13] within DKD pathogenesis. Critically, therapeutic targeting of PCD must balance efficacy with safety, considering impacts on physiological homeostasis.[15] Understanding these mechanisms holds significant scientific and clinical potential for developing novel DKD therapies.

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Apoptosis in Diabetic Kidney Disease

Apoptosis is one of the main causes of DKD cell death.[16] Apoptosis comprises two main stages: initiation and execution. Based on the initiation mechanism, apoptotic pathways include receptor-mediated (exogenous), perforin/granzyme, and mitochondrial (intrinsic) pathways. The process involves receiving apoptotic signals, regulating molecular interactions, activating caspases, and culminating in a cascade reaction.[17] High glucose stimulates podocytes to change albumin-related mitochondrial dynamics, leading to apoptosis.[18] STZ-induced α-2u globulin nephropathy during DKD is associated with dysmolar deterioration, tubular adaptive injury, and mitochondria-driven apoptosis.[19] CD36 promotes DKD progression by mediating apoptosis through the Wnt/β-catenin pathway;[20] conversely, its inhibition ameliorates DKD by suppressing NLRP3 inflammasome activation, thereby reducing inflammation and tubular epithelial cell apoptosis.[21] In DKD, extracellular vesicle (EV) transfer between small tubular epithelial cells and macrophages forms a negative feedback loop, promoting renal inflammation, apoptosis, and disease progression.[22] The dysfunction of glomerular endothelial cells induced by the diabetic microenvironment secretes factors that cause podocyte apoptosis, and the increase of mitochondrial superoxide levels in glomerular endothelial cells leads to podocyte dysfunction and pathology, contributing to the loss of DKD glomerular filtration barrier.[23] Different genes are closely related to DKD through the regulation of apoptosis. Figure 1 shows that different factors regulate DKD through apoptosis (Figure 1). In DKD mice, microtubule associated protein 4 (MAP4) phosphorylation (p-MAP4) was elevated, crotubules and F-actin filaments were reordered, and cell permeability was enhanced. It is also associated with dedifferentiation and apoptosis of podocytes.[24] Under high glucose conditions, Smad3-dependent ezrin activation upregulates Nox4 expression and ROS production by suppressing PKA activity; MPC2 mediates mitochondrial dysfunction; and histone deacetylase 4 (HDAC4) promotes calcineurin upregulation, collectively contributing to podocyte apoptosis.[25,26] In addition, pro-

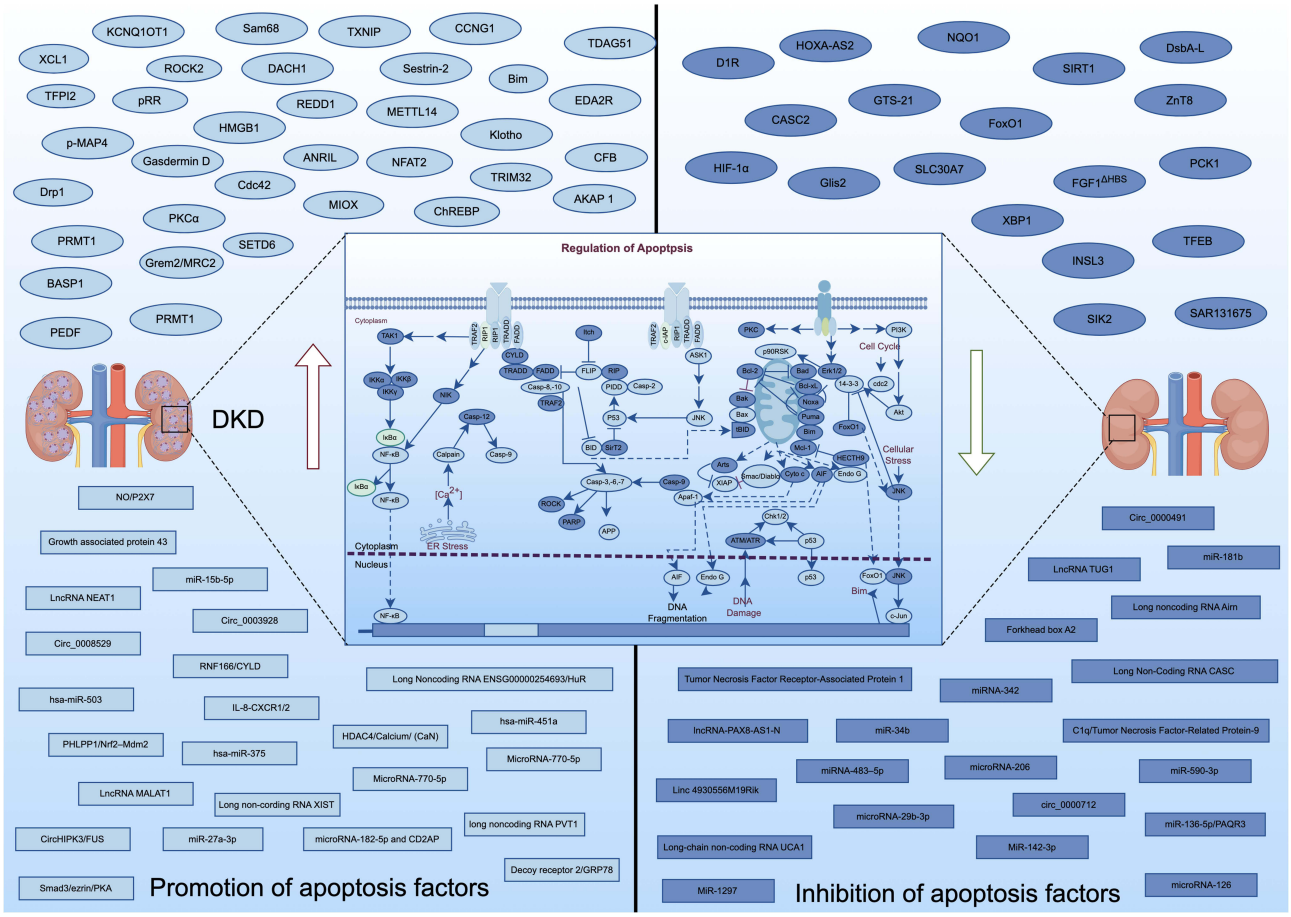

Figure 1 Shows that different factors regulate DKD through apoptosis. By Figdraw.

apoptotic factor Bim promotes the activation of nuclear factor of activated T cells 1 (NFAT2) and induces the down-regulation of lncRNA NONHSAT179542.1, leading to cytoskeletal injury, and promoting high glucose-induced podocyte injury.[27] Klotho activates Nuclear factor-erythroid 2-related factor 2 (Nrf2) signaling or regulates endoplasmic reticulum stress (ERS) and reactive oxygen species (ROS) and improves renal function and glomerulosclerosis in podocyte injury and DKD mice by regulating apoptosis.[27] Firstly, the study of different genes promoting DKD through apoptosis was discussed. Notch signaling pathway regulates oxidative damage and apoptosis by regulating mitochondrial dynetin and biogenetic genes,[28] Nrf2 regulates mitochondrial ribosomal protein L12 (MRPL12) transcription by changing mitochondrial function and apoptosis level,[29] ATP binding cassette subfamily A member 1 (ABCA1) deficiency leads to apoptosis and inflammation, destroys endocalyx barrier, and induces ERS.[30] A-kinase anchoring protein (AKAP) 1 mediates mitochondrial fission by regulating the phosphorylation of dynamin-related protein 1 (Drp1), which enhances podocyte apoptosis.[31] BASP1 (brain acid-soluble protein) activates p53 and induces podocyte apoptosis by regulating Wilms' tumor 1 transcription factor (WT1),[32] gremlin 2, DAN family BMP antagonist (Grem2) and mannose receptor C-type 2 (MRC2) can induce apoptosis,[33,34] ectodysplasin A2 receptor (EDA2R) can induce apoptosis and dedifferentiation of podocyte cells by enhancing ROS production,[35] Decoy receptor 2 interacts with glucose regulated protein 78 (GRP78) to regulate the apoptosis phenotype mediated by caspase-3,[36] renal (pro)renin receptor (pRR) induces mitochondrial dysfunction and upregulates the mitochondrial NADPH oxidase 4 (NOX4)/superoxide dismutase 2 (SOD2)/uncoupling protein 2 (UCP2) signaling pathway,[37] up-regulation of cell division cycle 42 (Cdc42) can increase BCL2 (B-cell lymphoma-2) associated X (Bax) and cleaved caspase-3 levels and decrease the expression of Bcl-2, inducing podocyte apoptosis,[38] Alk1 haploinsufficiency leads to glomerular apoptosis, glomerular basement membrane thickening, and podocyte loss,[39] and X-C motif chemokine ligand 1 (XCL1) induces inflammation and cell apoptosis by regulating p53/Nuclear Factor -Kappa B (NF-κB) pathway,[40] the PH domain and leucine rich repeat protein phosphatase 1 (PHLPP1)/Nrf2-Mdm2 axis induces apoptosis of renal cells by regulating the forkhead box O1 (FoxO1) cytoplasmic shuttle,[41] Rho associated coiled-coil containing protein kinase 2 (ROCK2) can inhibit peroxisome proliferator-activated receptors α (PPARα), rewiring cell programs, and negatively regulate transcription of fatty acid oxidation-related genes induce apoptosis,[42] Sestrin-2 regulates mitochondrial dysfunction and apoptosis of podocytes through protein kinase AMP-activated catalytic subunit alpha 1 (AMPK),[43] Myo-inositol Oxygenase (MIOX) overexpression can enhance apoptosis by regulating oxidative and ERS,[44] methyltransferase 14 (METTL14) activates MAPK/mitogen-activated protein kinase 1 (ERK) pathway through m6A modification of taurine up-regulated 1 (TUG1) to promote apoptosis of renal tubular epithelial cells and ERS,[45] promote DKD renal injury, and aggravate renal dysfunction. Inhibition of activating transcription factor 5 (ATF5) promotes mitochondrial ROS levels and apoptosis by regulating mitochondrial unfolded protein response,[46] inducing DKD kidney injury. The progression of DKD in mice with phosphofurin acidic cluster sorting protein 2 (PACS-2) gene knockout was accelerated, with mitochondria-associated ER membranes (MAM) dysfunction apoptosis, and fibrosis.[47] At the same time, regulating some genes can also treat DKD by controlling apoptosis. A carbohydrate responsive element binding protein (ChREBP) deficiency can inhibit oxidative stress (OS) and ERS, down-regulate the expression of Bax, upregulate the expression of Bcl-2, and down-regulate cleaved caspase-3 levels,[48] METTL14 silence reduces ROS production and inflammatory cytokine levels and inhibits apoptosis.[49] The complement component 1, q subcomponent (C1q)/Tumor Necrosis Factor-Related Protein-9 inhibits apoptosis of cells under OS,[50] D(P)H: quinone oxidoreductase 1 (NQO1) enhances intracellular NAD+/NADH level regulation Sirtuin 1 (Sirt1), decreased Bax/Bcl-2 ratio and cleaved caspase-3 expression,[51] GTS 21, a selective alpha 7 nicotinic acetylcholine receptor agonist, reduced diabetes-induced kidney injury by decreasing DKD mesangial matrix expansion and apoptosis, and Bax and cleaved caspase-3 expression,[52] cancer susceptibility candidate 2 (CASC2) increased Bcl-2 levels by regulating the miR-144/suppressor of cytokine signaling 2 (SOCS2) axis. Decreased cleaved caspase-3 expression reduces apoptosis, inflammation, and fibrosis,[53] and dopamine 1 receptor (D1R) activation protects DKD podocytes from apoptosis and oxidative damage through the PKA/NADPH oxidase 5 (NOX-5)/p38 MAPK axis.[54] The absence of thioredoxin-interacting protein (TXNIP) mitigated podocellular apoptosis by inhibiting p38 AMPK or mechanistic target of rapamycin kinase (mTOR) signaling pathways,[55] and silted cyclin G1 (CCNG1) improved the expression of Bcl-2, Bax, and p53 by modulating the MDM2/p53 signaling pathway.[56] Down-regulation of SET domain containing 6 (SETD6) can improve mitochondrial dysfunction and inhibit apoptosis by activating the Nrf2-Keap1 signaling

pathway.[57] After RING-finger protein 166 (RNF166) knockout interacts with CYLD to reduce cleaved Caspase-9 expression and inhibit mitochondrial damage and apoptosis.[58] The zinc transporter 7 in SLC30 family (SLC30A7) regulates apoptosis through NFE2 like bZIP transcription factor 2 (NFE2L2)/heme oxygenase 1 (HMOX1) signaling pathway,[59] GLIS family zinc finger 2 (Glis2) alleviates apoptosis through β-catenin signaling pathway.[60] HIF-1α (hypoxia inducible factor 1 subunit alpha) alleviates ROS accumulation and apoptosis through mitochondrial kinetic control mediated by HO-1 (heme oxygenase 1),[61] Forkhead box A2 mediated upregulation of lncRNA SOX2OT inhibits OS and apoptosis by promoting SIRT1,[62] while lack of complement factor B (CFB) improves apoptosis, ERS, and OS by inhibiting ceramide synthesis.[63] INSL3 (insulin like 3) can inhibit the rate of apoptosis.[64] Polysulfide-mediated sulfhydration of SIRT1 can inhibit OS, apoptosis, and inflammation by inhibiting the phosphorylation and acetylation of p65 NF-κB and signal transducer and activator of transcription 3 (STAT3).[65] FoxO1 inhibits STAT1 level and attenuates apoptosis,[66] FGF1ΔHBS inhibits apoptosis and inflammatory response by activating PPARα.[67] Tumor Necrosis Factor Receptor-Associated Protein 1 alleviates OS and apoptosis by preventing abnormal opening of mPTP and maintaining mitochondrial structure and function.[68] SIK2 (salt inducible kinase 2) overexpression activates HSF1 (heat shock transcription factor 1)/Hsp70 (heat shock protein 70) by inhibiting histone acetyltransferase activity of p300, thereby reducing ERS-mediated apoptosis of tubule epithelial cells,[69] and SAR131675 inhibits EGF-C and VEGFR-3, reducing OS, apoptosis, and related inflammatory responses,[70] Disulphide-bond A oxidoreductase-like protein (DsbA-L) by maintaining the mitochondrial associated ER membrane and the integrity of MAM plays an anti-apoptotic role,[71] and the lack of TDAG51 (pleckstrin homology like domain family A member 1) activates Nrf2 through the Akt-GSK (inosine/guanosine kinase) 3β pathway, reducing apoptosis, OS and inflammation.[72] Gasdermin D knockdown down-regulates the expression of Bax and caspase-3 through the C-Jun N-Terminal Kinase (JNK) pathway and reduces REDD1 (DNA damage inducible transcript 4)-regulated AKT/GSK-3β/Nrf2 pathway by regulating apoptosis and inflammation.[73] Both decreasedDNA damage response 1 (REDD1) expression[74] and Tripartite motif-containing protein 32 (TRIM32) inhibition[75] confer protection against high glucose-induced podocyte injury through convergent potentiation of Nrf2 signaling via modulation of the AKT/GSK-3β pathway. Inhibition of high mobility group box 1 (HMGB1) can reduce podiocyte apoptosis by regulating autophagy flux,[76] and ZnT8 can inhibit the expression of apoptotic protein through the (TNFAIP3) TNF alpha induced protein 3NF-κB pathway and play an anti-apoptotic role.[77] IL-8 (interleukin-8)-CXCR1/2 axis blockade could alleviate podocyte apoptosis and DNA damage,[78] and overexpression of PCK1 (phosphoenolpyruvate carboxykinase 1) could reduce apoptosis and collagen IV deposition around the tube, protecting mitochondrial defects.[79] ANRIL knockdown can improve metabolic pathway, apoptosis, extracellular matrix synthesis and degradation, NF-κB-related pathway, AGE (advanced glycation end products)-RAGE (receptor for advanced glycation end products) interaction, etc.;[80] TFPI2 (tissue factor pathway inhibitor 2) interacts with TGF-β2 (transforming growth factor beta 2) pathway to promote EMT of DKD and knockdown TFPI2 can reduce apoptosis.[81] (+)-trans-Cannabidiol-2-hydroxy pentyl is a dual CB1R antagonist/CB2R agonist to reduce CD3+T cell infiltration by inhibiting apoptosis and inflammatory response.[82]

