Journal of Translational Medicine

REVIEW Open Access

Important regulatory role of mitophagy in diabetic microvascular complications

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Abstract
Microvascular complications of diabetes pose a significant threat to global health, mainly including diabetic kidney disease (DKD), diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN), and diabetic cardiomyopathy (DCM), which can ultimately lead to kidney failure, blindness, disability, and heart failure. With the increasing prevalence of diabetes, the search for new therapeutic targets for diabetic microvascular complications is imminent. Mitophagy is a widespread and strictly maintained process of self-renewal and energy metabolism that plays an important role in reducing inflammatory responses, inhibiting reactive oxygen species accumulation, and maintaining cellular energy metabolism. Hyperglycemia results in impaired mitophagy, which leads to mitochondrial dysfunction and ultimately exacerbates disease progression. This article summarizes the relevant molecular mechanisms of mitophagy and reviews the current status of research on regulating mitophagy as a potential treatment for diabetic microvascular complications, attempting to give new angles on the treatment of diabetic microvascular complications.

Keywords Mitophagy, Diabetic kidney disease, Diabetic peripheral neuropathy, Diabetic retinopathy, Diabetic cardiomyopathy

Introduction

Diabetes is a metabolic disease characterized by chronic hyperglycemia. By 2030, there will be 643 million diabetes worldwide, and by 2045, there will be 784 million [1]. Chronic complications of diabetes are categorized into macrovascular and microvascular complications, and diabetic microvascular complications mainly include diabetic kidney disease (DKD), diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN), and diabetic cardiomyopathy (DCM). Diabetic microvascular complications can lead to blindness, renal failure, disability, and death. These results have a substantial deterioration in patients' life quality, causing significant psychological distress to patients and a huge economic burden to society [2–5]. Epidemiology shows that approximately 40% of diabetic patients develop DKD, but this figure changes according to the diagnostic guidelines for DKD [6, 7]. DKD has a high disease burden worldwide and significantly increases the risk of renal failure and cardiovascular events [8]. DR is one of the leading causes of vision loss in middle-aged and older adults, and approximately 33% of diabetic patients have DR [9]. Nearly 50% of diabetics are affected by DPN, which is a common complication of diabetes [10]. DPN patients are prone to falls and

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injuries, which may further lead to infections and amputations, greatly affecting their quality of life [11]. DCM is characterized by left ventricular hypertrophy and diastolic dysfunction [12, 13]. DCM is the main cardiovascular complication of DM, which is closely related to the occurrence of heart failure and is one of the main causes of death in Diabetes Mellitus (DM) patients [14].

Mitochondria, an important organelle, is the site of oxidative phosphorylation of eukaryotic cells to produce ATP and serves as the primary source of energy in all eukaryotic cells [15]. Mitochondria perform important functions in bioenergetics, metabolism, and apoptosis [16]. Autophagy is necessary for regular cellular function and aids in maintaining intracellular homeostasis by eliminating senescent organelles and misfolded proteins [17]. In mammalian cells, autophagy is divided into three main categories, macroautophagy, microautophagy, and molecular chaperone-mediated autophagy [18]. Macroautophagy, commonly known as autophagy, refers to the formation of bilayer membrane vesicles (autophagosomes) that extend and wrap the cytoplasm or organelles, and then bind to lysosomes to form autophagolysosomes, thereby removing damaged cells [17]. Microautophagy refers to the process in which lysosomal membrane invagination encapsulates intracellular substances and subsequently degrades them [19]. Molecular chaperone-mediated autophagy is a specific protein that binds to chaperone proteins, such as heat shock homolog 70 (Hsc70), after binding, the targeted lysosomal membrane is directly transported to the lysosome and then degraded [20]. Mitophagy belongs to macroautophagy, which selectively clears damaged mitochondria and has a vital role in maintaining mitochondrial quality [21].

Mitochondrial dysfunction is linked to numerous diseases, including metabolic syndrome, cardiovascular disease, cancer, and neurodegeneration [22]. This article reviews the molecular mechanism of mitophagy, focusing on the specific regulatory role of mitophagy in microvascular complications of diabetes and the existing research progress in this field.

Mitophagy

In 2005, Lemasters noticed that the destruction of mitochondria was a signal to initiate mitophagy and proposed the concept of mitophagy [23]. Since then, research on the mechanism of mitophagy has received extensive attention. Under reactive oxygen species (ROS), hypoxia, toxic chemicals, cellular senescence, etc., mitochondria are damaged by depolarization, and mitochondria become dysfunctional. Mitophagy occurs in the cell to preserve mitochondrial and cellular balance. Firstly, the dysfunctional mitochondria are depolarized and the membrane potential disappears, then the autophagosome extends and wraps around the mitochondria to form the mitochondrial autophagosome, and then the mitochondrial autophagosome fuses with the lysosome [24]. Dysfunctional mitochondria are degraded after fusion, thus completing mitophagy. The following two main categories of mechanisms have been identified in current studies: ubiquitin (Ub)-dependent pathways and non-ubiquitin-dependent pathways. This section will focus on the mechanisms of these two types of mitophagy pathways (Fig. 1).

Ubiquitin-dependent pathway

Mechanism of PINK1 and parkin stabilization and activation

The ubiquitin-dependent mechanism utilizes extensive ubiquitination of mitochondrial surface proteins to enhance mitophagy. Among these pathways, the PTEN-induced putative kinase 1 (PINK1)/Parkin pathway is currently the greatest extensively studied [24]. PINK1 is encoded by the PARK6 gene and is a protein kinase; PINK1 contains an N-terminal mitochondrial targeting sequence (MTS), transmembrane domain (TM), non-conserved region, Ser/Thr kinase domain, and a conserved C-terminal region (CTR) with unknown function and structure [25]. Parkin is encoded by the PARK2 gene and is an E3 ubiquitin ligase; Parkin consists of an N-terminal ubiquitin-like domain (UBL), a truly interesting new gene 0 (RING0), RING1, RING2, repressor element of parkin (REP), and an in-between-RING (IBR) [26, 27]. Under normal circumstances, mitochondrial outer membrane translocase 20 (TOM20) recognizes MTS sequences with the help of mitochondrial outer membrane translocase 22 (TOM22) and mitochondrial outer membrane translocase 70 (TOM70) and transfers PINK1 to the ectopic pore formed by mitochondrial outer membrane translocase 40 (TOM40); through the ectopic pore, it enters the translocase of inner mitochondria membrane 23 (TIM23) complex in the mitochondrial inner membrane, and once it has crossed the mitochondrial inner membrane, it is segmented by mitochondrial processing peptidase (MPP) and presenilin-associated rhomboid protein (PARL) and then degraded [28–30]. Under normal mitochondrial function, Parkin is inhibited and exists in the cytoplasm.

If mitochondria are damaged, adenine nucleotide transport protein (ANT) interacts with the translocase of inner mitochondria membrane 44 (TIM44) and prevents PINK1 from entering the TIM23 complex, while at the same time, mitochondrial outer membrane translocase 7 (TOM7) binds to the C-terminus of PINK1, causing PINK1 to remain on the outer mitochondrial membrane [30, 31]. PINK1 accumulates continuously at the outer layer of the mitochondrial membrane and under the action of TOM complexes undergoes autophosphorylation and activation, thereby initiating mitophagy [32]. First PINK1 phosphorylates the ubiquitin protein (Ub),

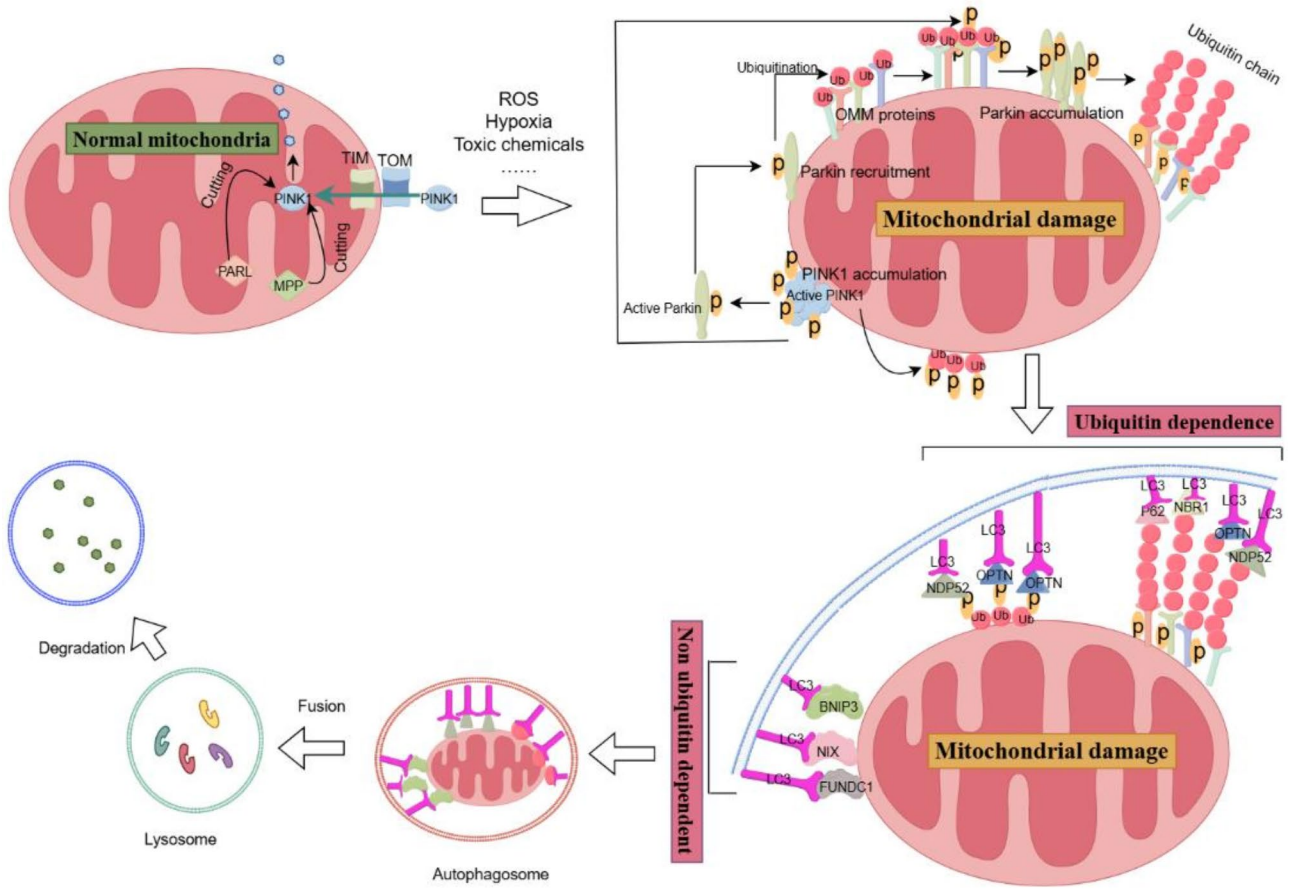

Fig. 1 Activated PINK1 phosphorylates Parkin, which is activated to ubiquitinate some mitochondrial outer membrane proteins, and these ubiquitinated proteins are further phosphorylated by PINK1, which will recruit more Parkin into the mitochondria, thus producing more ubiquitin chains. The ubiquitin chains require autophagy junction proteins (P62, NBR1, OPTN, NDP52, etc.) to fuse with the autophagosome membrane. Non-ubiquitin-dependent pathway: When mitochondria are damaged, some mitochondrial proteins (FUNDC1, BNIP3, and Nix) can directly bind to LC3 to initiate mitophagy

and the phosphorylated ubiquitin (pUb) subsequently binds to RING1, leading to the release of UBL, which is immediately followed by phosphorylation of UBL by PINK1, and binding of the phosphorylated UBL to RING0, and the subsequent release of RING2 [33, 34].

Autophagy adaptor protein

Through the above changes in Parkin's structure, Parkin changes from a self-inhibited state to an active state. Some outer mitochondrial membrane (OMM) proteins are ubiquitinated by active Parkin, and these mitochondrial OMM proteins include voltage-dependent anion channel protein 1 (VDAC1), mitochondrial fusion 1 (MFN1), mitochondrial fusion 2 (MFN2), and Mitochondrial Rho GTPase 1 (MIRO1) [35–37]. Immediately following this PINK1 phosphorylates the above proteins ubiquitinated by Parkin and attracts additional Parkin to the mitochondria, resulting in the generation of more ubiquitin chains [38]. Due to the inability of ubiquitin chains to directly bind to autophagosome membranes and Autophagy-related protein 8 (ATG8) family proteins, an intermediary is required, known as autophagy adaptor proteins [39]. The role of autophagy adaptor proteins is to recognize ubiquitin-labeled mitochondria and also recognize microtubule-associated protein 1 light chain 3 (LC3) that interacts with ATG8 family proteins. Autophagy adaptor proteins mainly include sequitosome-1 (P62/SQSTM1), nuclear dot protein 52 (NDP52/ALCOCO2), optineurin (OPTN), human T-cell leukemia virus type I binding protein 1 (TAX1BP1), neighbor of BRCA1 gene 1 (NBR1), etc [40–44]. The above-mentioned autophagy adaptor proteins can initiate mitophagy by interacting with LC3 through their own LIR region [39, 45, 46]. Autophagy adaptor proteins are important in the formation of PINK1/Parkin mitochondrial autophagosomes, with NDP52 and OPTN being the main adaptor proteins for PINK1/Parkin mediated mitophagy [47, 48]. In addition, TAX1BP1 can recruit autophagosomes through LC3-independent pathways [49].

Other E3 ubiquitin ligases

Besides the PINK1/Parkin mechanism, PINK1 can also directly activate mitophagy independently of Parkin by directly recruiting NDP52 and OPTN into mitochondria via ubiquitin phosphorylation [48]. In other words, without Parkin, PINK1 can induce lower mitophagy due to low basal mitochondrial ubiquitin levels, whereas Parkin can produce more ubiquitin substrates and induce robust and rapid mitophagy [48]. Mitochondrial surface proteins can also be ubiquitinated by some other E3 ubiquitin ligases to induce mitophagy, which include smad ubiquitination regulator-1 (SMURF1), mitochondrial E3 ubiquitin protein ligase 1 (MUL1), and glycoprotein 78 (Gp78) [50, 51]. Studies have found that SMURF1 can control the entry of transcription factor EB (TFEB) into the nucleus to activate lysosomal biogenesis [52]. SMURF1 can ubiquitinate ultraviolet resistance-related genes (UVRAG), thereby promoting the maturation of autophagosomes [53]. Studies have also shown that SMURF1 promotes autophagy through the p62/LC3 autophagy pathway to maintain cell homeostasis [54]. MUL1 is an E3 ubiquitin ligase embedded in OMM, also known as mitochondrial anchor protein ligase (MAPL), which shares many mitochondrial substrates with Parkin, such as dynein-associated protein 1 (Drp1) and mitochondrial fusion protein (MFF) [55, 56]. Studies have found that MUL1 is parallel to the PINK1/Parkin pathway and can participate in the regulation of mitochondrial fusion proteins and compensate for the loss of PINK1/Parkin [57]. Notably, some scientists have identified MUL1 as a mediator of PINK1 stability on the mitochondrial membrane, and it can directly induce mitophagy independent of mitochondrial depolarization [58]. Gp78 serves as an E3 ubiquitin ligase anchored to the endoplasmic reticulum (ER) membrane, participating in the ubiquitination and subsequent degradation of specific proteins, leading to mitophagy. Gp78-induced mitophagy is independent of Parkin [59].

Non-ubiquitin-dependent pathway

Mitophagy-related receptors

There are many proteins on the OMM, some of which contain LC3 interaction region (LIR) regions, and these LIR regions can function as autophagy receptors, which begin to undergo mitophagy upon mutual binding with LC3. In mammals, these receptors for autophagy mainly include FUN14 structural domain-containing protein-1 (FUNDC1) receptor, Nip3-like protein X (NIX) receptor, BCL2-interacting protein 3 (BNIP3) receptor, BCL2-like protein 13 (BCL2L13), autophagy and Beclin 1 Regulator 1 (AMBRA1), and recombinant FK506 Binding Protein 8 (FKBP8), etc [24, 60, 61]. NIX is also recognized as the BCL2-interacting protein 3-like (BNIP3L) receptor. The following section focuses on FUNDC1, NIX, and BNIP3 receptors.

The regulation of FUNDC1's phosphorylation and dephosphorylation states is important for its interaction with LC3. FUNDC1 itself contains the LIR region and this LIR region can directly bind either LC3 or ATG8, and mitophagy occurs upon binding [62]. Under normal conditions, the tyrosine at position 18 (Tyr18) in the LIR region in FUNDC1 and the serine at position 13 (Ser13) close to the LIR is highly phosphorylated, at which time FUNDC1 has a low affinity for LC3 [62]. When mitochondria are damaged by changes in the external environment, especially by hypoxia or Carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP) treatment, FUNDC1 can be dephosphorylated at Ser13 by phosphoglycerate mutase family member 5 (PGAM5) phosphatase and enhance its interaction with LC3 for selective mitophagy [62, 63]. Interestingly, unc-51-like kinase 1 (ULK1) can phosphorylate FUNDC1 at the serine 17 site, Which promotes the interaction between FUNDC1 and its target to LC3, and when mitochondria are damaged, FUNDC1 recruits more ULK1 into mitochondria to induce mitophagy [63].

BNIP3 is located in OMM and is an important pro-apoptotic member of the Bcl-2 family, belonging to the BH3-only subfamily [64]. BNIP3 contains a C-terminal region and an N-terminal region [46]. The N-terminal region of BNIP3 contains a LIR motif surrounded by serine at position 17 (Ser17) and serine at position 24 (Ser24), and the binding of BNIP3 to GABARAPL2 and LC3B is closely related to the phosphorylation of Ser17 and Ser24 [65]. Therefore, the phosphorylation level of BNIP3 is essential for stimulating mitophagy compared to the total protein level [46].ULK1 promotes mitophagy by stabilizing BNIP3 protein and stimulating interaction with LC3 through phosphorylation of Ser17 [66]. One study found that knockdown of BNIP3 significantly reduced neuronal mitophagy and apoptosis, leading to upregulation of NIX expression, but the reduction in mitophagy caused by knockdown of BNIP3 was not increased as a result [67].

NIX, also known as BNIP3L, which shares 56% homology with BNIP3, is a member of the pro-apoptotic subfamily of the B-cell lymphoma-2 (Bcl-2) family, possessing the BH3 structural domain and capable of binding to Bcl-2 [68]. The initial report about NIX was that it could clear mitochondria during the maturation process of red blood cells [69]. Impaired mitophagy and exacerbation of ischemic brain damage were found in NIX knockout mice [70]. NIX can directly bind to LC3 in the BH3 domain, recruiting phagosomes (precursors of autophagosomes) to mitochondria and acting as autophagy receptors, mediating mitochondrial clearance after mitochondrial damage and red blood cell differentiation [71].

Lipid-mediated mitophagy

There is a mutual connection between mitophagy and mitochondrial lipid signaling, and both ceramides and cardiolipin (CL) have been shown to promote mitophagy [72]. CL is an important part of the mitochondrial membrane [73]. In healthy mitochondria, about 3% of the CL is in the OMM and the remaining 97% is in the IMM [74]. With mild mitochondrial damage, CL translocates to the OMM and is recognized by autophagosomes as a marker of dysfunctional mitochondria, and when mitochondria are severely damaged, CL undergoes increased oxidation and accumulates on the OMM, which can lead to the onset of apoptosis [75]. It has been found that CL is transported to the OMM and is capable of interacting with the N-terminal structural domain of LC3, which ultimately leads to the formation of autophagosomes and promotes the onset of mitophagy in neuronal cells to remove damaged mitochondria [76]. CL located on OMM can interact with Beclin1 to induce mitophagy [73]. Mitochondrial fission plays a key part in mitophagy, and inhibition of mitochondrial fission attenuates the level of mitophagy [77]. In some specific cases, Drp1 is directed from the cytoplasm towards the OMM and fragments the mitochondria, and Drp1 binds strongly to the CL [78]. However, whether CL in combination with Drp1 plays a role in mitophagy and the specific mechanisms involved remain to be investigated [60]. Ceramides are a class of bioactive lipids that can serve as structural components of cell membranes and as signaling molecules. Ceramides can bind to LC3B-II at the mitochondrial membrane, thereby inducing mitophagy [79]. It has been shown that ceramide accumulation increases mitochondrial fission regulators, such as Drp1 and MFF, as well as LC3B and PINK1, and promotes mitophagy [80]. Lipid-protein interactions in OMM promote autophagosome recruitment and expansion and induce mitophagy; however, lipid-induced mitophagy is still understudied, and in-depth studies on its specific molecular mechanisms are still needed.