miRNA Regulates Cell Apoptosis and DKD

miRNA regulates apoptosis and DKD. Sequencing of patients with type 2 DKD showed that mirnas of urinary extracellular vesicles such as hsa-miR-375, hsa-miR-503, and hsa-miR-451a were involved in apoptosis and inflammation and promoted the occurrence of DKD[83] and MicroRNA-494-3p promotes apoptosis by targeting SOCS6 (suppressor of cytokine signaling 6).[84] Mir-27a-3p regulation prohibition and TMBIM6 (transmembrane BAX inhibitor motif containing 6) inhibition of extracellular matrix accumulation, mitochondrial dysfunction, ERS, and apoptosis.[85] Noncoding RNA XIST can regulate apoptosis through the miR-423-5p/HMGA2 (high mobility group AT-hook 2) axis.[86] MicroRNA-182-5p and CD2AP (CD2 associated protein) dysregulation induce podocyte apoptosis,[87] and miR-770-5p promotes podocyte apoptosis and inflammatory response by targeting TIMP3 (TIMP metallopeptidase inhibitor 3).[88] CircHIPK3/FUS complex leads to the upregulation of ectodysplasin A2 receptor (EDA2R) and promotes the activation of apoptosis.[89] Long Noncoding RNA (lncRNA) ENSG00000254693 interacts with HuR to induce inflammation and apoptosis,[90] LncRNA MALAT1 induces apoptosis, ROS production, and inflammation through activation of LIN28A (lin-28 homolog A) and the Nox4/AMPK/mTOR signaling axis[91] and increases apoptosis and inflammation through miR-15b-5p/TLR4 (toll like

receptor 4) signaling axis.[92] LncRNA NEAT1 regulates inflammation, OS, and apoptosis through the miR-423-5p/GLIPR2 (GLI pathogenesis related 2) axis,[93] miR-20a over-expression enhanced cell proliferation, inhibited cell apoptosis, and suppressed the inflammatory response of HK-2 cells,[94] and high glucose induces mesangial cell apoptosis through miR-15b-5p.[95] High glucose-induced KCNQ1OT1 (KCNQ1 opposite strand/antisense transcript 1) increases Sema3A (semaphorin 3A) expression through sponging miR-23b-3p, promoting inflammatory response and apoptosis;[96] Circ_0003928 acted as a sponge for miR-506-3p, HDAC4 (histone deacetylase 4) regulates OS and apoptosis,[97] DACH1 (dachshund family transcription factor 1), a novel target of miR-218, promote apoptosis and inflammatory response,[98] encourages and is implicated in preventing DKD kidney injury and renal dysfunction. Circ_LARP4 is decreased in the DKD model, after sponging miR-424 treatment, Circ_LARP4 overexpression leads to increased apoptosis.[99] LncRNA PVT1 silencing enhances Bcl-2 expression by upregating FOXA1. Down-regulation of Bax and cleaved caspase-3 expression inhibited podocyte apoptosis,[100] and Circ_0000491 inhibited apoptosis, inflammation, OS, and fibrosis by regulating miR-455-3p/Hmgb1 (high mobility group box 1) signaling axis.[101] The miR-181b promotes cell survival and inhibits apoptosis,[102] LncRNA Airn alleviates the decline of cell viability and inhibits apoptosis by binding Igf2bp2 (insulin like growth factor 2 mRNA binding protein 2) and promoting the translation of Igf2 and Lamb2 (laminin subunit beta 2);[103] LncRNA TUG1 reduces ERS and apoptosis by inhibiting PU.1/RTN1 (reticulon 1) signaling pathway.[104] Circ_0008529 knockdown can reduce inflammation and apoptosis through the Circ_0008529-mediated miR-485 5p/WNT2B (Wnt family member 2B) signaling pathway,[105] and mirNA-483-5p targets HDCA4 (histone deacetylase 4) to inhibit inflammation, ROS production, and apoptosis.[106] miRNA 342 targets SOX6 (SRY-box transcription factor 6) to inhibit apoptosis,[107] upregulates miR-20a to inhibit CXCL8 (C-X-C motif chemokine ligand 8) expression and inhibit apoptosis and inflammation,[94] and miR-34b improves inflammation and apoptosis through IL-6R (interleukin 6 receptor) /JAK2 (Janus kinase 2) /STAT3 (signal transducer and activator of transcription 3) signaling pathway.[108] GDF11 (growth differentiation factor 11), a target of miR-32-5p, inhibits mitochondrial dysfunction and apoptosis through the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway,[109] and inhibition of miR-17-92 Cluster inhibits cell apoptosis, inflammation and fibrosis.[110] Hsa_circ_0003928 inhibits apoptosis and OS through the axis of miR 136 5p/PAQR3 (progestin and adipoQ receptor family member 3),[111] and microRNA-29b-3p inhibits apoptosis and inflammatory response through modification of EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit).[112] LncRNA UCA1 inhibits apoptosis and inflammation of renal tubular epithelial cells by targeting microRNA-206.[113] CircRNA circ_0000712 inhibits apoptosis, OS, and inflammation by targeting miR-879-5p /SOX6 axis,[114] and miR 1423p inhibits apoptosis and OS by targeting cell division 1 (BOD1).[115] Mir-1297 inhibits inflammation and apoptosis by targeting COL1A2 (collagen type I alpha 2 chain),[116] and miR-590-3p inhibits apoptosis, inflammation, and OS by targeting C-X3-C motif chemokine ligand 1 (CX3CL1).[117] The microRNA-126 inhibits inflammation and apoptosis through the VEGF-mediated PI3K/AKT signaling pathway[118] and inhibits DKD both in vivo and in vitro.

Drugs and Compounds Ameliorate DKD by Modulating Cell Apoptosis

Drugs and compounds improve DKD by regulating apoptosis. Sodium-glucose cotransporter type 2 inhibitors (SGLT2), dapagliflozin inhibits inflammation-related expressions by improving the expression of apoptotic markers Bcl-2 and Bax[119] and inhibits of ERS.[120] Empagliflozin inhibits apoptosis and improves mitochondrial function by regulating mitochondrial fission and fusion;[121] ursolic acid and empagliflozin inhibit abnormal apoptosis of glomerular cells induced by high glucose. Reducing inflammation and OS can improve the renal histopathological changes of DKD.[122] Liraglutide promotes the browning of white fat and inhibits apoptosis of podocytes in DKD mice through GLP-1R.[123] Telmisartan can inhibit dimerization of angiotensin type-1 receptor and adiponectin receptor-1 and alleviate cell apoptosis.[124] Fenofibrate inhibited apoptosis through AMPK/FOXA2 (forkhead box A2) /MCAD (medium-chain acyl-CoA dehydrogenase) pathway,[125] and Tacrolimus reduced Bax/Bcl-2 and cleaved caspase-3 levels by down-regulating TRPC6 (transient receptor potential cation channel subfamily C member 6), reducing the percentage of apoptosis.[126] Tacrolimus can reduce inflammatory markers and apoptosis by inhibiting nuclear factor of activated T cells 1 (NFATc1) / TRPC6 pathway.[127] Verapamil can inhibit apoptosis,[128] hydralazine can inhibit XO/NADPH glycosylase and activate Nrf-2/HO-1 to reduce ROS production. Down-regulation of the poly (ADP-ribose) polymerase (PARP) /caspase-3 signaling pathway can reduce apoptosis,[129] and Linagliptin can inhibit podocyte apoptosis by regulating the insulin

receptor substrate 1 (IRS1) /Akt signaling pathway.[130] Galantamine can reduce inflammation and apoptosis by regulating the activity of p38 MAPK and caspase-1 pathway[131] and play a role in treating DKD.

In addition, the combination of drugs has also shown therapeutic effects. Cyproheptadine, a SET7/9 inhibitor, reduced apoptosis and inflammation and alleviated DKD tubular epithelial cell fibrosis by decreasing H3K4Me1 expression and E.R. stress.[132] LCZ696 (valsartan/sacubitril) inhibits the expression of Bax and caspase-3 protein, enhances the expression of Bcl-2 protein, improves apoptosis and inflammation, and protects DKD kidney injury.[133] The alpha-lipoic acid (ALA) supplementation inhibits renal fibers through anti-inflammatory, antioxidant, and anti-apoptotic effects and delays the progression of DKD.[134] The sinapic acid and ellagic acid can synergistically inhibit caspase 3-mediated apoptosis, improve DNA damage and structural changes, and improve renal function in DKD patients.[135] Paricalcitol and omega-3 fatty acids can reduce TGF-β1/iNOS/NGAL (neutrophil gelatinase-associated lipocalin) /KIM-1 (kidney injury molecule 1) /caspase-3 and apoptosis index and protect DKD through anti-inflammatory, antioxidant, and anti-apoptosis effects.[136] Intermedia (IMD) intervention in DKD rats has been shown to block endoplasmic reticulum stress, alleviate podocyte apoptosis and F-actin rearrangement, reduce diaphragm protein synthesis, and protect DKD.[137] Renalase inhibits apoptosis and improves DKD tubulointerstitial fibrosis through the p38 MAPK signaling pathway.[138] Praliciguat inhibits inflammation and apoptosis and delays the progression of DKD.[139] Pyruvate can inhibit ERS and apoptosis and alleviate the damage of renal tubular epithelial cells induced by high glucose.[140] Hyperoside targets miR-499e5p/APC axis to reverse the increase of Bax and the decrease of Bcl-2, enhance the activity caspase-3, inhibit cell apoptosis, and alleviate kidney damage and fibrosis in DKD mice.[141] Phosphocreatine protects DKD by reducing the expression of Bax/Bcl-2 ratio, caspase-9, and caspase-3 through the ERK/Nrf2/HO-1 signaling pathway and reducing the production of ROS.[142] The prostaglandin E1 (PGE1) reduced Bax, caspase-3, and cleaved caspase-3 levels by inhibiting the JNK/Bim pathway and inhibited apoptosis to protect DKD rats from proximal renal tubule injury.[143] CY-09 inhibits NLRP3, reduces caspase-1 and apoptosis in a dose-dependent manner, and alleviates DKD renal injury.[144] β-Amyrin regulates the miR-181b-5p/HMGB2 axis to inhibit the inflammatory response and apoptosis and alleviate the renal histopathological changes of DKD.[145] Inhibition of caspase-3 by Z-DEVD-FMK can improve proteinuria, renal function, and tubulointerstitial fibrosis of DKD.[146] SC preparations mitigate renal cell apoptosis and mitochondrial dysfunction through Nrf2-dependent mechanisms.[147] Finerenone ameliorates apoptosis in diabetic nephropathy by suppressing macrophage mineralocorticoid receptor (MR) and its downstream G protein subunit alpha i2 (Gnαi2) signaling, thereby reducing inflammation.[148] Isoferulic acid (IFA) ameliorates apoptosis in diabetic nephropathy by inhibiting the CXCL12/CXCR4 signaling axis and its downstream PI3K/Akt/mTOR/p53/CASK pathways, while activating autophagy.[149] β-Sitosterol ameliorates apoptosis in diabetic nephropathy by inhibiting the TLR4/NF-κB signaling pathway, thereby reducing oxidative stress and inflammation in podocytes and renal tubular cells exposed to high glucose.[150] Micheliolide ameliorates apoptosis in diabetic kidney disease by activating the Nrf2/Keap1 antioxidant pathway and inhibiting the TLR4/MyD88/NF-κB inflammatory axis.[151]

Traditional Chinese medicine (TCM) compounds, single TCM, and TCM extracts can improve DKD by regulating apoptosis. Loganin and catalpol inhibit podocyte apoptosis and improve kidney injury in DKD mice by targeting AGE-RAGE and its downstream pathways p38 MAPK and Nox4.[152] Huperzine A (Hup A) ameliorates apoptosis in diabetic nephropathy by modulating the Apoe/Apoc2 pathway and restoring lipid metabolism, while concurrently enhancing microbial homeostasis.[153] Grifola frondosa (PGF) inhibits the TLR4/NF-κB pathway, reduces inflammatory response and apoptosis, and improves early DKD.[154] Paclitaxel can inhibit the expression of inflammatory cytokines, down-regulate the expression of apoptosis markers Bax and caspase-3 and improve the damage and fibrosis of DKD podocytes.[155] Resveratrol relies on the activation of AMPK to inhibit OS-mediated podocellular apoptosis and alleviate DKD kidney injury.[156] Sinomenine can inhibit OS, reduce renal cell apoptosis, and improve DKD renal fibrosis by regulating the JAK2/STAT3/SOCS1 (suppressor of cytokine signaling 1) pathway.[157] Puerarin alleviates podocyte apoptosis and DKD kidney injury by interacting with Guanidine nucleotide-binding protein Gi subunit alpha-1 (Gnai1) subunit.[158] Diosgenin inhibits ROS production through the regulation of NOX4 and mitochondrial respiratory chain, down-regulates the expression of caspase 3 and caspase 9, upregulates the expression of Bcl-2, inhibits mitochondrial apoptosis, and improves DKD kidney injury through ERS.[159] Salidroside inhibits the expression of inflammatory factors and OS markers through the Akt/GSK-3β signaling pathway, attenuates apoptosis characteristics, and improves DKD renal

dysfunction.[160] Hedysarum polypores polysaccharides can reduce apoptosis and inflammatory infiltration by inhibiting the HMGB1/RAGE/TLR4 pathway and improving DKD renal fibrosis.[161] Grape seed Proanthidin extract targets p66Shc to improve mitochondrial dynamic homeostasis, apoptosis, and ROS production and treat DKD.[162] Cordyceps sinensis can down-regulate the expression of Bax and caspase-3, inhibit apoptosis and cell proliferation, and inhibit DKD.[163] Through anti-apoptosis and antioxidant effects, pectin-lyase-modified ginseng extract and Ginsenoside Rd protect against DKD renal dysfunction.[164] Akebia Saponin D inhibits renal tubule cell apoptosis and OS by activating the Nrf2/HO-1 pathway, inhibiting the NF-κB pathway, and improving renal injury in DKD mice.[165] Ginsenoside Rh1 improves cytochrome c, Bax, Bcl-2, Bcl-XL, cleaved-caspase 9, and cleaved-caspase 3 in the NF-κB signaling pathway through AMPK/PI3K/Akt. DKD is improved by inhibiting inflammation and apoptosis.[166] Panax japonicus C.A. Meyer (P.J.) regulates the Bcl-2/caspase-3 signaling pathway, inhibits apoptosis, and alleviates kidney damage in DKD mice.[167] 20 (S)-Ginsenoside Rg3 reduces apoptosis, inhibits inflammatory response, and alleviates renal histological changes in DKD rats.[168] Jujuboside A (JuA) down-regulates the expression of apoptotic proteins Bax, CytC, Apaf-1, and caspase 9 by inhibiting mitochondrial and ERS, inhibits apoptosis, and improves renal pathological damage in DKD rats.[169] Phillygenin (PHI) inhibits inflammation and apoptosis in vitro and alleviates diabetic kidney injury in db/db mice by interfering TLR4/MyD88/NF-κB and PI3K/AKT/GSK3β signaling pathways.[170]