PHB2-mediated mitophagy

However, it is worth mentioning that Prohibitin 2 (PHB2) is an IMM autophagy receptor that is both a participant in ubiquitin-dependent mitophagy and is associated with non-ubiquitin-dependent mitophagy. During mitochondrial depolarization, PHB2 binds to specific proteins while PGAM5 from being sheared, and intact PGAM5 stabilizes PINK1 on the OMM, thereby enhancing PINK1-Parkin-mediated mitophagy [81]. PHB2 can recruit LC3 and mediate PINK1/Parkin-dependent mitochondrial autophagy [82]. It has been found that mitochondrial aurora kinase A, MAP1LC3, and PHB2 can form a complex, independent of PINK1-Parkin-mediated mitophagy [83]. Interestingly, it was found that Parkin ubiquitinates PHB2 and stimulates the interaction among PHB2 and LC3 to enhance mitophagy, where PHB2 serves as both the receptor for autophagosome recruitment and the basis for ubiquitin-mediated autophagosome recruitment [84].

The role of mitophagy

Mitophagy and mitochondrial dynamics work together to maintain mitochondrial homeostasis

The dynamics of mitochondria include the processes of fusion and fission, and mitochondria are in a dynamic equilibrium of constant fusion and fission [85]. Mitochondria are constantly undergoing fusion and fission, thus maintaining the normal morphology and number of mitochondria; mitophagy removes functionally impaired mitochondria; mitochondrial dynamics and mitophagy are crucial components in maintaining mitochondrial homeostasis. If damaged mitochondria are not removed but fused with functionally normal mitochondria, larger damaged mitochondria will be produced and more ROS will be released, resulting in more severe damage [86]. Mitochondrial fusion occurs through the mediation of.by MFN1, MFN2, and optic atrophy protein 1 (OPA1), and mitochondrial fission is mediated by Drp1, mitochondrial fission protein 1 (FIS1), and MFF [87, 88]. Mitochondrial kinetic-related proteins can promote mitophagy, and MFN1 and MFN2 can be ubiquitinated by activated Parkin, contributing to mitophagy [36]. Before the occurrence of mitophagy, mitochondrial fission is required to generate appropriately sized mitochondrial fragments to facilitate mitophagy [21]. Mitophagy and mitochondrial dynamics interact with each other to maintain mitochondrial homeostasis. Research has shown that enhanced expression of either PINK1 or Parkin in rat hippocampal neurons results in more mitochondria but smaller in size and volume, indicating a tendency towards more fission. Silencing PINK1 leads to a fusion of mitochondrial dynamics expression [89]. PHB2 is a multifunctional protein located in the inner mitochondrial membrane that binds to LC3 and triggers mitophagy, and when PHB2 is absent it causes a selective deletion of the long isoform of OPA1, which leads to abnormal mitochondrial cristae morphology and fragmentation [82, 90]. Similarly, it has been found that FUNDC1 can interact with Drp1 and Opa1, whereas under stress, FUNDC1 dephosphorylates to separate from OPA1 and binds to Drp1, and FUNDC1 recruitment to Drp1 is enhanced on the mitochondria-associated endoplasmic reticulum membranes (MAMs), promoting mitochondrial fission and mitophagy [91, 92]. Hyperglycemic environments are characterized by abnormal mitochondrial dynamics, a tendency for mitochondria to fission rather than to fuse, excessive mitochondrial fission, reduced mitochondrial fusion, and excessive ROS production in different cell

types under hyperglycemic conditions, ultimately leading to mitochondrial dysfunction [93, 94]. Mitochondrial dysfunction, in turn, accelerates ROS production, thereby exacerbating the development of diabetes [95]. Therefore, abnormal mitochondrial dynamics induced by hyperglycemia as well as abnormal mitophagy may be the common pathogenesis of diabetic microvascular complications.

Mitophagy affects apoptosis, necrosis, and necroptosis

Mitochondria serve a vital function in advancing apoptosis by releasing cytochrome c (Cyt c) and other pro-apoptotic factors. A complex and intimate connection exists between mitophagy and apoptosis, and some mitophagy receptors, such as BNIP3, NIX, and Bcl2-L-13 belong to the BCL2 family [61, 65, 71, 96]. The intrinsic link between mitophagy and apoptosis was emphasized above. BNIP3 is an autophagy receptor that promotes mitophagy through the LIR region's interaction with ATG8 proteins and can reduce apoptosis by decreasing Cyt c release [65]. Mitophagy can play a protective role for cells, and the anti-apoptotic effects of Parkin have been widely reported, with early studies showing that Parkin strongly inhibits the translocation of BCL-2-associated X protein (BAX) to mitochondria, thereby preventing apoptosis [97, 98]. When mitophagy occurs, further studies have shown that Parkin inhibits the apoptotic functions of Bcl-2 homologous antagonist/killer (BAK) and BAX through different mechanisms, thereby preventing erroneous apoptosis and removing damaged mitochondria [99]. Similarly, it has been found that PINK1 protects cortical neurons from thapsigargin-induced oxidative stress and neuronal apoptosis [100]. It has been found that after mitochondrial depolarization, PINK1 can interact with B-cell lymphoma-extra large (Bcl-xL) and phosphorylate Bcl-xL, blocking the pro-apoptotic cleavage of Bcl-xL and thus preventing cell death [101].

Physical or chemical damaging factors, as well as hypoxia and malnutrition, lead to cellular necrosis, which is characterized by cell swelling, rupture of cell membranes, spillage of cellular contents, and triggers an inflammatory response in the surrounding tissues. Mitochondrial damage leads to increased ROS production, and increased ROS activates inflammatory vesicles in renal tubular cells, leading to apoptosis or necrosis; mitophagy can regulate mitochondrial homeostasis and reduce ROS production, thus exerting a certain anti-apoptotic and reduced necrotic cell death effects [102]. It has been found that keratin 8 promotes mitophagy, reduces the number of damaged mitochondria, decreases oxidative stress, and reduces cell necrosis [103]. In summary, mitophagy removes damaged mitochondria to maintain the stability of the intracellular environment and prevent the occurrence of cell necrosis.

Necrotic apoptosis is a cell death mechanism distinct from apoptosis [104]. Necrotic apoptosis involves activation of receptor-interacting protein kinase (RIPK) and phosphorylation and activation of mixed lineage kinase domain-like protein (MLKL), causing rupture of the cell membrane and release of contents [105]. Mitophagy, as an intracellular quality control mechanism, can weaken necrotic apoptosis induced by mitochondrial dysfunction by eliminating excessive ROS [106]. Under intestinal ischemia-reperfusion, neutrophil extracellular trapping nets (NETs) are released, and NETs activate receptor-interacting protein kinase3 (RIPK3) by binding to Toll-like receptor 4 (TLR4), which phosphorylates FUNDC1, resulting in inhibition of mitophagy and the inability of the damaged mitochondria to be cleared promptly, triggering Mitochondria-dependent necrotic apoptosis, ultimately leading to necrotic apoptosis of intestinal epithelial cells [107]. Exosomes from Schwann cells attenuate mitochondrial dysfunction and necrotic apoptosis after spinal cord injury via mitophagy mediated by the adenylate-activated protein kinase (AMPK) signaling pathway [108]. It has been found that in a mouse model of infarction, increased RIPK3 expression, inhibition of AMPK-Parkin-mitophagy, and opening of the mitochondrial permeability transition pore (mPTP) lead to necrotic apoptosis in cardiomyocytes [109]. In summary, mitophagy can reduce the risk of necrotic apoptosis caused by mitochondrial dysfunction by removing damaged mitochondria.

Mitophagy and diabetic microvascular complications

Mitophagy and DKD

Molecular mechanisms of mitophagy in DKD

In high glucose (HG)-induced human podocytes and Zucker rat models, mitophagy was found to be inhibited, albumin leakage was increased in a hyperglycemic environment, and it was found that PINK1 plays an important role in insulin signaling and maintenance of podocyte permeability and that PINK1 possibly termed as a potential target for the treatment or prevention of DKD [110]. In ADP-ribosylation factor 2-interacting protein (Arfip2)-knockout human podocytes and Arfip2 knockout and streptozotocin (STZ)-induced mouse models, Arfip2 deficiency worsens autophagy in diabetic mice and leads to loss of pedicle protrusions, histopathological alterations, and early albuminuria, and in human podocytes, Arfip2 deficiency interferes with autophagy-associated protein 9a (ATG9A) transport and the PINK1/Parkin pathway, resulting in impaired mitochondrial fission and reduced mitophagy, thus Arfip2 may be a novel factor regulating autophagy and mitochondrial