In addition, modern novel therapies have also been shown to treat DKD by modulating apoptosis. The human umbilical cord-derived mesenchymal stem cells (hucMSCs) inhibited apoptosis by regulating Bax level through Nrf2 activation and alleviated renal oxidative damage of DKD.[171] Umbilical Cord-Derived Mesenchymal Stem Cells activate apoptosis signal-regulating kinase 1 (ASK1), which inhibits apoptosis and improves renal cell injury and proteinuria in DKD rats.[172] Mitochondria transfer from mesenchymal stem cells can enhance the expression of mitochondrial superoxide dismutase 2 and Bcl-2 and inhibit ROS production. Structural and functional repair of proximal renal tubule epithelial cell damage in DKD rats through antioxidant and anti-apoptotic effects.[173] Extracellular vesicles of podocytes treated with high glucose-induced apoptosis of proximal tubule epithelial cells and induced DKD.[174] Table 1 summarizes different interventions that delay the progression of DKD by regulating apoptosis (Table 1).

Autophagy in Diabetic Kidney Disease

Autophagy is vital in recycling excess or damaged cellular components and maintaining homeostasis and survival. During the process of autophagy, misfolded proteins and damaged organelles are brought into the double-membrane

Table 1 Different Intervention Methods Delayed the Progression of DKD by Regulating Apoptosis

Intervention	Object of Study	Key Targets/Pathways	Results	References
Dapagliflozin	Rats	Anti-inflamm(↓TNF-α/PEDF,↑PTX-3); Anti-apoptosis/anti-fibrosis(↑BCL-2/↓BAX); Pro-angiogenesis (↑VEGF).	Treatments with dapagliflozin showed improvements in histopathological examinations, apoptotic markers compared to diabetic vehicles in a dose-dependent manner.	[119]
Dapagliflozin	HK-2 cell and db/db mice	↓ER stress/apoptosis via elf2α-ATF4-CHOP pathway	The drug rescued C2 ceramide-induced ER stress-mediated apoptosis and ER stress-mediated apoptosis, which might occur in DN.	[120]
Empagliflozin	HK-2 cell	↓mito frag (↓DRP1/FIS1, ↑MFN1/2); ↓ROS, ↑MMP/ATP→↓apoptosis	Empagliflozin reduced the high glucose-induced cellular apoptosis and improved mitochondrial functions.	[121]
Ursolic acid and empagliflozin	Rats	↓inflamm (TNF-α/IL-1β/IL-6); ↓oxstress (↓MDA/NO,↑SOD/GSH/CAT); ↓fibrosis (↓FN/SMA-α/TGF-β1/SMAD/MAPK, ↑E-cad); ↓gluc/lipids; ↑renoprot; mutual side-effect offset.	The ursolic acid and empagliflozin reduce inflammation and oxidative stress by inhibiting abnormal apoptosis of glomerular cells induced by high glucose.	[122]

(*Continued*)

Table 1 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Liraglutide	Mice	↑White fat browning (↑PGC1α/UCP1)→↓podocyte apoptosis via adipocyte CM; GLP-1R+ podocytes → direct anti-apoptotic effect.	Liraglutide inhibits the apoptosis of DKD mouse podiocytes by glucagon like peptide-1 receptor (GLP-1R).	[123]
Telmisartan	Rats and rat NRK-52E cell	↓AT1R-AdipoR1 heterodimerization →↓MIP-1α/ICAM-1/MCP-1→↓fibrosis/↓apoptosis/↓albuminuria	Telmisartan could inhibit HG-induced AT1R-AdipoR1 dimerization and alleviate cell apoptosis in NRK-52E cells.	[124]
Fenofibrate	HK-2 cell	↑AMPK/FOXA2 →↑MCAD → ↑β-oxidation/↓lipid accum (↓TG) → ↓apoptosis/↑renal fxn	The renal function and tubular cell apoptosis were significantly improved by fenofibrate.	[125]
Tacrolimus	Rats and mouse podocytes (MPC5)	↓TRPC6 →↑nephrin,↓cleaved-casp3/↓Bax/Bcl-2→↓podocyte apoptosis/↓albuminuria	Tacrolimus possibly ameliorating podocyte apoptosis by downregulating the expression of TRPC6.	[126]
Tacrolimus	HK-2 cell and db/db mice	↓NFATc1 nucl. transloc.→↓TRPC6→↓IL-6/TNF-α/↓casp3/↓fibrosis→↓tubulointerstitial injury	Tacrolimus alleviates inflammatory markers and apoptosis by inhibiting the NFATc1/TRPC6 pathway.	[127]
Verapamil	C57/BL6J mice and HK-2 cell	↓TXNIP → ↓apoptosis/↓fibrosis → ↓tubular injury	Verapamil can inhibit apoptosis.	[128]
Hydralazine	Hydralazine and HK-2 cell	↓XO/↓NADPHox + ↑Nrf2/HO-1 → ↓ROS/↓uric acid/↓TNF-α/IL-6 → ↓fibrosis/↓albuminuria	Hydralazine reduced high glucose-induced apoptosis by downregulating PARP/caspase-3 signaling.	[129]
Linagliptin	Rats and podocytes	↑IRS1/p-Akt (insulin signal) + ↑Nrf2 → ↓podocyte apoptosis	High glucose-induced podocyte apoptosis is suppressed by linagliptin.	[130]
Galantamine	db/db mouse	Centr. choliner. → ↑GLP-1/↓p38 MAPK/↓casp1/↓SGLT2 → ↓inflamm (↓TNF-α/IL-6)/↓albuminuria	Galantamine alleviates inflammation and apoptosis by regulating the activity of p38 MAPK and caspase-1 pathways.	[131]
Cyproheptadine	NRK-52E cell	↓SET7/9 → ↓H3K4me1/↓ER stress → ↓inflamm/↓apoptosis/↓fibrosis	The cells treated with cyproheptadine showed significant suppression of H3K4Me1 and reduction in ER stress, inflammation, apoptosis, and fibrosis.	[132]
Sacubitril/Valsartan	Rats	↓TNF-α/IL-6/NF-κB + ↑IL-10/↑GSH + ↓Bax/↓casp3↑Bcl-2 → ↓creatinine/↓urea/↓histo-damage	LCZ696 alleviated DKD with possible mechanisms including inhibition of inflammation and apoptosis.	[133]
Alpha-lipoic acid(ALA)	Rats	↑β-cell fxn/↑insulin + ↑GSH/↑antioxid → ↓MDA/↓IL-1β/IL-6/↓α-SMA → ↓creatinine/↓albuminuria	ALA supplementation prevents early development and progression of DN by exerting anti-hyperglycemic, antioxidant, anti-inflammatory, anti-fibrotic and anti-apoptotic effects.	[134]
Sinapic acid and ellagic acid	Rats	SA+EA > mono: ↓casp3/↓8-OHdG + ↓MDA/↑GSH/CAT → ↓kidney hypertrophy/↓glomerular damage	The synergistic effect of sinapic acid and ellagic acid inhibits caspase 3-mediated apoptosis, improves DNA damage and structural changes, and improves renal function in DKD.	[135]
Paricalcitol and omega-3 fatty acids	Rats	↑IL-10/↑GSH/↑SOD1 + ↓TGF-β1/↓iNOS/↓IL-1β/IL-6 → ↓NGAL/↓KIM-1/↓casp3	Paricalcitol + omega-3 protocol exhibited the best improvements in metabolic control, renal functions, oxidative stress, inflammation, and apoptosis.	[136]

(*Continued*)

Table 1 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Intermedia	Rats	↓ER stress/UPR → ↑slit diaphragm/↑Bcl-2↓Bax/casp3 → ↓proteinuria	Intermedia(IMD) intervention in DKD rats has been shown to block endoplasmic reticulum stress, alleviate podocyte apoptosis and F-actin rearrangement, reduce diaphragm protein synthesis, and protect DKD.	[137]
Renalase	Rats and NRK-52E cell	↓RNLS → ↑p-p38MAPK → ↓tubular fibrosis/↓apoptosis	The reduction of renal tubular RNLS expression in DN mediates tubulointerstitial fibrosis and cell apoptosis via the activation of the p38MAPK signal pathway.	[138]
Praliciguat	ZSF1 rats	↑sGC/cGMP → ↓SMAD3/↓TGF-β/↓cytokines → ↓proteinuria (BP-independent)	Praliciguat inhibits inflammation and apoptosis and delays the progression of DKD.	[139]
Pyruvate	HK-2 cell	↓ER stress → ↓ROS/↓apoptosis → ↓tubular injury	The high glucose can induce reactive oxygen species production, apoptosis and ER stress in HK-2 cells, and that Pyr treatment can ameliorate these effects.	[140]
Hyperoside	C57BL/6 J mice	↑miR-499-5p → ↓APC → ↓ECM/↓inflamm/↓apoptosis → ↓renal dysfunction	Hyperoside targets miR-499e5p/APC axis to reverse Bax increase and Bcl-2 decrease, enhance caspase-3 activity, inhibit cell apoptosis, and alleviate kidney damage and fibrosis in DKD mice.	[141]
Phosphocreatine	SD rats and NRK-52E cell	↓p-ERK → ↑Nrf2/HO-1 → ↓ROS/↓Ca^{2+}/↓apoptosis → ↓DN injury	PCr in-vitro and in-vivo depends on suppressing apoptosis and ROS generation through ERK mediated Nrf-2/ HO-1 pathway.	[142]
Prostaglandin E1	rats and HK-2 cell	↓p-JNK → ↓Bim → ↓Bax/↓casp3 → ↓tubular apoptosis/↓proteinuria	The nephroprotective effects of PGE1 against apoptosis of proximal renal tubule in DKD rats via suppressing JNK-related Bim signaling pathway.	[143]
CY-09	HK-2 cell and db/db mice	↓NLRP3 → ↓casp1/↓IL-1β/IL-18 → ↓apoptosis/↓fibrosis → DKD renoprotection	CY-09 can inhibit NLRP3 and reduced caspase-1, IL-18, IL-1β andapoptosis in a dose-dependent manner.	[144]
β-Amyrin	HK-2 cell and C57BL/6 J mice	↑miR-181b-5p → ↓HMGB2 → ↓inflamm/↓apoptosis → ↓DKD injury	β-amyrin ameliorates DN in mice and suppresses inflammatory response and apoptosis of HG-stimulated HK-2 cells via the miR-181b-5p/HMGB2 axis.	[145]
Z-DEVD-FMK	ICR mice and HK-2 cell	↓Casp3 → ↓GSDME → ↓secondary necrosis → ↓fibrosis/↓albuminuria	Inhibition of caspase-3 by Z-DEVD-FMK can improve proteinuria, renal function and tubulointerstitial fibrosis of DKD.	[146]
Syzygium cumini (L.)	Rats	↑Nrf2 → ↑HO-1/↓ROS + ↓RAGE/NF-κB → ↓BAX/↓fibrosis/↓glycation	SC preparations mitigate renal cell apoptosis and mitochondrial dysfunction through Nrf2-dependent mechanisms.	[147]
Finerenone	Human Renal Biopsy Samples, C5aR1 Knockout Mice, RAW 264.7	↓MR (macrophage) → ↓Gnαi2 → ↓C5aR1/↓chemokines → ↓tubulointerstitial injury	Fenofibrate improves DKD by regulating the complement system.	[148]

(*Continued*)

Table 1 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Isoferulic acid	Rats, MPC5 podocytes	↓CXCL12/CXCR4 → ↓mTOR/↓p53 + ↑LC3-II/I → ↓apoptosis/↑podocyte integrity	IFA alleviates DKD by inhibiting CXCL12/CXCR4 signaling, suppressing apoptosis, and enhancing autophagy.	[149]
β-Sitosterol	Cells(HK-2)	↓TLR4/NF-κB + ↑Nrf2 → ↓ROS/↓cytokines/↓apoptosis	β-sitosterol exerts anti-inflammatory, anti-oxidative, and anti-apoptotic activities in HG-induced podocytes or HK-2 cells by inhibiting TLR4/NF-κB signaling.	[150]
Micheliolide	Rats	↑Nrf2/↓NOX + ↓TLR4/NF-κB → ↓TGF-β/↓fibrosis → ↓KIM-1/↓NGAL	The therapeutic benefits of micheliolide are linked to its dual effects on TGF-β/Smad/MAPK signaling.	[151]
Rehmanniae Radix (RR) and Cornus officinalis (CO)	KK-Ay mice	↓RAGE → ↓p38 MAPK/↓Nox4 → ↓NF-κB → ↓podocyte apoptosis	Log and Cat cooperatively resisted the apoptosis of podocytes upon DN by targeting AGEs-RAGE and its downstream pathways p38 MAPK and Nox4.	[152]
Huperzine A	Rats	↓Apoe →↓sphingosine dysmetab + ↑microbiota diversity → ↓podocyte apoptosis/↓DKD injury	We provide the first evidence of the therapeutic effect of Hup A on DKD, indicating that Hup A is a potential drug for the prevention and treatment of DKD.	[153]
Grifola frondosa	C57BL/6J mice and NRK-52E cell	↓TLR4/NF-κB → ↓inflamm/↓apoptosis → ↑renal function	The high glucose-induced inflammatory response and apoptosis of renal tubular epithelial cells were decreased by PGF treatment.	[154]
Paclitaxel	Mouse podocytes	↓ER stress/↓NOX4 + ↑cytoskeleton → ↓ROS/↓inflamm/↓fibrosis	The paclitaxel effects were accompanied by inhibition of the inflammatory cytokines, MCP-1, TNF-a, TNF-R2, and TLR4, as well as attenuation of the apoptosismarkers, Bax, Bcl-2, and Caspase-3.	[155]
Resveratrol	db/db mice and mouse podocytes	↑AMPK → ↓ROS → ↓podocyte apoptosis → ↓DKD injury	Resveratrol inhibits oxidative stress-mediated podocytes apoptosis and alleviates DKD renal injury by activation of AMPK.	[156]
Sinomenine	SD rats and HK-2 cell	↑GPX1/SOD2/GSH → ↓ROS + ↑SOCS1/↓JAK2/STAT3 → ↓apoptosis/↓fibrosis/↓inflamm	SIN protects nephrocytes and decreases renal tissue injury via inhibiting oxidative stress, reducing renal cell apoptosis and fibrosis, regulating the JAK2/STAT3/SOCS1 pathway in DKD rats.	[157]
Puerarin	db/db mice and human podocytes	↓Gnai1 ↑cAMP ↑PKA ↑p-CREB ↓Apoptosis	Puerarin alleviates podococyte apoptosis and DKD renal injury by interacting with Guanidine nucleotide-binding protein Gi subunit alpha-1 (Gnai1) subunit.	[158]
Diosgenin	SD rats and HK-2 cell	↓NOX4/↑MRC-I-V → ↓ROS + ↑Bcl2/↓caspase3,9/↓CytC & ↓p-PERK/↓CHOP/↓caspase12 → ↓apoptosis/↓DKD	DIO inhibited ROS production by modulating NOX4 and MRC complexes, which then suppressed apoptosis regulated by mitochondria and ER stress, thereby attenuating DN.	[159]

(*Continued*)

Table 1 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Salidroside	Rats	↑p-Akt/↑p-GSK-3β → ↓apoptosis + ↓ROS/↓inflammation ↓DKD	Salidroside inhibits the expression of inflammatory factors and oxidative stress markers through Akt/GSK-3β signaling pathway, attenuates apoptotic features, and improves DKD renal dysfunction.	[160]
Hedysarum polybotrys polysaccharide	C57BL/6 J mice	↓HMGB1/RAGE/TLR4 → ↓NF-κB ↓inflammation(↓IL-6/TNF-α/IL-1β) ↓fibrosis(↓FN/↓α-SMA/↓TGF-β1) ↓apoptosis ↓DKD(↓BG/↓Scr/↓UAE)	Hedysarum polybotrys polysaccharide alleviates apoptosis and inflammatory infiltration and improves DKD renal fibrosis by inhibiting HMGB1/RAGE/TLR4 pathway.	[161]
Grape seed proanthocyanidin extract	SD rats and HK-2 cell	↓p66Shc → ↑SIRT1/PGC-1α/NRF1/TFAM ↑Mit-bio and ↑MFN1/↓DRP1 ↑Mt-dynamics → ↑Mt-function ↓Apoptosis/↓DKD	GSPE significantly improved the renal function of rats, with less proteinuria and a lower apoptosis rate in the injured renal tissue.	[162]
Cordyceps sinensis	HK-2 cell	↓Bax/↓Caspase-3/↓VEGFA/↑PTEN → ↓P-AKT/↓P-ERK → ↑Proliferation & ↓Apoptosis ↓DKD	The fermented CS has nephroprotective effects significantly, which functions via promoting proliferation and inhibiting apoptosis of renal proximal tubular cells.	[163]
Pectin-Lyase-Modified Ginseng extract and Ginsenoside Rd	db/db mice	↓ROS(↓8-OHdG) ↓Apoptosis → ↓DKD	Pectin-Lyase-Modified Ginseng extract and Ginsenoside Rd protected DKD renal dysfunction through anti-apoptosis and antioxidant effects.	[164]
Akebia Saponin D	C57BL/6 J mice and HK-2 cell	↑NRF2/HO-1 → ↓ROS & ↓NF-κB → ↓inflammation/↓apoptosis ↓DKD	ASD prevented kidney damage, improved renal function and inflammatory reaction, ameliorated oxidative stress and inhibited apoptosis of renal tubular cells in DN mice.	[165]
Ginsenoside Rh1	C57BL/6 J mice	↑p-AMPK/PI3K/Akt → ↓Nox1/4 ↓NF-κB ↓AGEs ↑SOD/GSH ↓MDA ↓Apoptosis ↓DN	Ginsenoside Rh1 improves type 2 diabetic nephropathy through AMPK/PI3K/Akt-Mediated inflammation and apoptosis signaling pathway.	[166]
Panax japonicus C.A. Meye	Mice	↑Bcl-2/↓Caspase3 ↓Apoptosis & ↑Unsaturated-FA/↓Purine-metab ↓Lipids ↓DKD	Panax japonicus C.A. Meye(PJ) regulates the Bcl-2/caspase-3 signaling pathway, inhibits apoptosis, and alleviates kidney damage in DKD mice.	[167]
20(S)-Ginsenoside Rg3	Rats and NRK-52E cell	Rg3 ↓TGF-β1/↓NF-κB/↓TNF-α → ↓Fibrosis/↓Inflammation ↓Apoptosis ↓FBG/↓Scr/↓Proteinuria ↓DKD	20(S)-Ginsenoside Rg3 reduces apoptosis, inhibits inflammation and alleviates renal histological changes in DKD rats.	[168]
Jujuboside A	SD rats	↓Oxidative stress (↓NOX4/↑SOD, CAT, GPx/↑MRC) → ↓Apoptosis (↓mt-apoptosis/↓ER-apoptosis) → ↑Autophagy/mitophagy (↑CaMKK2-AMPK-mTOR /↑PINK1-Parkin)	JuA protected against type II diabetic nephropathy through inhibiting oxidative stress and apoptosis mediated by mitochondria and ER stress.	[169]
Ginsenoside Rb1	FVB mice and mouse podocyte cell	↓TLR4/MyD88/NF-κB and ↑PI3K/AKT/p-GSK3β → ↓Inflammation/↓Apoptosis → ↓DKD (↓UACR)	Ginsenoside Rb1 decreased apoptotic protein expression, alleviated mitochondrial damage and inhibited glomerular injury in DKD models.	[170]

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vesicles of the autophagosome for degradation by lysosomes.[175] Autophagy is divided into three main forms: Macroautophagy (hereafter referred to as autophagy), in which cellular cargo is isolated within a double-membrane vesicle called an autophagosome, and selection of the contents of the autophagosome can be carried out in a relatively non-selective manner. It may also involve the elimination of strictly regulated individual cellular components. In contrast, chaperone-mediated autophagy (CMA) is protein-specific autophagy; heat-shock cognate protein HSPA8/HSC70 first identified KFERQ-like motif-bearing proteins. The pathway is formed by oligomerizing the protein-bound LAMP2A (lysosomal-associated membrane protein 2A) and translocation into lysosomal degradation. Finally, microautophagy involves direct isolation of cellular material (including the KFERQ-flagged protein or many cytoplasmic contents) through membrane invasions formed on the surface of late endosomes or lysosomes.[176] The role of autophagy in cell death is mainly divided into autophagy-dependent cell death (ADCD) (or autophagic cell death, ACD) and autophagy-mediated cell death (AMCD).[177] Bioinformatics analysis of the data set of DKD patients showed that autophagy inhibition occurred in both glomeruli and renal tubules, of which podocyte inhibition was the most obvious, and the level of p62 protein in glomeruli was one of the predictive indicators for DKD patients to enter the stage of massive proteinuria.[178] Clock-dependent regulation of autophagy is essential for podocyte survival, and loss of circadian control of autophagy plays an important role in DKD podocyte injury and proteinuria.[179] A retrospective study included 120 patients with diabetes without albuminuria, diabetes with microalbuminuria, diabetes with macroalbuminuria, and a healthy control group. Studies have found that RUBCN (rubicon autophagy regulator), mTOR, and SESN2 (sestrin 2) are overexpressed in DKD patients, and RUBCN/ SESN2-mediated autophagy inhibition can be used as a biomarker for DKD.[180] The prolyl4-hydroxylase subunit beta (P4HB) was identified as a new autophagy-associated biomarker, and P4HB in renal tubules was associated with DKD renal function.[181] Figure 2 shows that different factors regulate DKD

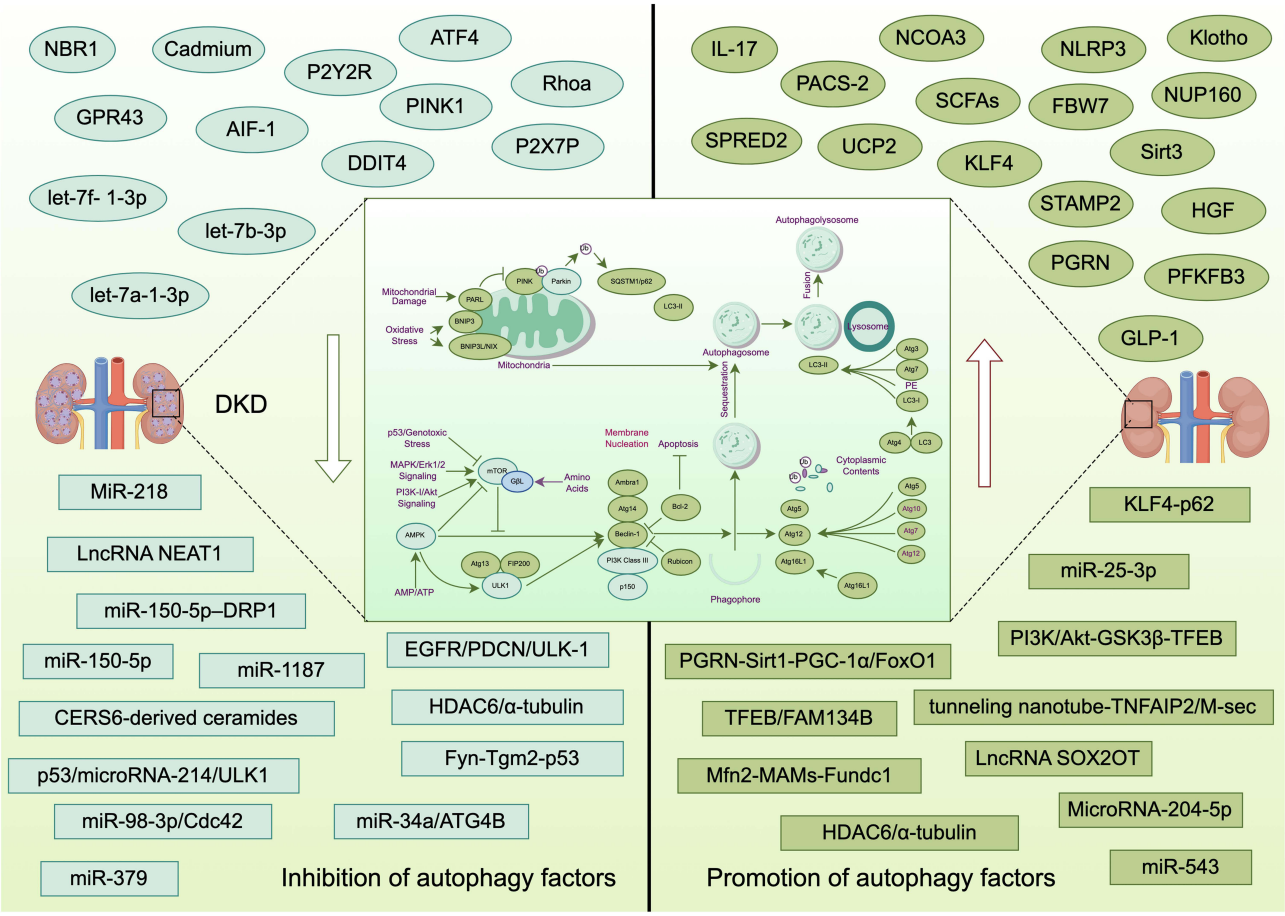

Figure 2 Shows that different factors regulate DKD through autophagy. By Figdraw.

through autophagy (Figure 2). Some factors promote the development of DKD by inhibiting autophagy. The increased expression of NBR1 and the decreased expression of autophagy related 4B cysteine peptidase (ATG4B) and VPS37 in kidney tissue are closely related to the inhibition of the autophagy pathway,[182] and the lack of IL-17 (interleukin 17) may be related to the occurrence or progression of DKD by inhibiting the formation of Autophagy in DKD mice.[183] When mice were injected with macrophage-derived exosomes stimulated by high glucose, renal dysfunction and mesangial matrix expansion were observed in mice, which may be related to the activation of NLRP3 inflammasome and the defects of autophagy.[184] In cadmium exposure, abnormal autophagy associated proteins and autophagosome count inhibit autophagy,[185] and PACS-2 deficiency inhibits autophagy of the ER by TFEB /FAM134B pathway.[186] GPR43 (free fatty acid receptor 2) activation-mediated lipotoxicity inhibits autophagy by regulating the ERK/EGR1 (early growth response 1) pathway,[187] and high glucose inhibits autophagy by activating the JAK/STAT pathway in mice and podocytes.[188] Allograft inflammatory factor-1 (AIF-1) regulates autophagy, OS, and inflammatory response through the miR-34a/ATG4B pathway.[189] Activating transcription factor 4 (ATF4) directly inhibit autophagy,[190] and ceramide synthase 6 (CERS6) -derived ceramides are involved in the pathogenesis of DKD by inhibiting mitochondrial autophagy mediated by PTEN-induced kinase 1 (PINK1).[191]