homeostasis in foot cells [111]. Some investigators found reduced levels of Progranulin (PGRN) in renal biopsies from DKD patients and in the kidneys of DM mice, and using PGRN-deficient mice and HG-induced human podocyte models, PGRN was found to prevent podocyte damage in DKD by promoting mitophagy and mitochondrial biogenesis [112]. In HG-induced human foot cell and db/db mouse models, Src activation was found to be increased and inhibited FUNDC1-mediated mitophagy, thereby promoting diabetic kidney injury [113]. In HG-induced mouse renal podocytes (MPC5) and STZ-induced C57BL/6 mouse models, the LncRNA SNHG17 was found to be elevated in DM mice and HG-treated MPC5, and further studies revealed that lncRNA SNHG17 knockdown reduced podocyte apoptosis by regulating Mst1 degradation and promoting Parkin-dependent mitophagy [114]. Using HG-induced mouse podocytes (CIMPs) and STZ-induced KM mouse models with lentiviral treatment overexpressing forkhead box protein O1 (FoxO1), FoxO1 was found to promote mitophagy in diabetic mouse podocytes through the PINK1/Parkin pathway [115]. Similarly, some researchers demonstrated that overexpressed FoxO1 acted to reduce apoptosis through the regulation of PINK1 in an HG-induced mouse podocyte model [116]. In HG-induced human renal proximal tubule cells (HK-2) and high-fat diet-fed combined streptozotocin (HFD/STZ)-induced diabetic mouse models, ubiquitin-like with PHD and ring finger domains 1 (UHRF1) overexpression through inhibition of thioredoxin-interacting protein (TXNIP) expression promotes PINK1 mediated mitophagy by inhibiting TXNIP expression, thereby inhibiting ferroptosis [117]. In the palmitic acid (PA)-induced ceramide synthase 6 (CERS6)-deficient HK-2 and CERS6 knockdown db/db mouse models, aggravation of DKD symptoms and renal interstitial fibrosis were found, possibly due to the interaction of CERS6-derived ceramide with PINK1 to inhibit PINK1/Parkin-mediated mitophagy, which aggravates DKD [118]. In the HK-2 model induced by HG, hypoxia-inducible factor-1α (HIF-1α) promotes PINK1/Parkin-mediated mitophagy to alleviate high glucose-induced cell damage [119]. In the HK-2 cell model transfected with KCa3.1 siRNA and cultured in a transforming growth factor-beta 1 (TGF-β1) environment, as well as in the STZ-induced KCa3.1+/+and KCa3.1-/- mouse models, it was found that calcium-activated potassium channel (KCa3.1) deficiency can restore abnormal mitophagy [120]. Some researchers found that the expression of phosphofurin acidic cluster sorting protein 2 (PACS-2), a key regulator of MAM formation, was significantly reduced in renal tubules of DN patients, and PACS-2 was found to attenuate renal tubular injury through advancing MAM formation and mitophagy in a cellular model of HG-induced HK-2 and PACS-2 overexpression, and in a mouse model of STZ-induced PACS-2 knockout [121]. In an HG-induced HK-2 model, dual-specificity protein phosphatase 1 (DUSP1) was found to attenuate renal tubular mitochondrial dysfunction by restoring Parkin-mediated mitophagy [122]. Similarly, on HG-induced HK-2, LncRNA NEAT1 was found to inhibit mitophagy and exacerbate HK-2 cell injury through the miR-150-5p-Drp1 axis, revealing a novel mechanism of DKD [123]. A team of investigators found that the expression of OPTN was significantly reduced in renal biopsies of patients with type 2 DKD, and OPTN was found to suppress the activation of NLRP3 inflammasomes by enhancing mitophagy on HG-induced renal tubular epithelial cell (RTEC) model in mice thus playing a therapeutic role in DKD [124]. One study found that silencing linc279227 restored the levels of autophagy/mitophagy-related proteins in HG-stimulated RTEC in an HG-treated RTEC cell model [125]. In miR-379KO mouse and HG-induced miR-379KO glomerular mesangial cell models, miR-379 deletion was found to ameliorate DKD by enhancing adaptive mitophagy via mitochondrial FIS1 [126]. Similarly, this team of investigators found that overexpression of OPTN served to alleviate senescence in RTEC by promoting mitophagy [127]. HG-PA-treated Fgf13 KD Human glomerular endothelial cells (HRGEC) and Fgf13 knockout mice and Fgf13 plus Prkn double KO mice and induced with HFD/STZ, found that Fgf13 deficiency could be important for the regulation of mitochondrial homeostasis in glomerular endothelial cell (GEC) and T2DN processes through the bifunctionality of Parkin in promoting mitophagy and inhibiting apoptosis [128].

Role of mitophagy in DKD therapy

Some studies have found that Tangshen formula (TSF) may reduce urinary protein and improve renal function in db/db mice by activating PINK1/Parkin-mediated mitophagy [129]. In the high-glucose hypoxia-induced HK-2 and unilateral nephrectomy combined with STZ-induced DKD rat models, Jin-Chan-Yi-Shen Tong-Luo formula (JCYSTL) activated PINK1/Parkin-mediated mitophagy by stabilizing HIF-1α to protect renal tubules from mitochondrial dysfunction and apoptosis, which provided a promising therapy for the treatment of DKD [130]. In HG-induced MPC5 and unilateral nephrectomy combined with STZ-induced SD rat models, activation of PINK1/Parkin-mediated mitophagy by the Qing-Re-Xiao-Zheng-Yi-Qi formula (QRXZYQ) ameliorated the pathological damage of DKD and protected podocytes [131]. In HG-induced HK-2 and HFD/STZ-induced C57BL/6 mice, Huangkui Capsules (HKC) ameliorated renal tubular lesions in DKD by inducing mitophagy through upregulation of STING1/PINK1 pathway [132]. In the HFD/STZ-induced SD rat model, the San-Huang-Yi-Shen Capsule (SHYS) promotes

PINK1/Parkin-mediated mitophagy, inhibits the activation of the NLRP3 signaling pathway, attenuates mitochondrial damage, and reduces inflammatory responses, which results in the improvement of DKD [133]. In the HG-induced MPC5 model, Dendrobium officinale polysaccharide (DOP) treatment resulted in the up-regulation of PINK1, Parkin, and LC3B and the down-regulation of autophagy receptor P62, which enhanced mitophagy to alleviate HG-induced damage in podocytes [134]. In HG-induced MPC-5 and STZ-induced SD rat models, Icariin (ICA) can increase Sesn2-induced mitophagy via the Keap1-Nrf2/HO-1 axis, thereby inhibiting the activation of NLRP3 inflammatory vesicles and exerting a renoprotective effect [135]. In the STZ-induced SD rat model, Astragaloside II (AS II) increased the expression of mitochondrial PINK1 and Parkin, partially restored the expression of mitochondrial kinetic-related proteins, improved mitochondrial function, and exerted a certain renoprotective effect [136]. In the HG-induced transfection of PINK1 siRNA in HK-2 cell model and HFD/STZ induced DKD rats model induced by HFD/STZ, a novel aldose reductase inhibitor (WJ-39) was found to inhibit aldose reductase activity, activate the PINK1/Parkin signaling pathway, promote mitophagy, and alleviate cell apoptosis, thereby exerting a certain therapeutic effect on DKD and inhibiting renal fibrosis [137]. In the HG/TGF-β-induced HK-2 and STZ-induced diabetic rat models, the expression of the relevant mitochondrial functional proteins PINK1, Parkin, Fundc1, LC3II, Atg5, MFN2, and MFN1 was significantly reduced, and vitamin D receptor (VDR) agonist treatment increased the expression of the relevant proteins, alleviated the dysfunction of mitophagy, inhibited mitochondrial fission, reduced mitochondrial ROS, and increased the integrity of MAMs, leading to the conclusion that VDR agonists can promote the restoration of mitophagy by regulating the MFN2-MAMs-Fundc1 pathway in renal tubular cells, and thus play a nephroprotective role [138]. In HG-treated HK-2 and HFD/STZ-induced C57BL/6J mouse models, Finerenone (FIN) was found to restore mitophagy, reduce oxidative stress and apoptosis, and alleviate renal tubular injury through the PI3K/Akt/eNOS signaling pathway, thus exerting a certain therapeutic effect on DKD [139]. In the HK-2 cell model treated with HG, Germacrone improved mitophagy inhibition in DKD and inhibited mtDNA STING signaling to improve iron death in renal tubular cells [140]. In HG-induced HK-2 and HFD + STZ-induced C57BL/6 mouse models, metformin activates mitophagy via the p-AMPK-PINK1-Parkin pathway and ameliorates renal oxidative stress and tubulointerstitial fibrosis in HFD/STZ-induced diabetic mice [141]. In HG-induced models of human renal cortical epithelial cells (HRCApiC) and human renal proximal tubular epithelial cells (HRPTEpic), metformin restored Parkin protein expression and mitophagy through protein phosphatase (PP2A) activation, and inhibited NF-κB activation, thereby reducing apoptosis of human renal epithelial cells under high glucose conditions [142]. In HG-induced mouse glomerular endothelial cell (mGEC) and db/db mouse models, coenzyme Q10 partially elevated PINK1 and Parkin expression and increased mitophagy, exerting beneficial effects [143].

In mice with Nrf2 knockout and HG-induced podocyte models, it was found that sulforaphane (SFN) alleviates podocyte injury in DKD by activating the Nrf2/PINK1 signaling pathway [144]. In HG-induced HK-2 and HFD/STZ-induced SD rat models, it was found that diosgenin (DIO) enhances mitophagy through the PINK1-MFN2-Parkin pathway to improve DKD [145]. In HG-induced HK-2 and HFD/STZ-induced C57BL/6 mouse models, melatonin accelerates the movement of PINK1 and Parkin to mitochondria, activates mitophagy, reduces oxidative stress, and inhibits inflammation, thus exerting a protective effect in DKD [146]. In HG-induced human glomerular mesangial cells and HFD/STZ-induced C57BL/6 mouse models, erythropoietin (EPO) activates PINK1/Parkin-mediated mitophagy, reduces ROS levels, improves renal function in DN mice, and reduces apoptosis of human glomerular mesangial cells [147]. In HG-induced rat renal tubular epithelial cells (NRK52E) and STZ-induced SD rat models, inositol treatment increased mitophagy through the PINK1/Parkin pathway, while up-regulating the Nrf2/SIRT1/PGC-1α axis enhanced mitochondrial biogenesis in renal tissues of diabetic rats, resulting in a certain nephroprotective effect [148]. In the HFD/STZ-induced SD rat model, Jujubeoside A (JuA) played a renoprotective role by enhancing mitophagy via the PINK1/Parkin pathway [149]. In db/db mice, it was found that the expression of PINK1 and Parkin decreased and cell apoptosis increased, intraperitoneal injection of mitochondrial-targeted antioxidant MitoQ partially reversed the expression of these proteins; in HG-induced HK-2, antioxidant MitoQ restored Nrf2 expression and partially upregulated PINK1 and Parkin expression, indicating that MitoQ has a certain therapeutic effect on DKD tubular injury through Nrf2/PINK1 [150]. In HG-induced MPC5 and STZ-induced SD rat models, placental-derived mesenchymal stem cells (P-MSCs) reduced podocyte damage and increased PINK1/Parkin-mediated mitophagy, providing a certain protective effect on the kidneys [151].