DKD Regulates miRNA-Modulated Autophagy

DKD is involved in regulating autophagy at the miRNA level.MiR-1187 can inhibit autophagy levels in podocytes and glomerulus of DKD mice with high glucose exposure,[192] MiR-218 can inhibit Spred2-mediated autophagy and promote OS and inflammation.[193] LncRNA NEAT1 inhibits mitochondrial autophagy through the miR-150-5p-DRP1 axis,[194] and the p53/microRNA-214/ULK1 axis damages renal tubular autophagy.[195] Arsenic alters autophagy through miRNA-mRNA axles of let-7a-1-3p, let-7b-3p, let-7f-1-3p, miR-98-3p/Cdc42, Mapk1, and Rhoa,[196] which aggravate kidney damage in DKD. P2X7P is elevated in DKD condition, and podocyte autophagy is inhibited by Akt-mTOR pathway,[15,197] and UCP2 deficiency inhibits podocyte autophagy.[198] Lack of nuclear receptor coactivator 3 (NCOA3) inhibits podocyte autophagy,[199] and the activation of EGFR signal in podocyte accelerates the progression of DKD by inhibiting autophagy to a certain extent by increasing the expression of Rubicon.[200] Studies have also shown that mitochondrial biogenic markers are reduced in podocytes treated with high glucose, and PINK1/parkin-dependent mitochondrial autophagy is inhibited in cells, which is the mechanism of glomerular and podocyte injury induced by high glucose.[201] DNA damage-inducing transcription factor 4 (DDIT4) participates in the vitamin D receptor (VDR) -mTOR pathway, and DDIT4 processing participates in DKD by regulating autophagy.[202] AdipoRon is an autophagy-promoting adiponectin receptor activator, which can relieve the high glucose-induced decrease in the level of lipid deposition in HK-2 cells, suggesting that autophagy-mediated lipid deposition (ELD) plays a key role in DKD renal ELD and lipid-related kidney injury.[203] In DKD mice, Fyn regulates autophagy-mediated p53 expression through Transglutaminase 2 (Tgm2), suggesting the role of the Fyn-TGm2-p53 axis in developing DKD.[204]

Many studies have shown that different factors delay the development of DKD by inducing autophagy. Studies have suggested that different genes regulate autophagy. Overexpression of STAMP2 can promote autophagy by inhibiting mTOR and activating AMPK/SIRT1 signaling pathway,[205] and progranulin (PGRN) can maintain mitochondrial homeostasis through mitochondrial biogenesis mediated by PGRN-SIRT1-PGC-1α /FoxO1 signaling and mitochondrial autophagy.[206] The KLF4-p62 axis regulates the mTOR/S6K pathway and autophagy,[207] and hepatocyte growth factor (HGF) improved the podocyte autophagy lysosomal pathway by regulating the PI3K/Akt-GSK3β-TFEB axis.[208] Klotho improves renal tubule autophagy through AMPK and ERK pathways,[209] NUP160 regulates autophagy by activating the JAK2/STAT3 signaling pathway,[210] and FBW7 (F-box and WD repeat domain containing 7) gene overexpression can enhance autophagy by inhibiting the mTOR signaling pathway and improve inflammation and fibrosis.[211] SCFAs enhance podocyte autophagy through the histone deacetylase 2 (HDAC2)/unc-51 axis like ULK1,[212] α-tubulin deacetylation mediated by HDAC6 regulates autophagy and enhances podocyte motility.[213] In the absence of P2Y2R, the expression of SIRT-1 and FOXO3a is increased, which enhances the autophagy reaction.[214] KLF4 activates podocyte autophagy through the mTOR signaling pathway,[215] and Sirt3 promotes autophagy by inhibiting the Notch 1/ HIS1 signaling pathway.[216] GLP-1 regulates LC3 (light chain 3) and p62 through the AMPK-mTOR signaling pathway to promote autophagy progression.[217] 6 phosphofructo 2 kinase/fructose 2,6 bios Phase 3 (PFKFB3) silences can induce

autophagy,[218] tunneling nanotube-TNF alpha induced protein 2 (TNFAIP2) /M-sec system mediates the exchange of autophagosome and lysosome,[219] The activated mitofusin 2 (MFN2) -AMS-FundC1 (FUN14 domain containing 1) pathway restores the activity of mitochondrial ATP and complex V and the integrity of mitochondria-associated MAM, promoting the recovery of autophagy,[220] thereby mediating the protective effect of DKD. LncRNA SOX2OT regulates Akt-mTOR-mediated autophagy,[221] miR-543 increases autophagy by targeting TSPAN8,[222] and miR-379 inhibition enhances adaptive mitochondrial autophagy through FIS1.[223] MicroRNA-204-5p restores autophagy by regulating the Keap1/Nrf2 pathway,[224] and silencing miR-150-5p exerts reno-protective effects in DKD by targeting SIRT1 to promote its interaction with p53, thereby suppressing p53 acetylation and eliciting AMPK-dependent autophagy in podocytes and renal tissue,[225] M2 macrophage-derived exosomal miR-25-3p attenuates high glucose-induced podocyte injury by activating autophagy through suppression of DUSP1 expression,[226] protection of DKD from the epigenetic level.

Various Drugs or Components Protect DKD by Activating Autophagy

Studies have shown that different drugs or components protect DKD by activating autophagy. Empagliflozin and DPP4 Inhibitor Linagliptin activated glomerulus autophagy and restored autophagosomes, autopilots, and autophagosomes, Engglitazin can reduce albumin exposure and prevent proximal tubular autophagy stagnation.[227,228] Ferulic acid promotes the expression of LC3, Inhibit the levels of p62, NLRP3 and IL-1β, enhance autophagy and inhibit inflammation,[229] aagliprazin can inhibit the expression of HMGB1 in kidney and restore autophagy,[230] montelukast can inhibit HMGB1, TLR4, NF-κB, NLRP3, and IL-1β, and can stimulate autophagy.[231] Celastrol inhibits the thickening of the glomerular basement membrane in DKD rats through the PI3K/AKT pathway and protects podocyte homeostasis.[232] Soluble epoxide hydrolase (sEH) inhibitor t-AUCB can restore autophagy flux and improve mitochondrial function.[233] Metformin-activated AMPK mitigates DKD progression by enhancing renal autophagy, suppressing partial EMT in renal tubular epithelial cells ((RTECs)), and attenuating tubulointerstitial fibrosis(TIF).[234] Visceral adipose tissue-derived serine protease inhibitor (vaspin) acts by improving ERS, autophagy injury and lysosome dysfunction of DKD.[235] Vitamin D enhanced autophagy activity and improved the number of autophagosomes by improving the expression of LC3, Beclin-1, and Vsp34.[236–238] Isoorientin acted as an autophagy activator by activating autophagy and inhibiting the PI3K-AKT-TSC2-mTOR pathway.[239] Melatonin enhances autophagy and improves mitochondrial dysfunction by upregulating the AMPK/SIRT1 axis,[240] and Dihydromyricetin regulates the PI3K/AKT/mTOR signaling pathway and promotes autophagy by regulating miR-155-5p/PTEN signaling.[241] Metformin can regulate the AMPK-mTOR-autophagy axis,[242] and Cordyceps militaris polysaccharides can improve the autophagy defect in DKD mice and increase the renal autophagy rate.[243] Cyclocarya paliurus triterpenic acids fraction inhibited kidney damage by autophagy regulated by AMPK-mTOR,[244] while isorhamnetin improved the kidney lipid profile of DKD rats by regulating autophagy epigenetic regulatory factors, and autophagosomes increase in the kidney.[245] Zinc oxide nanoparticles can enhance autophagy activity, reduce inflammation, and regulate the correlation between autophagy and Nrf2/TXNIP/NLRP3 signal transmission.[246] Carbon monoxide improves autophagy-mediated partly by dissociated Beclin-1-Bcl-2 complex through senescence-related secretory phenotype (SASP).[247] Epidermal growth factor (EGF) protects against high glucose-induced podocyte injury by promoting cell proliferation, suppressing cell apoptosis, and modulating autophagy via the PI3K/AKT/mTOR pathway.[248] Calcium Dobesilate (CaD) can restore autophagy by blocking VEGF/VEGFR2 and inhibiting the PI3K/AKT/mTOR signaling pathway,[249] and Exogenous spermine can promote autophagy by regulating the AMPK/mTOR signaling pathway.[250] Sinensetin can significantly restore the autophagy activity of podocytes induced by high glucose.[251] Paecilomyces cicadae-fermented Radix astragali can enhance autophagy by inhibiting PI3K/AKT/mTOR signaling pathway,[252] Huang Gui Solid Dispersion (HGSD) activated autophagy by enhancing AMPK phosphorylation level and autophagy-related protein expression.[253] Korean red ginseng (KRG) blocks the activation of TGF-β1 by inducing autophagy,[254] and Nuciferine (NF) regulates autophagy through PI3K Akt mTOR pathway, inhibits the expression of TGF β and p-smad3, and improves stage IV renal fibrosis in DKD mice.[255] Astragalus mongholicus Bunge and Panax notoginseng (Burkill) F.H. Chen Formula upregulated autophagy by inhibiting mTOR and activating the PINK1/Parkin signaling pathway;[256] Icariin can restore autophagy by regulating the miR-192-5p/GLP-1R pathway,[257] dasatinib and quercetin (DQ) can activate autophagy and Notch pathways to alleviate podocyte dedifferentiation.[258] Geniposide can enhance ULK1-mediated autophagy,[259] and the Dendrobium mixture can activate

autophagy by inhibiting the PI3K/Akt/mTOR signaling pathway.[260] Tripterygium glycoside (TG) upregulates autophagy through the mTOR/Twist1 pathway.[261] TCM and their active chemical components protect DKD by activating autophagy. Novel therapies also have a similar effect. Intravenous injection of hucMSCs activates Autophagy through a parasecretory mode of action.[262] The hUC-MSCs by reducing circulating TGF-β1 levels and restoring intracranial autophagy,[263] the Placental Mesenchymal Stem Cells (MSCs) regulate mitochondrial autophagy by regulating the SIRT1-PGC-1alpha-TFAM pathway,[264] and the Placenta-derived mesenchymal stem cells enhance podocyte autophagy by regulating the SIRT1/FOXO1 pathway.[265] Human placental mesenchymal stem cells (hP-MSCs) derived Extracellular vesicles(EVs) can mitigate renal injury in DKD by modulating the miR-99b-5p/mTOR/autophagy pathway.[266] Table 2 summarizes different interventions that delay the progression of DKD by regulating autophagy (Table 2).

Table 2 Different Interventions Delayed the Progression of DKD by Regulating Autophagy

Intervention	Object of Study	Key Targets/Pathways	Results	References
Empagliflozin and linagliptin	db/db mice	↑Glomerularautophagy (↑beclin-1/↑LAMP-1/↑LC3B) and ↑Bcl-2/↓caspase-3 →↓Podocyte injury (↓effacement) → ↓Albuminuria	Empagliflozin and linagliptin activated glomerular autophagy and restored autophagosomes, autopolutes and autophagosomes.	[227]
Empagliflozin	Wild–type mice	↓Intraglomerular pressure→↓ALB reabsorption (↓LRP2) →↑Functional autophagy (ATG5-dep) →↓Lipotoxicity/↓Inflammation/↓Fibrosis →↓Renal vulnerability	Empagliflozin reduces ALB exposure and prevents autophagic stagnation in the proximal tubules even without overt albuminuria.	[228]
Ferulic acid	C57BL/6 J mice	↑Autophagy (↑LC3/↓p62) and ↓NLRP3 inflammasome (↓IL-1β) → ↓Renal injury (↓24-h UP/↓BUN/↓Cr)	Ferulic acid ameliorates renal injury via improving autophagy to inhibit inflammation in diabetic nephropathy mice.	[229]
Dapagliflozin	C57BL/6 J mice	↓HMGB1 → ↑Autophagy & ↓Oxidative/ER stress → ↑Podocyte integrity (↑Podocin/↑Nephrin) → ↓DKD	Amelioration of diabetic kidney injury with dapagliflozin is associated with suppressing renal HMGB1 expression and restoring autophagy in obese mice.	[230]
Montelukast	SD rats	↓HMGB1 → ↓TLR4/NF-κB → ↓NLRP3/IL-1β and ↑Autophagy (↓p62/↑LC3-II) and ↑Redox balance (↓MDA/↑TAC) → ↓Necrosis/↓Fibrosis → ↓DKD	The renoprotective effect of Mon is potentially associated with its modulatory effect on inflammatory cytokines, antioxidant properties, and autophagy.	[231]
Celastrol	SD rats	↓PI3K/p-AKT → (↓mTOR and ↓NF-κB mRNA) → ↑Autophagy (↑LC3II) and ↑Podocyte integrity (↑Nephrin) → ↓Albuminuria/↓DN	Celastrol slows the progression of early diabetic nephropathy in rats via the PI3K/ AKT pathway.	[232]
t-AUCB	HK-2 cell and db/db mice	↓sEH → ↑EpFAs → ↑Autophagic flux → ↓Mitochondrial dysfunction (↓ROS/↓Bax) and ↓ER stress → ↓Tubular apoptosis → ↓DKD	Soluble epoxide hydrolase (sEH) inhibitor t-AUCB can restore autophagy flux and improve mitochondrial function.	[233]
Metformin	Renal tubular epithelial cells (RTECs) and SD rats	↑p-AMPK → ↑Autophagy & ↓EMT (↓fibronectin/↓collagen I) → ↓Tubulointerstitial fibrosis → ↓DKD progression	Metformin attenuates renal tubulointerstitial fibrosis via upgrading autophagy in the early stage of diabetic nephropathy.	[234]

(*Continued*)

Table 2 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Vitamin D	HK-2 cell and vdr knockout (vdr-KO), VDR specifically overexpressed in kidney proximal tubular epithelial cells (Vdr-OE) mice	↑Ca^{2+}-CAMKK2 → ↑p-AMPK → ↑Autophagy (VDR-dep) → ↓Albuminuria/↓Tubule injury	Vitamin D-VDR regulates defective autophagy in renal tubular epithelial cell in streptozotocin-induced diabetic mice via the AMPK pathway.	[236]
Vitamin D	Renal biopsies exhibiting diabetic nephropathy, SD rats and MPC5 cell	↑Atg16L1 → ↑Autophagy → ↓Podocyte injury → ↓DKD	Vitamin D/vitamin D receptor/ Atg16L1 axis maintains podocyte autophagy and survival in DKD.	[237]
Vitamin D	db/db mice and mouse podocyte cell	↑Autophagy (↑LC3II/↑Beclin-1/ ↓p62) → ↓Podocyte injury (↓desmin/↑slit diaphragms) → ↓Proteinuria/↓Glomerulosclerosis	Vitamin D ameliorates podocyte injury by enhancing autophagy activity in DKD.	[238]
Isoorientin	C57BL/6 J mice and MPC5 cell	↓PI3Kp85α(SH2) → ↓PI3K-AKT → ↓p-TSC2(S939) →↓mTOR →↑Autophagy/Mitophagy → ↓Podocyte injury	Renoprotective effect of isoorientin in diabetic nephropathy via activating Autophagy and Inhibiting the PI3K-AKT-TSC2-mTOR Pathway.	[239]
Melatonin	SD rats and NRK-52E cell	AMPK → ↑SIRT1 → ↑Autophagy & ↑Mito biogenesis (↑PGC-1α/ ↑TFAM) → ↓Renal injury	Melatonin might mediate the renoprotective effect by upregulating the AMPK/SIRT1 axis, enhancing the autophagy and mitochondrial health in diabetic nephropathy.	[240]
Dihydromyricetin	SD rats and NRK-52E cell	↓miR-155-5p → ↑PTEN → ↓PI3K/ AKT/mTOR → ↑Autophagy & ↓Fibrosis (↓α-SMA/↓Collagen) → ↓DKD	Dihydromyricetin promotes autophagy and attenuatesrenal interstitial fibrosis by regulating miR-155-5p/PTENsignaling in diabetic nephropathy.	[241]
Metformin	db/db mice	↑p-AMPK → ↓mTOR → ↑Autophagy → ↓Oxidative stress/ ↓Apoptosis/↓Inflammation (↓TNF-α/ ↓IL-1β) → ↓Fibrosis	Metformin attenuates diabetic renal injuryvia the AMPK-autophagy axis.	[242]
Cordyceps militaris polysaccharides	C57BL/6 J mice	↑Autophagy (↑Atg5/↑beclin1/↑LC3/ ↓p62) → ↓Podocyte injury (↓desmin) and ↓Inflammation (↓CD68/↓IL-1β/IL-6) and ↓Metabolic stress (↓TC/TG) → ↓DKD	Cordyceps militaris polysaccharides exerted protective effects on diabetic nephropathy in mice via regulation of autophagy.	[243]
Cyclocarya paliurus triterpenic acids	SD rats	↑p-AMPK → ↓p-mTOR → ↑autophagy → ↓renal damage	Cyclocarya paliurus triterpenic acids fraction attenuates kidney injury via AMPK-mTOR-regulated autophagy pathway in diabetic rats.	[244]
Isorhamnetin	Rats	↓miRs (15b/34a/633) → ↑autophagy genes → ↑autophagy → ↓renal damage	Epigenetic modulation of autophagy genes linked to diabetic nephropathy by administration of isorhamnetin in Type 2 diabetes mellitus rats.	[245]

(*Continued*)

Table 2 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Zinc oxide nanoparticles	Rats	↓AGEs/↑Nrf2 → ↓TXNIP → ↓NLRP3/↓IL-1β and ↑autophagy → ↓renal damage	Zinc oxide nanoparticles can enhance autophagy activity, reduce inflammatory response, and regulate the correlation between autophagy and Nrf2/TXNIP/NLRP3 signaling.	[246]
Carbon monoxide	C57BL/6 J mice, HK-2 cell, HBZY-1 cell and HPC cell	↑Beclin-1 (dissoc.) → ↑autophagy → ↓SASP → ↓senescence/↓renal loss	Carbon monoxide alleviates senescence in DKD by improving autophagy.	[247]
Epidermal growth factor	Cell	↑autophagy and mod PI3K/Akt/mTOR → ↑proliferation/↓apoptosis → ↓podocyte injury	EGF exerted protective effects on HG-induced podocytes injury via enhancing cell proliferation and inhibiting cell apoptosis.	[248]
Calcium dobesilat	KK-Ay mice	↓VEGF/VEGFR2 & ↓PI3K/AKT/mTOR → ↓autophagy (↓LC3-II /Atg5/beclin1 ↑p62) → ↓albuminuria/↑renal repair	Calcium dobesilate restores autophagy by inhibiting the VEGF/PI3K/AKT/mTOR signaling pathway.	[249]
Spermine	Rat podocytes and rats	↑p-AMPK → ↓p-mTOR → ↑autophagy (↑LC3II/I/Beclin1/Atg5 ↓p62) → ↓podocyte injury	Sperminemay have the potential to prevent diabetic kidney injury in rats by promoting autophagy.	[250]
Sinensetin	C57BL/6 J mice and MPC5 cell	↑autophagy → ↓podocyte injury/↑renal function	SIN efficiently improved autophagy in the kidney tissue of DN mice.	[251]
Paecilomyces cicadae-fermented Radix astragali	Podocytes and C57BL/6 J mice	↓p-PI3K/p-AKT/p-mTOR → ↑autophagy → ↓podocyte apoptosis → ↑renal function	Paecilomyces cicadae-fermented Radix astragali activates podocyte autophagy by attenuating PI3K/AKT/mTOR pathways to protect against diabetic nephropathy in mice.	[252]
Huang-Gui Solid Dispersion	Rats	↑p-AMPK → ↑autophagy and ↓mesangial matrix → ↑renal function	HGSD protected against diabetic kidney dysfunction by inhibiting glomerular mesangial matrix expansion and activating autophagy.	[253]
Red ginseng	SD rats and HK-2 cell	↓TGF-β1/↓mTOR → [↓inflammation/↓fibrosis and ↑autophagy] → renal protection	KRG can suppress renal inflammation, injury, and fibrosis by blocking TGF-β1 activation and can induce cellular autophagy.	[254]
Nuciferine	KK-AY mice	↓PI3K-AKT-mTOR → ↑autophagy → ↓TGFβ/Smad3 → ↓renal fibrosis	The results demonstrated that NF inhibited the expression of TGFβ and p-Smad3 by regulating autophagy through the PI3K-AKT-mTOR pathway, thereby ameliorating renal fibrosis at stage IV in mice.	[255]
Chen formula	C57BL/6 mice	(↓mTOR / ↑PINK1/Parkin) → ↑autophagy → ↓(TNFα/IL-1β/IL-6) → ↓renal injury	APF may protect the kidneys from inflammation injuries in DKD by upregulating autophagy via suppressing mTOR and activating PINK1/Parkin signaling.	[256]
Icariin	SD rats and HK-2 cell	AR/miR-192-5p/GLP-1R pathway → ↑autophagy → ↓tubulointerstitial fibrosis	Icariin alleviates tubulointerstitial fibrosis by restoring autophagy through the miR-192-5p/ GLP-1R pathway.	[257]

(*Continued*)

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Table 2 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Dasatinib and quercetin	Mouse podocytes and db/db mice	↓Notch → ↑autophagy → ↑podocyte differentiation → ↓renal injury	DQ protects against DKD by activation of autophagy to alleviate podocyte dedifferentiation via the Notch pathway.	[258]
Geniposide	C57BL/6 J mice	(↑AMPK/↓AKT) → ↑ULK1-autophagy and ↓(oxidative stress/inflammation/fibrosis)	Geniposide enhances ULK1-mediated autophagy and reduces oxidative stress, inflammation and fibrosis.	[259]
Dendrobium mixture	SD rats	↓p-PI3K/Akt/mTOR → ↑(LC3/Beclin-1) → ↑autophagy → ↓renal injury	DMix has protective effects on the kidney of rats with DN, which may be associated with the inhibition of the PI3K/Akt/mTOR signaling pathway and activation of renal autophagy by this traditional medicine.	[260]
Tripterygium glycoside	Patient renal biopsies, C57BL/6 J mice and MPC5 cell	↑autophagy (mTOR/Twist1) → ↓EMT/↓apoptosis → ↓podocyte injury	Tripterygium glycoside suppresses epithelial-to-mesenchymal transition of DKD podocytes by targeting autophagy through the mTOR/Twist1 pathway.	[261]

Pyroptosis in Diabetic Kidney Disease

For the clinical transformation and application of pyroptosis, it is essential to deepen the theoretical knowledge of the pyroptosis pathway and develop targeted drugs.[267] Start with It is triggered by a variety of inflammasomes When the inflammasome assembly is completed, caspases are activated, and gastrin proteins are cleaved to produce toxic fragments mediating cell membrane perforation.[268] Pyroptosis is a major response to harmful damage such as pathogen ligands, abnormal levels of host metabolism, and environmental stimulation.[269] As part of the innate immune system, the primary role of pyroptosis is to protect the host from pathogens.[270] Under normal circumstances, moderate pyroptosis helps the host to defend against pathogen infection, but excessive pyroptosis can lead to uncontrolled inflammatory response, massive cell death, and serious tissue damage.[271] For the clinical transformation and application of pyroptosis, deepening the theoretical knowledge of the pyroptosis pathway and developing targeted drugs[267] is essential. Figure 3 shows that different factors regulate DKD through pyroptosis (Figure 3). Activation of caspase-1 induces maturation of IL-1β, and activation of caspase-3 mediates cleavage of GSDME (gasdermin E) and cytoplasmic release of mIL-1β, suggesting that GSDME has a pyrogenic effect and is upregulated in DKD model.[272] GSDMD (gasdermin D) expression is positively correlated with tubular injury. In addition, DKD animal models have shown that TLR4 can aggravate tubular injury and fibrosis through the GSDMD-mediated pyrogen pathway.[273] The non-classical pathway of caspase-11/GSDMD promotes scorification of glomerular endothelial cells (GECs) during DKD, thickening of glomerular basement membrane, extracellular matrix proliferation, and blurring of glomerular boundaries in DKD mice.[274] Different factors induce DKD by participating in the pyroptosis pathway. miR-21-5p in macrophage-derived extracellular vesicles affects pyroptosis by regulating A20,[275] circACTR2 is upregulated by participating in inflammation and pyroptosis pathways.[276] Mir-6675p can also promote inflammatory response and cause pyroptosis.[277] CircRNA COL1A2 mediates hyperglycemic-induced pyroptosis and OS by regulating the miR-424-5p/SGK1 (serum/glucocorticoid regulated kinase 1) axis.[278] LncRNA NEAT1 mediates the miR-34c/NLRP3 axis to regulate caspase1 expression and promote cell pyroptosis.[279] LncRNA-antisense noncoding RNA in the INK4 locus facilitated Caspase1-mediated oxidative destruction through the miR-497/thioredoxin-interacting protein axis.[280] LncRNA MALAT1 promotes cell pyrogen via sponging miR-30c targeting NLRP3,[281] CircLARP1B/miR-578/TLR4 axis inhibition blocks the cell cycle of G0-G1 phase and

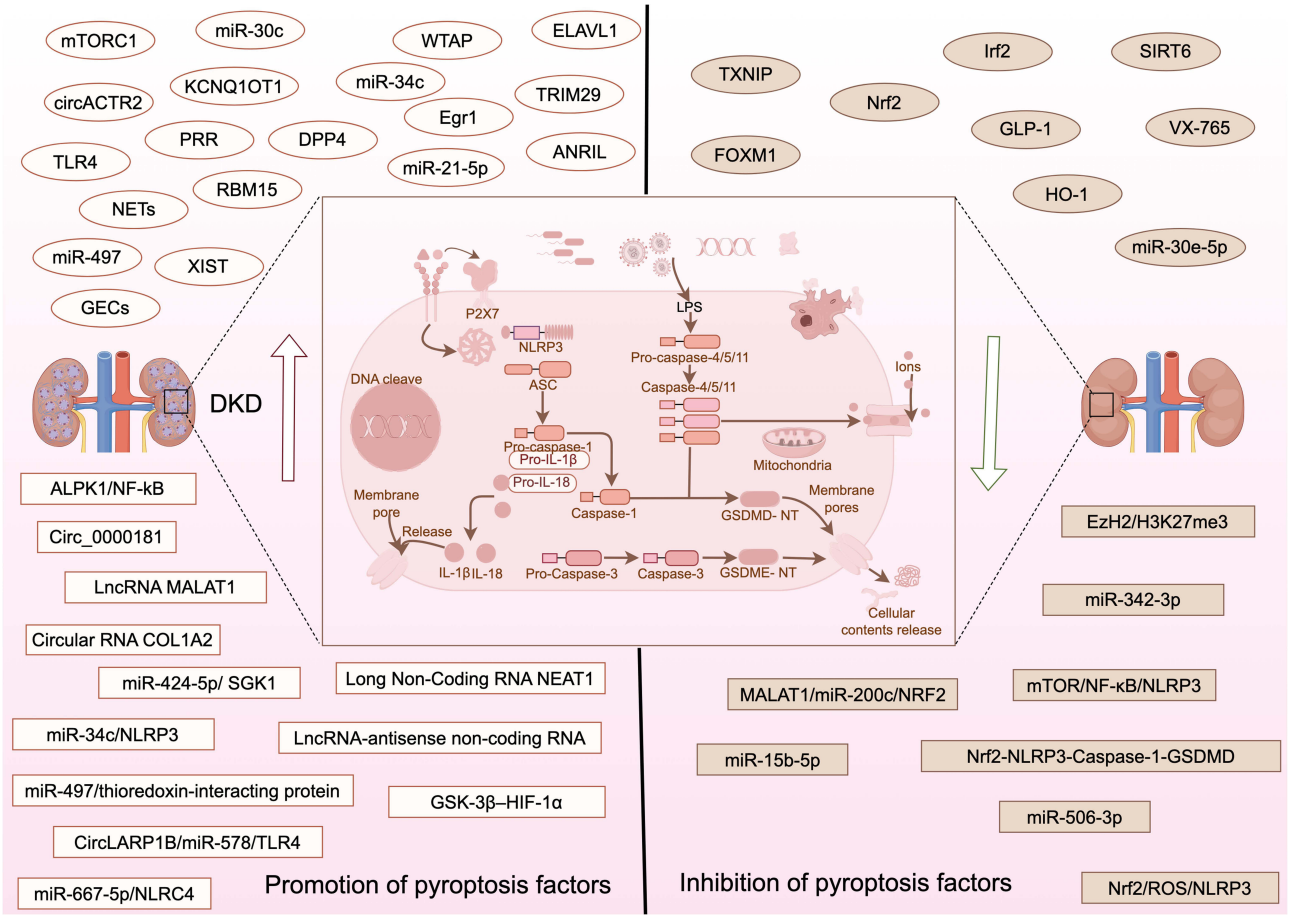

Figure 3 Shows that different factors regulate DKD through pyroptosis. By Figdraw.

promotes cell pyrogen and the release of inflammatory factors.[282] WTAP (WT1 associated protein) can promote the m6A methylation of NLRP3 mRNA and induce pyroptosis,[283] TRIM29 (tripartite motif containing 29) can promote podocyte pyroptosis by activating the NF-κB /NLRP3 pathway.[284] RBM15 (RNA binding motif protein 15), an m6A-related gene, can activate the AGE-RAGE pathway by promoting inflammation, OS, and pyroptosis.[285] Alpha-kinase 1 (ALPK1) /NF-κB pathway activates the caspase-1-GSDMD pyroptosis pathway,[286] and ERS is involved in pyroptosis through the NF-κB/NLRP3 pathway.[287] GECs indicate that charge-related pyroptosis is involved in neutrophil extracellular traps (NETs).[288] The pRR promotes the pyroptosis of renal tubular epithelial cells through the dipeptidyl peptidase 4 (DPP4), which mediates signal transduction.[289] Gsk-3β-hif-1α signaling pathway mediates pyroptosis.[290] Lysophosphatidic Acid induces NLRP3 inflammatory activation by down-regulating EzH2/H3K27me3 and upregulating Egr1 expression, leading to endocytosis.[291] Dihydroxyacetone phosphate (DHAP) leads to pyroptosis by regulating the mTORC1 pathway and promotes podiocyte injury.[292] Discoid domain receptor 1 (DDR1) may promote pyroptosis through the NF-κB/NLRP3 pathway[293] and induce the occurrence and development of DKD. Overexpression of miR-30e-5p or knockdown of ELAV-like RNA binding protein 1 (ELAVL1) can directly inhibit the pyro reaction,[294] and down-regulation of KCNQ1OT1 can upregulate the expression of miR-506-3p. Inhibition of pyroptosis of HK-2 cells induced by high glucose[295] and the down-regulation of ADAM metallopeptidase domain 10 can reduce inflammation, apoptosis, and pyroptosis by inhibiting AMPK signaling pathway,[296] FOXM1 (forkhead box M1) activates SIRT4 through transcription and inhibits NF-κB/NLRP3. Alleviating podocyte pyroptosis,[297] X inactive specific transcript (XIST) silences inhibit TLR4 by upregulation of miR-15b-5p and improve DKD kidney injury by inhibiting NLRP3/caspase-1-mediated pyroptosis.[298] Pyrroloquinoline quinone (PQQ) inhibited the pyroptosis pathway by alleviating mitochondrial dysfunction and reducing ROS production and NF-κB and caspase-1 expression.[299] Hyperoside regulates