It's important to mention that the aforementioned evidence suggests mitophagy is suppressed in DKD. and increasing mitophagy can improve DKD. However, there are still some cases where mitophagy levels are abnormally activated during DKD due to different models or research protocols and stages. Inhibiting mitophagy can improve DKD. Researchers have found that

PINK1/Parkin-mediated mitophagy is activated in db/db mice, after treatment with Huangqi-Danshen decoction (HDD), enhanced mitochondrial fission and PINK1/Parkin-mediated mitophagy were inhibited in db/db mice, improving kidney damage in db/db mice [152]. Similarly, some investigators found that PINK1/Parkin-mediated mitophagy was abnormally activated in db/db mice, which could be down-regulated after astragaloside IV (AS-IV) treatment [153]. In the beagle dog model induced by the combination of alloxan and STZ, the levels of BNIP3, NIX, and FUNDC1 were significantly upregulated, indicating that DKD can induce non-ubiquitin-dependent mitophagy, and N-acetyl-L-cysteine (NAC) treatment reduced the levels of BNIP3, NIX, and FUNDC1, suggesting that NAC can alleviate mitophagy and reduce kidney damage in DKD [154]. In HG-induced MPC5 and STZ-induced C57BL/6 mouse models, Fuling acid A (PAA) can have a certain therapeutic effect on DKD by downregulating mitophagy induced by FUNDC1 [155].

In the above-mentioned studies, some researchers used traditional Chinese medicine formulas or extracts, some researchers used Chinese patent drugs, some researchers used chemical drugs, and some researchers used biological products or natural plant extracts for research. The research subjects include animals and cells, and the research methods chosen are also quite different. In the above studies, only HDD, AS-IV, NAC, and PAA were found to inhibit mitophagy and improve DKD, while the rest were found to promote mitophagy and improve DKD, as shown in Table 1. To summarize, mitophagy is crucial in the management of DKD, and an imbalance of mitophagy can lead to an increase in apoptosis, cellular iron death, accelerated cellular senescence, ROS production, as has the intensity of inflammatory responses, activation of the NLRP3 inflammatory vesicles, an augmentation in oxidative stress, and a decrease in mitochondrial biogenesis, but these can be solved through drugs or compounds such as TSF, JCYSTL, and metformin (Figs. 2 and 3; Table 1).

Mitophagy and DR

Increasing mitophagy plays a therapeutic role in DR

Some researchers incubated human retinal pigment epithelial cell line (ARPE-19) with 15 mM and 50 mM glucose, respectively, and found that ROS increased in the low glucose (15 mM) environment, which did not have a significant effect on apoptosis and cell proliferation; however, in the high-glucose (50 mM) environment, ROS production was increased, PINK1 and Parkin protein expression was downregulated, mitophagy and cell proliferation were inhibited, and apoptosis increased [156]. In another study, researchers have found that under HG conditions, the expression of Sirt3 is reduced in retinal pigment epithelial (RPE) cells, the Foxo3a/PINK1/Parkin pathway is inhibited, mitophagy is weakened, and overexpression of Sirt3 can activate the Foxo3a/PINK1/Parkin signaling pathway, increase mitophagy, and inhibit cell apoptosis [157]. Further research indicates that, in HG-induced rat retinal Müller cell (rMC-1) and db/db mouse models, Panax ginseng saponin R1 (NGR1) increased the levels of PINK1 and Parkin in the retina as well as in rMC-1 cells of db/db mice, increased the LC3-II/LC3-I ratio, and decreased the levels of p62/SQSTM1, however, knockdown of PINK1 eliminated the protective effect of NGR1, inferring that NGR1 prevents DR through PINK1-dependent enhancement of mitophagy [158]. Furthermore, it has been observed that, in HG-induced rat retinal endothelial cells and STZ-induced SD rat models, it was found that PKC δ/Drp1 mediated mitochondrial fission increased and HK-II-PINK1 mediated mitophagy decreased; use of Drp1 inhibitor Midivi-1 and autophagy agonist rapamycin reduced mitochondrial fission and increased mitophagy, thereby exerting a certain therapeutic effect on DR [159]. Similarly, the research team found that membrane G protein-coupled bile acid receptor 5 (TGR5) enhances mitophagy and inhibits mitochondrial fission by regulating the PKC δ/Drp1-HK2 signaling pathway in HG-induced human retinal endothelial cells (RMEC) and STZ induced SD rat models, thus having a certain therapeutic effect on retinal dysfunction [160]. Thereafter, in HG-induced human retinal capillary endothelial cells (HRCEC), it was found that increased expression of Drp1, decreased expression of MFN2, increased mitochondrial reactive oxygen species (mtROS), and activation of NLRP3 inflammatory vesicles, and decreased protein expression of PINK1, Parkin, and VDAC1, whereas overexpression of VDAC1 could promote PINK1 expression and inhibit the activation of NLRP3, thus it was concluded that VDAC1 may be a potential target for the prevention and treatment of DR [161]. A recent study has shown that, in ARPE-19 cells and DR mouse models, it was found that TERF1 Interacting Nuclear Factor 2 (TIN2) inhibits mitophagy by promoting mTOR pathway activity, thereby inducing the aging of RPE cells under high glucose conditions; knocking down TIN2 improved RPE cell aging and retinal morphology under high glucose conditions [162].

Inhibition of mitophagy and therapeutic effect on DR

Research shows, that TNF-α released by retinal Müller cells aggravates apoptosis of retinal pigment epithelial cells by up-regulating mitophagy [163]. Further research has found that mitochondria-associated fission protein, and mitochondria autophagy-related proteins (PINK1, BNIP3, and NIX) were elevated and apoptosis was increased in high glucose and hypoxia-induced human retinal pigment epithelial cell (ARPE-19) model;

Table 1 The role of mitophagy in DKD

Drug/Targets	Models (Cells or Animals)	Influence pathways	Effects on mitophagy	Findings	Reference
Tangshen Formula (TSF)	db/db mice	PINK1/Parkin	Enhanced	TSF activates mitophagy, reduces urinary protein in db/db mice, and improves renal function	[129]
JinChan YiShen TongLuo (JCYSTL) Formula	High glucose hypoxia-induced HK-2 and unilateral nephrectomy combined with STZ-induced DKD rat models	PINK1/Parkin	Enhanced	JCYSTL formula activates PINK1/Parkin mediated mitophagy through HIF-1α, protecting renal tubules from mitochondrial dysfunction and cell apoptosis	[130]
Qing-Re-Xiao-Zheng-Yi-Qi Formula (QRXZYQ)	HG-induced MPC5 and unilateral nephrectomy combined with STZ-induced SD rat models	PINK1/Parkin	Enhanced	QRXZYQ formula activates PINK1/Parkin mediated mitophagy, reduces proteinuria in diabetes rats, improves glucose and lipid metabolism disorder improves renal fibrosis, and protects podocytes	[131]
Huangkui Capsules(HKC)	HG-induced HK-2 and HFD/STZ-induced C57BL/6 mice	STING1/PINK1	Enhanced	HKC induces mitophagy by upregulating the STING1/PINK1 pathway, reducing ACR in DKD mice, and improving renal tubular injury	[132]
San-Huang-Yi-Shen Capsule (SHYS)	HFD/STZ-induced SD rat model	PINK1/Parkin	Enhanced	SHYS Capsules promote PINK1/Parkin-mediated mitophagy and inhibit NLRP3 inflammasome activation, thereby improving mitochondrial damage and inflammatory response	[133]
Dendrobium officinale polysaccharide (DOP)	HG-induced MPC5 model	PINK1/Parkin	Enhanced	DOP can enhance mitophagy, reduce mitochondrial membrane potential, decrease ROS, and alleviate cell damage	[134]
Icariin (ICA)	HG-induced MPC-5 and STZ-induced SD rat models	Keap1-Nrf2/HO-1	Enhanced	ICA can increase Sesn2-induced mitophagy through the Keap1-Nrf2/HO-1 axis, inhibit the activation of NLRP3 inflammasome, and protect the kidneys	[135]
Astragaloside II (AS II)	STZ-induced SD rat model	Nrf2/PINK1	Enhanced	AS II increased the expression of PINK1 and Parkin related to mitophagy, and improved podocyte injury and mitochondrial dysfunction in diabetes rats	[136]
Novel aldose reductase inhibitor (WJ-39)	HG-induced transfection of PINK1 siRNA in HK-2 cell model and HFD/STZ-induced DKD rats	PINK1/Parkin	Enhanced	WJ-39 activates the PINK1/Parkin signaling pathway, promotes mitophagy, and reduces cell apoptosis, thereby exerting a certain therapeutic effect on DKD and inhibiting renal fibrosis	[137]
vitamin D receptor (VDR) agonist	HG/TGF-β-induced HK-2 and STZ-induced diabetic rat models	MFN2-MAMs-Fundc1	Enhanced	VDR agonist enhanced mitophagy, decreased urinary albumin and serum creatinine levels in diabetes rats, and alleviated renal tubulointerstitial fibrosis. Relieve mitophagy dysfunction, and MAMs integrity, inhibit mitochondrial fission, and reduce ROS in cellular models	[138]
Finerenone (FIN)	HG-treated HK-2 and HFD/STZ-induced C57BL/6J mouse	PI3K/Akt/eNOS	Enhanced	FIN restores mitophagy through the PI3K/Akt/eNOS signaling pathway, reducing oxidative stress, mitochondrial fragmentation, and apoptosis	[139]
Germacrone	HK-2 cell model treated with HG	---	Enhanced	Germacrone improves mitophagy inhibition in DKD and protects renal tubular cells from ferroptosis	[140]
Metformin	HG-induced HK-2 and HFD / STZ-induced C57BL/6 mouse	p-AMPK-Pink1-Parkin	Enhanced	Metformin activates mitophagy through the p-AMPK-Pink1-Parkin pathway, improving renal oxidative stress and tubulointerstitial fibrosis in diabetes mice	[141]
Metformin	HG-induced models of human renal cortical epithelial cells (HRCApiC) and human renal proximal tubular epithelial cells (HRPTEpic)	---	Enhanced	Metformin activates protein phosphatase (PP2A) to restore Parkin protein expression and mitophagy, reducing cell apoptosis	[142]