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extracellularly regulated protein kinases 1/2/mitogen-activated protein kinase signaling the pathway is used to inhibit OS, thereby alleviating the pyroptosis of renal tubular epithelial cells.[300] Syringaresinol inhibits the NLRP3/caspase-1/GSDMD pyroptosis pathway through upregulating the Nrf2 signaling pathway.[301] Hirudin regulates interferon regulatory factor 2 (Irf2) to inhibit GSDMD-mediated pyroptosis,[302] Carnosine targeting Caspase-1-mediated pyroptosis,[303] Sodium butyrate (NaB) regulates typical pyroptosis pathways of caspase-1/GSDMD,[304] while Puerarin inhibits caspase-1-mediated pyroptosis.[305] The GLP-1 analog liraglutide regulates NLRP3-induced inflammation and cell pyroptosis.[306] VX-765 is a caspase-1 inhibitor and can interfere with DKD models in vivo and in vitro through cell pyroptosis.[307] Dapagliflozin improved podocytosis through HO-1.[308] Atorvastatin inhibit podocytosis through MALAT1/miR-200c/NRF2.[309] Human Umbilical Cord Mesenchymal Stem Cells inhibited the pyroptosis of renal tubular epithelial cells under DKD conditions through miR-342-3p/ Caspase1 signaling pathway.[310] TCM and active ingredients have also been shown to protect DKD by inhibiting the pathway of pyroptosis. Chuanxiong active components can improve the pyroptosis level under high glucose.[311] Triptolide (TP) inhibits OS and pyroptosis through Nrf2/ROS/NLRP3 axis,[312] and Astragaloside IV (AS) increased the expression of sirtuin 6 (SIRT6). The expression of hypoxia-inducible factor 1 subunit alpha (HIF-1a) was decreased, and ROS was inhibited from alleviating podocyte pyroptosis.[313] Biochanin A regulates the pyroptosis cascade and NF-kB/NLRP3 axis of renal tubular epithelial cells[314] and improve DKD renal dysfunction and renal injury. Table 3 summarizes different interventions that delay the progression of DKD by regulating pyroptosis (Table 3).

Table 3 Different Intervention Methods Delayed the Progression of DKD by Regulating Pyroptosis

Intervention	Object of Study	Key Targets/Pathways	Results	References
Pyrroloquinoline quinone	C57BL/6 J mice and HK-2 cell	↓ROS/↓mitochondrial dysfunction → ↓NF-κB/ pyroptosis → ↓renal fibrosis	Pyrroloquinoline quinone ameliorates renal fibrosis in diabetic nephropathy by inhibiting the pyroptosis pathway.	[299]
Hyperoside	C57BL/6 J mice and HK-2 cell	↓ERK1/2 → ↓ROS/ ↓pyroptosis → ↓tubular injury	Hyperoside mediates protection from diabetes kidney disease by regulating ROS-ERK signaling pathway and pyroptosis.	[300]
Syringaresinol	Primary renal tubular epithelial cells (RTECs) and C57BL/6 J mice	↑NRF2 → ↓ROS/↓NLRP3 → ↓pyroptosis/↓fibrosis → ↓renal injury	Syringaresinol inhibits the NLRP3/Caspase-1/ GSDMD pyroptosis pathway through up-regulating the Nrf2 signaling pathway.	[301]
Hirudin	C57BL/6 J mice	↑mTORC1 → ↑ROS/ ↑NLRP3-pyroptosis → podocyte injury	Hirudin regulates interferon regulatory factor 2 (Irf2) to inhibit GSDMD-mediated pyroptosis.	[302]
Carnosine	C57BL/6 J mice and MPC5 cell	↓caspase-1 → ↓pyroptosis → ↓podocyte injury	Carnosine alleviates podocyte injury in diabetic nephropathy by targeting caspase-1-mediated pyroptosis.	[303]
Sodium butyrate	Human renal glomerular endothelial cells (GECs)	↓NF-κB → ↓caspase-1/ GSDMD → ↓pyroptosis → ↓GEC injury	Sodium butyrate alleviates high-glucose-induced renal glomerular endothelial cells damage via inhibiting pyroptosis.	[304]
Puerarin	C57BL/6 J mice and MPC5 cell	↑SIRT1→↓NLRP3/Caspase-1 → ↓pyroptosis→↓podocyte injury/↓renal inflammation	Puerarin alleviates diabetic nephropathy by inhibiting Caspase-1-mediated pyroptosis.	[305]
Liraglutide	C57BL/6 J mice	↑GLP-1R → ↓NLRP3/ pyroptosis → ↓podocyte injury	Liraglutide protects DKD mouse podocytes by regulating GLP-1R in renal tissues and byregulating NLRP3-induced inflammation and pyroptosis.	[306]
VX-765	CD1 (ICR) mice and HK-2 cell	↓caspase-1 → ↓NLRC4/ pyroptosis → ↓inflammation/ ↓fibrosis	VX-765 ameliorates renal injury and fibrosis in diabetes by regulating caspase-1-mediated pyroptosis and inflammation.	[307]

(*Continued*)

Table 3 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Dapagliflozin	MPC5 cell	↑HO-1 → ↓NLRP3/ pyroptosis → ↓podocyte injury	Dapagliflozin alleviates renal podocyte pyroptosisvia regulation of the HO-1/NLRP3 axis.	[308]
Atorvastatin	MPC5 cell	↓MALAT1 → ↓miR-200c → ↑NRF2/HO-1 → ↓pyroptosis/↓OS	Atorvastatin regulates MALAT1/miR-200c/NRF2 activity to protect against podocyte pyroptosis induced by high glucose.	[309]
Umbilical cord mesenchymal stem cells	Rats	↑miR-342-3p → ↓Caspase1 → ↓pyroptosis → ↓renal injury	UC-MSC-derived miR-342-3p inhibited pyroptosis of renal tubular epithelial cells through targeting the NLRP3/Caspase1 pathway.	[310]
Chuanxiong	Databases	↓DHCR24/CHI3L1/ CACNB2 → ↓pyroptosis/ ↓inflammation	The improvement of DN by Chuanxiong is related to the change of pyroptosis.	[311]
Triptolide	C57BL/6 J mice and MPC5 cell	↑Nrf2/HO-1 → ↓ROS/ ↓NLRP3 → ↓pyroptosis/↓OS → ↓podocyte injury	TP alleviated podocyte injury in DN by inhibiting OS and pyroptosis viaNrf2/ROS/NLRP3 axis.	[312]
Astragaloside IV	SD rats and podocytes	↑SIRT6 → ↓HIF-1α → ↓ROS/ ↓pyroptosis → ↓podocyte injury	Astragaloside IV inhibited podocyte pyroptosis in DKD by regulating SIRT6/HIF-1a axis.	[313]
Biochanin A	Rats and NRK-52E cell	↓NF-κB/↓TGF-β → ↓NLRP3/ ↓fibrosis → ↓renal injury	Biochanin A regulates the pyroptosis cascade and the NF-kB/NLRP3 axis of renal tubular epithelial cells.	[314]

Ferroptosis in Diabetic Kidney Disease

The regulation of ferroptosis is closely related to iron metabolism disorder, lipid metabolism abnormality, oxidation, and antioxidant imbalance. Iron has two oxidation states: ferrous (Fe^{2+}) and iron (Fe^{3+}). The reductase of the kernel can reduce Fe^{3+} to Fe^{2+}, and when Fe^{2+} is abnormally elevated, it will promote ferroptosis.[315] The typical characteristic of ferroptosis was the inactivation of glutathione peroxidase 4 (GPX4) and the damage of cystine transport System XC- (xCT). These include the solute carrier family 7-member 11 (Slc7a11), increased cell membrane density, dysregulation of iron homeostasis, and accumulation of lipid peroxides, leading to mitochondrial atrophy.[316–318] Proteinuria in DKD patients is related to the reabsorption of a large amount of transferrin into renal tubular epithelial cells and the degradation of lysozyme, resulting in excessive Fe^{2+} retention.[319] Progressive iron overload can produce nephrotoxicity, which is manifested by the accumulation of Fe^{2+} in cells that catalyzes the production of many ROS through the Fenton reaction, and ROS can directly attack the phospholipids containing PUFAs (polyunsaturated fatty acids) in cell membranes, causing phospholipperoxidation and triggering ferroptosis in cells.[320] Figure 4 shows that different factors regulate DKD through ferroptosis (Figure 4). Recent studies have found that iron overload exists in various DKD models, such as db/db, streptozotocin induction, and the ZSF1 model. In addition, the expression of ACSL4 (acyl-CoA synthetase long-chain family member 4), prostaglandin-endoperoxide synthase 2 (PTGS2), NCOA4 (nuclear receptor coactivator 4), and other ferroptosis markers were increased, while the expression of anti-lipid oxide GPX4 was decreased.[321–324] In addition, GPX4 is significantly associated with proteinuria, ACR, serum creatinine (Scr), eGFR, and glomerular sclerosis rates, and patients with low GPX4 have a higher incidence of ESRD.[325] A cross-sectional study showed that for T2DM patients, with the increase of urinary albumin excretion rate (UAER), the levels of GPX4, Fe, and Tf gradually decreased, while the levels of ACSL4 increased. At the same time, with the decrease in estimated glomerular filtration rate (eGFR), GPX4 and Tf levels gradually decreased, while ACSL4 levels increased, and UAER and ACSL4 were independently and positively correlated.[326] Bioinformatic analysis of renal tubulointerstitial injury in DKD patients showed that D44, PTEN, ALOX5, and NCF2 were negatively correlated with eGFR, while VEGFA and DDIT3 were positively correlated with eGFR. These genes may be molecular mechanisms involved in the occurrence and development of DKD.[327] A prospective observational study of 118 patients showed that the combined detection of GPX4, ACSL4, MDA, and

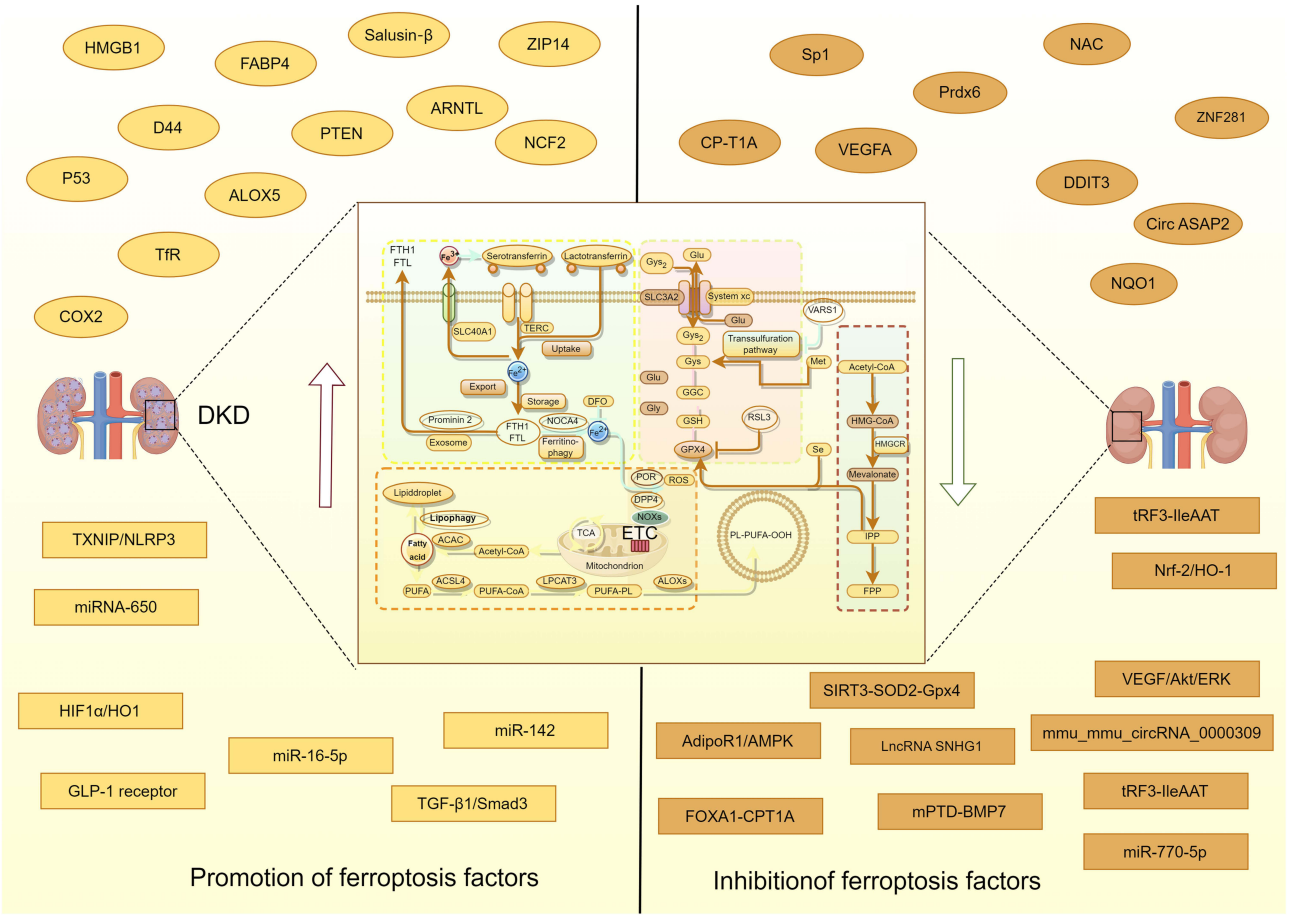

Figure 4 Shows that different factors regulate DKD through ferroptosis. By Figdraw.

ROS had good predictive value for DKD. In addition, ferritin level, serum iron, transferrin, and GPX4 were independently correlated with massive proteinuria.[328] Compared with non-diabetic patients, the mRNA expressions of xCT and GPX4 in renal biopsy tissue of diabetic patients were decreased. Ferrostatin 1 (Fer-1) was found increased in the in vivo and in vitro DKD models with reduced lipid peroxidation, ferroptosis, and renal tissue injury.[329]

Diverse Factors Promote DKD Progression by Inducing Ferroptosis

Different factors promote the progression of DKD by inducing ferroptosis. HMGB1 regulates ferroptosis through the Nrf2 pathway,[330] IME imbalance causes ferroptosis,[331] and the expression of fatty acid binding protein 4 (FABP4) increases. Inhibit the expression of carnitine palmitoyltransferase-1A (CP-T1A), reduce superoxide dismutase, increase mitochondrial damage, and induce ferroptosis.[332] ZRT/IRT-like protein 14 (ZIP14) is involved in iron accumulation and ferroptosis as a transporter.[333] Salusin β is involved in ferroptosis in a Nrf 2 dependent manner,[334] accelerating renal dysfunction and kidney injury in DKD. KAT2A promotes ferroptosis in DKD through H3K79succ-mediated upregulation of SAT2, thereby driving renal injury and inflammation.[335] Different factors that inhibit ferroptosis have therapeutic effects on DKD. The mmu_mmu_circRNA_0000309, a circular RNA, regulates the ferroptosis pathway by regulating the miR-188-3p/GPX4 signaling pathway,[336] LncRNA SNHG1 down-regulates the targeting of miR-16-5p/ACSL4 axis to inhibit ferroptosis.[337] Circ ASAP2 inhibits inflammation and ferroptosis through SOX2/SLC7A11 mediated by miR-770-5p.[338] Preupregulation of peroxiredoxin 6 (Prdx6) mediated by specificity protein 1 (Sp1) alleviated OS and ferroptosis pathway,[339] while Vitexin decreased ROS, Fe^{2+} and MDA levels by activating GPX4.[340] Down-regulation of Aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL) reduces OS and ferroptosis and alleviates mitochondrial morphological changes.[341] N-acetylcysteine (NAC) activates the SIRT3-SOD2-Gpx4 signaling pathway to maintain mitochondrial REDOX homeostasis

and reduce ferroptosis,[342] GLP-1 drug somaluretide (SMG) further reduces renal inflammation and fibrosis by inhibiting iron death.[343] The tRF3-IleAAT inhibits ferroptosis by targeting zinc finger protein 281 (ZNF281),[344] and Umbelliferone inhibits ferroptosis by down-regulating ACSL4 and upregulating GPX4 by activating the Nrf-2/HO-1 pathway.[345] Puerarin (PUR) inhibits excessive extracellular matrix (ECM) accumulation to prevent DKD.[346] Protein transduction domain (PTD)-fused BMP7 in micelles (mPTD-BMP7) can accelerate the regeneration of the diabetic pancreas and inhibit ferroptosis,[347] Aspirin supposes the activation of cyclooxygenase-2 (COX2), which is a potential target of ferroptosis and inhibits ferroptosis,[348] Carnosine is a scavenger of iron ion and reactive oxygen species and acts as NrF2-mediated ferroptosis.[349] Canagliflozin improves the fatty acid oxidation (FAO) and ferroptosis of renal tubular epithelial cells through the FOXA1-Carnitine palmitoyl transferase 1A (CPT1A) axis.[350] Dapagliflozin improves DKD by inhibiting ferroptosis, promoting β-hydroxybutyrate (BHB) production, and regulating Ca2+/calmodulin-dependent protein kinase 2 (CaMKK2).[351] Total flavones from Abelmoschus manihot (TFA) and daglizin can improve iron deposition, lipid peroxidation capacity, and expression of ferroptosis-related proteins, inhibit ferroptosis,[352] and treat DKD.

TCM has been shown to have a regulatory effect on ferroptosis to treat DKD. Rosa laevigata Michx. inhibits ferroptosis.[353] Natural botanical PDB (and its active constituents quercetin, kaempferol, β-sitosterol) inhibits ferroptosis in diabetic kidney disease by activating the Nrf2 signaling pathway, upregulating HO-1/GPX4/SLC7A11 and restoring glutathione homeostasis.[354] Rhodiola decreased iron load and inhibited lipid peroxidation by inhibiting TFR1 expression.[355,356] Leonurus reduces Fe2+ and ROS by upregulating GPX4 levels.[357] Glycyrrhiza inhibits NCOA4 expression, upregulates GPX4 level, and mediates Slc7a11/SLC3A2 to down-regulate TFR1 protein expression.[358] Quercetin inhibits ferroptosis in renal tubular epithelial cells by regulating the Nrf2/HO-1 signaling pathway to treat DKD.[359] In addition, the sleeve gastrectomy (SG), a type of bariatric surgery, inhibits ferroptosis by inhibiting the TGF-β1/Smad3 signaling pathway, improves metabolic parameters and glucose homeostasis in DKD rats, reduces the impact of DKD on renal function indicators and tissue morphology, and reduces renal tubules injury.[360] Table 4 summarizes different interventions that delay the progression of DKD by regulating ferroptosis (Table 4).

Table 4 Different Interventions Delayed the Progression of DKD by Regulating Ferroptosis

Intervention	Object of Study	Key Targets/Pathways	Results	References
Umbelliferone	HK-2 cell and db/db mice	↑Nrf2/HO-1 → ↓ferroptosis → ↓renal injury	Umbelliferone delays the progression of diabetic nephropathy by inhibiting ferroptosis through activation of the Nrf-2/HO-1 pathway.	[345]
Puerarin	SD rats and HBZY-1 cell	↑iron homeostasis → ↓ferroptosis → ↓ECM/fibrosis	Puerarin against excessive extracellular matrix accumulation through inhibiting ferroptosis in diabetic nephropathy.	[346]
Bone morphogenetic protein-7	C57BL/6 mice and cells	↓TGF-β → ↓ferroptosis → ↓DN progression	BMP7 impedes the progression of diabetic nephropathy by inhibiting the canonical TGF-β pathway, attenuating ferroptosis, and helping regenerate diabetic pancreas.	[347]
Aspirin	DBA/2J mice and HK-2 cell	↓COX2 → ↓ferroptosis → ↓tubular injury/↓DKD progression	Aspirin mediates protection from DKD by inducing ferroptosis inhibition.	[348]
Carnosine	C57BL/6 J mice and HK-2 cell	(Fe^{2+}/ROS scavenging) → ↑NRF2 nuclear translocation → ↑HO-1/GPX4 → ↓ferroptosis (↓ACSL4/↓LPO/↑GSH) → ↓tubular injury	Carnosine alleviates kidney tubular epithelial injury by targeting NRF2 mediated ferroptosis in diabetic nephropathy.	[349]
Canagliflozin	HK-2 cell and db/db mice	↑FOXA1 → ↑CPT1A transcription → ↑fatty acid oxidation (↑ATP/↓lipid droplets) → ↓lipid peroxidation → ↓ferroptosis → ↓renal injury	Canagliflozin improves fatty acid oxidation and ferroptosis of renal tubular epithelial cells via FOXA1-CPT1A axis in DKD.	[350]

(*Continued*)

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Table 4 (Continued).

Intervention	Object of Study	Key Targets/Pathways	Results	References
Dapagliflozin	C57BL/6J mice	↑BHB → ↓CaMKK2 → ↓ferroptosis (↓lipid peroxidation/↑mitochondrial health) → ↓kidney injury	Dapagliflozin improves DKD by inhibiting ferroptosis, promoting BHB production, and regulating CaMKK2.	[351]
Abelmoschus Manihot and Dapagliflozin	SD rats and NRK-52E cell	↓iron deposition/↑antioxidant capacity → ↓ferroptosis → ↓tubular injury	Total flavones from Abelmoschus manihot (TFA) and Dapaglizin improved iron deposition, lipid peroxidation capacity and expression of iron death-related proteins, inhibiting ferroptosis.	[352]
Rosa laevigata Michx.	C57BL/6 J mice	↑tryptophan/riboflavin metabolism →↓ferroptosis/↓apoptosis(PI3K/AKT) → ↓renal injury	Rosa laevigata Michx. Polysaccharide ameliorates diabetic nephropathy in mice through inhibiting ferroptosis.	[353]
Potentilla Discolor Bunge	Rats and HK-2 cell	Nrf2/HO-1/GPX4 axis → ↓ferroptosis (↓ROS/↓MDA/↓Fe^{2+}) → ↓DKD progression	PDB delays the progression of DKD by upregulating the Nrf2 signaling pathway and inhibiting the initiation of ferroptosis.	[354]
Salidroside	Wild-type and Nrf2 mice,	↑Nrf2 → ↑SLC7A11/GPX4 → ↓ferroptosis (↓lipid peroxidation/↓iron) → ↓lung IRI	Salidroside postconditioning attenuates ferroptosis-mediated lung ischemia-reperfusion injury by activating the Nrf2/SLC7A11 signaling axis.	[355]
Salidroside	SAMP8 mice	↓ferroptosis (↓lipid peroxidation/↓iron dysregulation) → ↓TGF-β/α-SMA → ↓renal fibrosis	SAL delays renal aging and inhibits aging-related glomerular fibrosis by inhibiting ferroptosis in SAMP8 mice.	[356]
Leonurine	Nrf2 KO mice	↑Nrf2 → ↑GPX4/xCT → ↓ferroptosis (↓iron/↓lipid peroxidation) → ↓AKI	Nrf2 activation on cisplatin-induced acute kidney injury are achieved, at least partially, by inhibiting lipid peroxide-mediated ferroptosis, highlighting the potential of leonurine in acute kidney injury treatment.	[357]
Glabridin	SD rats and NRK-52E cell	↓VEGF/AKT/ERK & ↑GPX4/SLC7A11 → ↓ferroptosis/↓fibrosis → ↓renal injury	Glabridin ameliorates diabetic nephropathy by regulating ferroptosis and the VEGF/Akt/ERK pathways.	[358]
Quercetin	HK-2 cell and db/db mice	↑Nrf2/HO-1 → ↑GPX4/↑SLC7A11/↑FTH-1 and ↓TFR-1 → ↓ferroptosis → ↓tubular injury	Quercetin ameliorates diabetic kidney injury by inhibiting ferroptosis via activating Nrf2/HO-1 signaling pathway.	[359]

Other PCD in Diabetic Kidney Disease

Mitotic catastrophe (MC) causes the loss of podocytes in the urine of diabetic patients.[361] The senescence of RTECs plays a crucial role in the progression of DKD, and insufficient mitophagy is closely related to RTEC senescence. Studies have shown that yeast mitochondrial escape 1-like 1 (YME1L) mediated senescence plays an anti-aging role in renal tubular cells in diabetic conditions and hinders the progression of DKD.[362] Elevated circulating growth hormone levels (GH) are associated with diabetic podocyte damage and proteinuria. Studies have shown that GH induces mitotic mutations in glomerular podocytes, leading to proteinuria.[363] Murine double minute 2 (MDM2) is a cell cycle regulator widely expressed in kidney cells, including podocytes.[364,365] MDM2 is involved in high glucose-induced podocyte mitosis mutation through the Notch1 signaling pathway.[366]

In addition, several PCD modes have been discovered, including necroptosis, parthanatos, entotic cell death, mitotic cell death, lysosome-dependent cell death, alkalosis, and oxeiptosis. A microarray-based transcriptome analysis and single-core RNA sequencing analysis revealed that DKD is associated with the four core PCD pathways: entotic cell death, apoptosis, necroptosis, and pyroptosis. The WGCNA algorithm was further applied to screen four core death genes (CASP1, CYBB, PLA2G4A, and CTSS), and the CDS risk score was constructed based on these genes. The CDS risk

score was more efficient in diagnosing DKD patients.[367] There are still some unclear relationships between PCD and DKD, which may provide new ideas for further exploration of the pathogenesis of DKD.

Discussion

DKD progression is fundamentally driven by dysregulated PCD pathways, where apoptosis, autophagy, pyroptosis, and ferroptosis collectively exacerbate renal injury through distinct mechanisms. Apoptosis induces podocyte and tubular cell loss via mitochondrial dysfunction (eg, Bim/NFAT2) and caspase activation; impaired autophagy accelerates damage by accumulating toxic cellular debris, exhibiting dual roles (deficiency in PINK1/Parkin mitophagy vs detrimental overactivation); pyroptosis amplifies inflammation through NLRP3/GSDMD-driven gasdermin cleavage, though species-specific GSDME effects exist; while ferroptosis promotes iron-dependent lipid peroxidation (GPX4↓/ACSL4↑ correlating with proteinuria). Critically, these pathways exhibit extensive crosstalk (eg, NLRP3 pyroptosis → ferroptosis via ROS; autophagy defects → ERS-dependent apoptosis), forming an interconnected network that amplifies DKD pathogenesis.

Therapeutically, targeting PCD holds significant promise: Pharmacological agents (eg, SGLT2 inhibitors restoring autophagy flux, GLP-1 analogs suppressing pyroptosis), natural compounds (eg, berberine modulating ferroptosis via Nrf2), and RNA-based strategies (eg, miR-30e-5p inhibiting apoptosis/pyroptosis) demonstrate efficacy in preclinical models. However, key controversies impede translation: Compartmentalized PCD effects (GSDMD-tubular vs GSDME-glomerular), stage-dependent autophagy outcomes, and inconsistent ferroptosis biomarkers in human cohorts necessitate precision targeting. Clinically, interventions like combined enalapril/paricalcitol therapy synergistically attenuate multiple PCD pathways, improving proteinuria and glomerulosclerosis. Emerging approaches—including stem cell-derived extracellular vesicles and CRISPR-based gene editing—offer novel precision tools to reprogram PCD dynamics.

Nevertheless, key limitations persist. Mechanistic crosstalk between PCD modes remains incompletely mapped, necessitating multi-omics studies to decode signaling networks. Translational gaps are evident, as most evidence derives from animal models; validating urinary PCD biomarkers (eg, LC3B for autophagy, GPX4 for ferroptosis in human cohorts is imperative. Emerging PCD modes like necroptosis and parthanatos are underexplored in DKD, while clinical safety concerns—such as off-target effects of pan-caspase inhibitors (eg, Z-DEVD-FMK)—demand rigorous long-term assessment. Future research must prioritize combinatorial therapies, patient stratification based on PCD profiles, and human trials to translate these mechanistic insights into effective clinical strategies against DKD.

Conclusion

DKD progression is orchestrated by interconnected PCD pathways: apoptosis mediating cell loss, autophagy exhibiting dual protective/detrimental roles, pyroptosis driving inflammation, and ferroptosis accelerating lipid peroxidation. Their crosstalk creates an amplifying injury network. While therapeutic targeting shows promise, unresolved controversies—including stage-dependent effects, cell-type specificity, and biomarker gaps—demand patient-stratified combinatorial approaches for clinical translation.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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