Table 1 (continued)

Drug/Targets	Models (Cells or Animals)	Influence pathways	Effects on mitophagy	Findings	Reference
Coenzyme Q10	HG-induced mouse glomerular endothelial cell (mGEC) and db/db mouse	Nrf2/ARE	Enhanced	The partially elevated expression of PINK1 and Parkin by coenzyme Q10 increases mitophagy alleviates mitochondrial dysfunction, reduces apoptosis, and exerts renal protective effects	[143]
Sulforaphane (SFN)	Mouse model with nuclear factor erythroid 2-related factor 2 (Nrf2) knockout and HG-induced podocyte model	Nrf2/PINK1	Enhanced	SFN alleviates podocyte damage in DKD by activating the Nrf2/PINK1 signaling pathway and balancing mitophagy	[144]
Diosgenin (DIO)	HG-induced HK-2 and HFD/STZ-induced SD rat	PINK1-MFN2-Parkin	Enhanced	Enhances mitophagy through the PINK1-MFN2-Parkin pathway to improve DKD	[145]
Melatonin	HG-induced HK-2 and HFD/STZ-induced C57BL/6 mouse	PINK1/Parkin	Enhanced	Melatonin can activate mitophagy, reduce oxidative stress, inhibit inflammation, and exert a certain protective effect on the kidneys	[146]
Erythropoietin (EPO)	HG-induced human glomerular mesangial cells and HFD/STZ-induced C57BL/6 mouse	PINK1/Parkin	Enhanced	EPO activates PINK1/Parkin-mediated mitophagy, reduces oxidative stress, and minimizes kidney damage	[147]
Inositol	HG-induced rat renal tubular epithelial cells (NRK52E) and STZ-induced SD rat	PINK1/Parkin	Enhanced	Inositol treatment increases mitophagy, thereby exerting a certain renal protective effect	[148]
Jujuboside A(JUA)	HFD/STZ-induced SD rat	PINK1/Parkin	Enhanced	JuA inhibits oxidative stress and apoptosis, increases autophagy and mitophagy, and has a certain renal protective effect	[149]
MitoQ	Db/db mice and HG-induced HK-2	Nrf2/PINK1	Enhanced	MitoQ has a certain renal protective effect by restoring Nrf2 expression, upregulating PINK and Parkin expression, and increasing mitophagy	[150]
Placental-derived mesenchymal stem cells (P-MSCs)	HG-induced MPC5 and STZ-induced SD rat	PINK1/Parkin	Enhanced	P-MSCs increase PINK1/Parkin-mediated mitophagy, thereby exerting a certain renal protective effect	[151]
Huangqi Danshen decoction (HDD)	Db/db mice	PINK1/Parkin	inhibitory	HDD inhibited PINK1/Parkin mediated mitophagy in db/db mice and improved renal injury in db/db mice	[152]
Astragaloside IV(AS-IV)	Db/db mice	PINK1/Parkin	inhibitory	AS-IV improved renal pathological damage in db/db mice, inhibited PINK1/Parkin mediated mitophagy, and delayed DKD progression in type 2 diabetes mice	[153]
N-acetyl-L-cysteine (NAC)	Induction of Beagle Dogs by Tetraoxypyrimidine Combined with STZ	Non-ubiquitin-dependent	inhibitory	NAC reduced the levels of BNIP3, NIX, and FUNDC1, alleviated mitophagy, and reduced kidney damage in DKD	[154]
Fuling acid A(PAA)	HG-induced MPC5 and STZ-induced C57BL/6 mouse	Non-ubiquitin-dependent	inhibitory	PAA can play a beneficial role in the treatment of DKD by downregulating mitophagy induced by FUNDC1	[155]

the expression level of the above proteins was decreased after melatonin was applied, and mitochondria biosynthesis was increased and apoptosis was decreased, which has some therapeutic value for diabetic macular edema (DME) with certain therapeutic value [164].In addition, in HG-induced mouse retinal ganglion cells (RGC-5) and HG/HFD-induced SD rat models, liraglutide was found to inhibit the PINK1/Parkin pathway to suppress mitophagy, which exerted a preventive effect on DR [165]. The final study showed that TXNIP expression increased in STZ-induced rats and HG-induced retinal Müller cells, and mitophagy mediated by TXNIP increased; after TXNIP was knocked out, DR was improved to some extent [166].

The above study is the research progress of mitophagy in DR. Due to different research purposes, different research subjects were selected, as shown in Table 2. The existing research on mitophagy in DR can help discover potential therapeutic targets, such as Sirt3, VDAC1, TIN2, etc. However, existing mitophagy detection

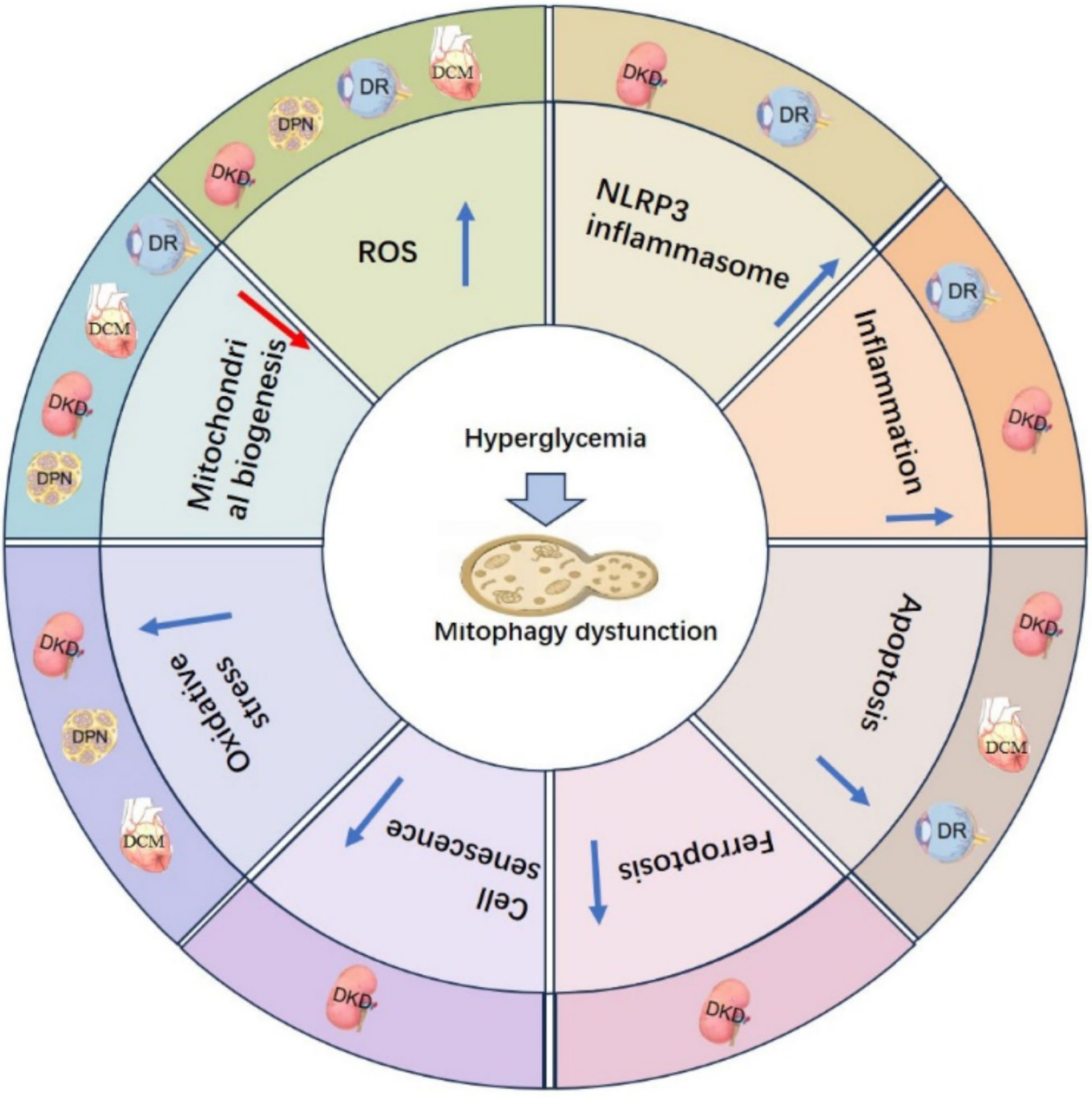

Fig. 2 Hyperglycemia induces dysregulation of mitophagy, leading to increased ROS production, NLRP3 inflammasome activation, increased inflammatory response, increased apoptosis, cellular iron death, accelerated cellular senescence, oxidative stress, decreased mitochondrial biogenesis, and ultimately aggravation of diabetic microvascular complications

techniques currently cannot directly observe the dynamic process of mitophagy. In addition, existing research mainly focuses on the protective and damaging effects of DR, but we still lack a thorough grasp of the specific regulatory mechanisms. Mitophagy is an extremely dynamic process, leading to inconsistent results due to inconsistencies in the models adopted in different experiments as well as the time points of the experiments. Given the above studies, we have gained a greater insight into models, experimental methods, and related pathways involved in mitophagy in DR treatment (Table 2). An imbalance of mitophagy in DR leads to increased apoptosis, increased ROS production, increased inflammatory response, activation of NLRP3 inflammatory vesicles, and decreased mitochondrial biogenesis (Figs. 2 and 4). This section is valuable for a more in-depth understanding of mitophagy in DR.

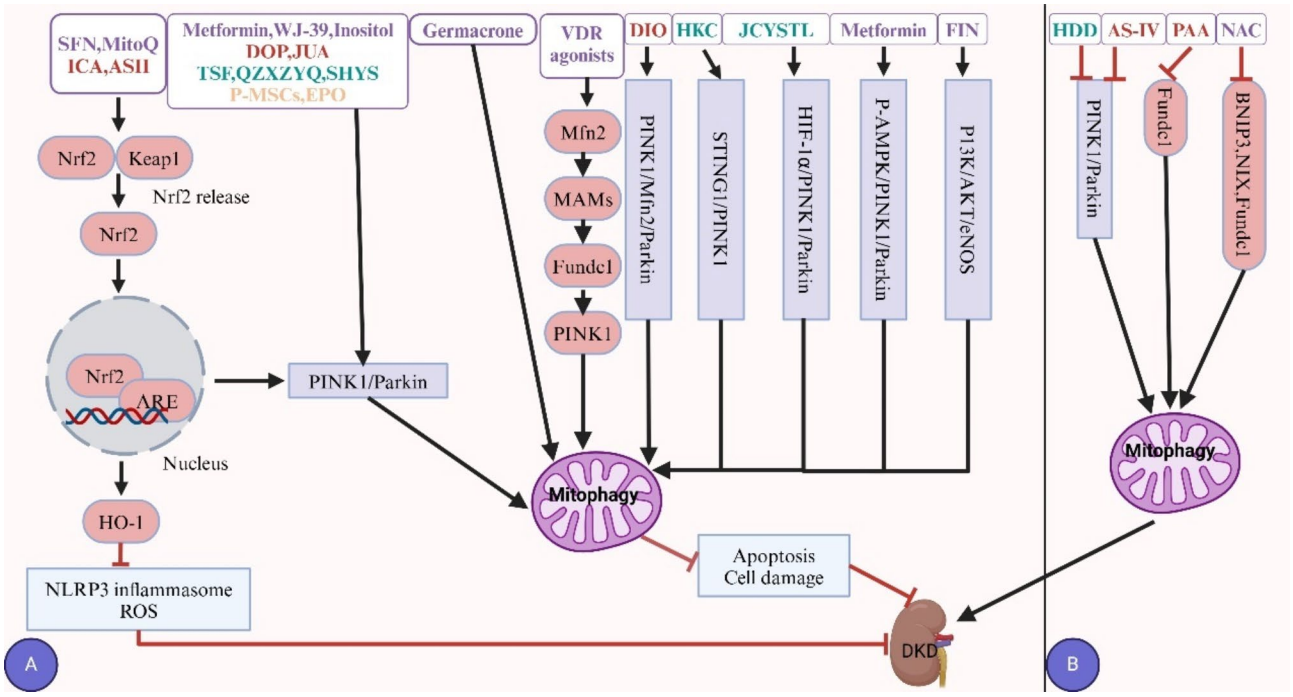

Fig. 3 The role of mitophagy in DKD. Purple font: compound; green font: Chinese medicine prescription or Chinese patent medicine; red font: Chinese medicine extract; orange font: other types of substances. →: activation; ⟞: inhibition. The diagram is divided into **A** and **B** parts. Part **A** indicates that activation of mitophagy plays a therapeutic role in DKD, and part **B** indicates that inhibition of mitophagy plays a therapeutic role in DKD

Mitophagy and DPN

Silymarin (SBN), a sirtuin 1 activator, ameliorated sciatic nerve injury and oxidative damage in HG-induced mouse neuroblastoma cells (N2A) and STZ-induced SD rats and enhanced autophagy and mitophagy, which exerted some neuroprotective effects [167]. Piceatannol (PCN), a SIRT1 activator, was found to increase mitotic biogenesis and mitophagy via the SIRT1-PGC-1α-NRF2-TFAM and SIRT1-PINK1-Parkin axes in the STZ-induced SD rat and HG-induced murine Neuro2a cell models, thus exerting some neuroprotective protective effects [168]. In addition, STZ-induced C57BL/6 mice and Park2 knockout (KO) mice were used as models, and hypoxia-inducible factor 1α subunit (HIF-1α) was found to up-regulate mitophagy in DPN mice, thus exerting some therapeutic effects on DPN [169]. In addition, in the HFD/STZ-induced SD rat model, Sirt3 overexpression improves painful diabetes neuropathy by activating FoxO3a/PINK1/Parkin-Mediated mitophagy [170]. Studies also found that inhibition of mitophagy in dorsal root ganglion neurons by poly (ADP-ribose) polymerase 1 (PARP1) leads to peripheral neurologic injury in a db/db mouse model, and the application of PARP1 inhibitors ameliorates symptoms of associated neurologic injury [171]. Finally, it is worth noting that in the HG-induced rat Schwann cell line (RSC96) model, Astragaloside IV (AS-IV) significantly reduced ROS levels, decreased the over-activation of mitophagy, maintained mitochondrial morphology, and had a therapeutic effect on HG-induced RSC96 [172].

This section outlines the position of regulating mitophagy in the cure of DPN, in which an imbalance of mitophagy leads to increased oxidative stress, increased ROS production, and decreased mitochondrial biogenesis (Figs. 2 and 5; Table 3). At present, there is limited research on mitophagy in DPN, mainly focusing on ubiquitin-dependent pathways. From the existing research, there are relatively few studies, mainly focusing on the activation and inhibition of related molecules, such as the application of SIRT1 activators, overexpression of Sirt3, upregulation of HIF-1α, and the application of PARP1 inhibitors. We hope that future research will explore the specific mechanisms by which compounds and signaling pathways play a role in mitophagy to provide a more comprehensive understanding. Mitophagy has the functions of maintaining energy metabolism, protecting cells from oxidative damage, and preventing apoptosis. There are many pathogenesis of DPN, but oxidative stress is an important pathogenesis. According to the function of mitophagy and the pathogenesis of DPN, it can be speculated that mitophagy may play an important role in DPN. Since there are not many basic studies at present, a large number of basic studies are needed to verify to provide a certain direction for future clinical treatment.

Table 2 The role of mitophagy in DR

Drug/Targets	Models (Cells or Animals)	Influence pathways	Effects on mitophagy	Findings	Reference
---	HG-induced human retinal pigment epithelial cell line (ARPE-19)	ROS/PINK1/Parkin	Inhibition of mitophagy in a high glucose environment	High blood glucose promotes apoptosis in retinal pigment epithelium (RPE) cells and inhibits cell proliferation as well as mitophagy by regulating the inactivation of the ROS/PINK1/Parkin signaling pathway mediated by reactive oxygen species (ROS)	[156]
Sirt3	HG-induced retinal pigment epithelial (RPE) cells	Foxo3a/PINK1-Parkin	Enhanced	Sirt3 can activate mitophagy through the Foxo3a/PINK1 Parkin pathway and reduce HG-induced RPE cell apoptosis	[157]
Notoginsenoside R1 (NGR1)	HG-induced rat retinal Müller cells (rMC-1) and db/db mouse	PINK1/Parkin	Enhanced	NGR1 enhances mitophagy through PINK1 dependence to prevent and treat diabetic retinopathy	[158]
Drp1 inhibitor Midivi-1 and autophagy agonist rapamycin	HG-induced rat retinal endothelial cells and STZ-induced SD rat	HK-II-PINK1	Enhanced	The Drp1 inhibitor Midivi-1 and autophagy agonist rapamycin can reduce mitochondrial fission and increase mitophagy, thereby exerting a certain therapeutic effect on DR	[159]
Membrane G protein-coupled bile acid receptor 5 (TGR5)	HG-induced human retinal endothelial cells (RMEC) and STZ-induced SD rats	PKCδ/Drp1-HK2	Enhanced	TGR5 inhibits mitochondrial fission and enhances mitophagy in RMEC by regulating the PKC δ/Drp1-HK2 signaling pathway, thus having a certain therapeutic effect on retinal dysfunction	[160]
VDAC1	HG-induced human retinal capillary endothelial cells (HRCEC)	---	Enhanced	Overexpression of VDAC1 promotes PINK1 expression, inhibits NLRP3 activation, and alters cellular biological behavior under HG conditions	[161]
TIN2	ARPE-19 cells and DR mouse models	---	Inhibition	TIN2 inhibits mitophagy by promoting mTOR pathway activity, thereby inducing the aging of RPE cells under high glucose conditions. Knocking down TIN2 improved RPE cell aging and retinal morphology under high glucose conditions	[162]
---	Müller cells in the retina	---	Increased mitophagy in diabetes	TNF - α released by retinal Müller cells aggravates apoptosis of retinal pigment epithelial cells by up-regulating mitophagy in diabetes	[163]
Melatonin	high glucose and hypoxia-induced human retinal pigment epithelial cells (ARPE-19)	---	Inhibition	Melatonin reduces the expression of PINK, BNip3, NIX, and other related proteins, and decreases cell apoptosis	[164]
Liraglutide	HG-induced mouse retinal ganglion cells (RGC-5) and HG/HFD-induced SD rats	PINK1/Parkin	Inhibitory	Liraglutide inhibits the PINK1/Parkin pathway, suppresses mitophagy, and has a certain preventive effect on DR	[165]
TXNIP	STZ-induced rats and HG-induced retinal Müller cells	---	Enhanced	Knocking out TXNIP can reduce mitophagy and have a beneficial effect on DR	[166]

Mitophagy and DCM

DCM is often associated with oxidative stress and mitochondrial dysfunction [173]. In HFD-fed Atg7 cKO mice and Parkin KO mouse models, some investigators found that deletion of Atg7 and Parkin inhibited mitophagy increased lipid accumulation, and exacerbated diastolic dysfunction, whereas injection of Tat-Beclin1 (TB1) increased mitophagy and attenuated cardiac dysfunction [174]. Melatonin treatment, via a rat experimental model of HFD/STZ-induced diabetes, was able to activate the SIRT6-AMPK-PGC-1α-AKT pathway, promote mitochondrial biosynthesis enhance mitophagy, and delay DCM progression [175]. Similarly, researchers have found that melatonin promotes mitophagy and ameliorates myocardial damage in STZ-induced C57BL/6 mouse and primary mouse cardiomyocyte models [176]. In HG-induced rat cardiomyocytes (H9C2) and HFD/STZ-induced C57BL/6J mouse models, it was found that mitophagy was impaired under hyperglycemic conditions, and that canagliflozin was able to increase the phosphorylation of AMPK and activate PINK1/Parkin-dependent mitophagy at the same time, which could improve the function of mitochondria and play a certain role in the DCM therapeutic effects [177]. In addition, Secreted frizzled-related protein 2 (SFRP2) was found to activate mitophagy to play a certain cardioprotective role

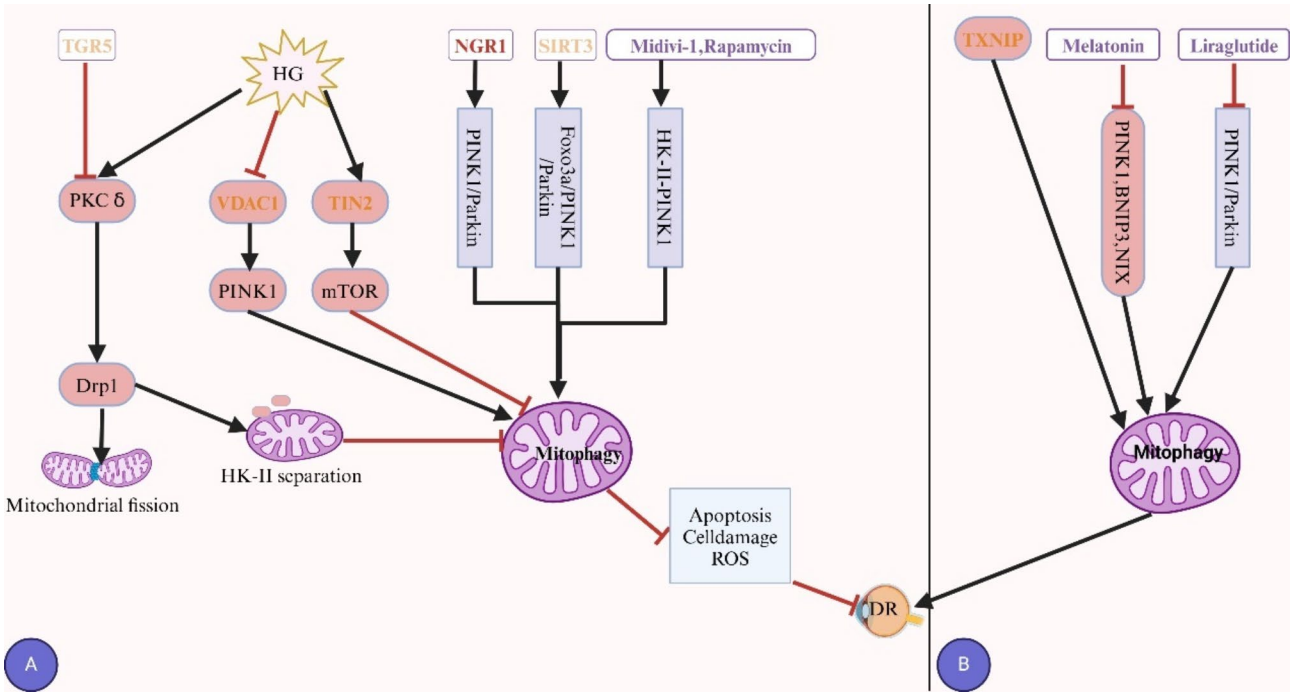

Fig. 4 The role of mitophagy in DR. Purple font: compound; red font: Chinese medicine extract; orange font: other types of substances. →: activation; ⟞: inhibition. The diagram is divided into **A** and **B** parts. Part A indicates that activation of mitophagy plays a therapeutic role in DR, and part B indicates that inhibition of mitophagy plays a therapeutic role in DR

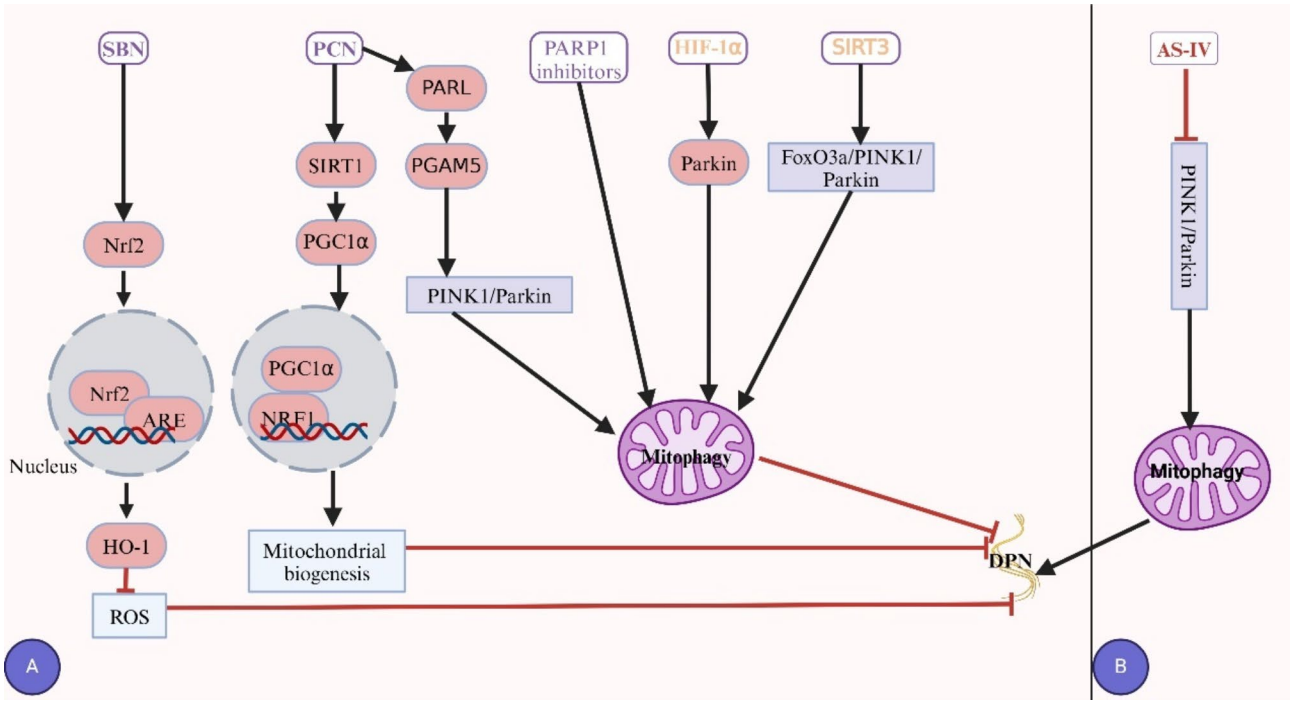

Fig. 5 The role of mitophagy in DPN. Purple font: compound; red font: Chinese medicine extract; orange font: other types of substances. →: activation; ⟞: inhibition. The diagram is divided into **A** and **B** parts. Part **A** indicates that activation of mitophagy plays a therapeutic role in DPN, and part **B** indicates that inhibition of mitophagy plays a therapeutic role in DPN

Table 3 The role of mitophagy in DPN

Drug/Targets	Models (Cells or Animals)	Influence pathways	Effects on mitophagy	Findings	Reference
Silibinin(SBN)	HG-induced mouse neuroblastoma cells (N2A) and STZ-induced SD rat	---	Enhanced	SBN upregulates PARL, PINK1, PGAM5, and LC3 levels to increase autophagy and mitophagy, activate SIRT1 activation, and enhance antioxidant mechanisms	[167]
Piceatannol (PCN)	STZ-induced SD rats and HG-induced mouse Neuro2a cells	SIRT1-PINK1-Parkin	Enhanced	PCN can increase mitosis and mitophagy through the SIRT1-PGC-1 α - NRF2-TPAM and SIRT1-PINK1 Parkin axes, thereby exerting a certain neuroprotective effect	[168]
Hypoxia-inducible factor 1α subunit (HIF-1α)	STZ-induced C57BL/6 mice and Park2 knockout (KO) mice	---	Enhanced	HIF-1α upregulates mitophagy in the spinal cord of DNP mice, resulting in a therapeutic effect on DPN	[169]
SIRT3	HFD/STZ-induced SD rat	FoxO3a/PINK1/Parkin	Enhanced	SIRT3 overexpression improves painful diabetes neuropathy by activating FoxO3a/PINK1/Parkin-Mediated mitophagy	[170]
PARP1 inhibitors	db/db	---	Enhanced	Application of PARP1 inhibitors ameliorates symptoms of associated neurologic injury	[171]
Astragaloside IV(AS-IV)	HG-induced rat Schwann cell line (RSC96) model	HK-II-PINK1	Inhibitory	AS-IV significantly reduces ROS levels, decreases excessive activation of mitophagy, and maintains mitochondrial morphology	[172]

in glycolipid environment-induced H9C2 cells and HFD/STZ-induced SD rat models [178]. Studies also found that the combination of Ginseng Dingzhi Decoction (GN) and metformin (MET) was found to activate mitophagy and protect cardiomyocytes in an HG-induced cardiomyocyte model in mice [179].

A study shows that L-carnitine increases PINK1-Parkin-dependent mitophagy and reduces microvascular dysfunction in DCM via the CPT1a-PHB2-PARL pathway in high glucose and free fatty acid (HG/FFA)-induced human cardiac microvascular endothelial cell (HCMEC) and db/db mouse model [180]. Another study found that up-regulation of Bnip3/Nix by Fucoxanthin (FX) enhances mitophagy and reduces oxidative stress, ameliorates myocardial fibrosis, and attenuates HG-induced hypertrophy of H9C2 cells in diabetic rats and HG-induced H9C2 cells in STZ-induced diabetic rat models [173].In addition, in STZ-induced Sirt3 KO mouse and primary neonatal mouse cardiomyocyte models, Sirt3 was found to exert cardioprotective effects on DCM through activation of Foxo3A-Parkin-mediated mitophagy [181]. Similarly, researchers have found that Mst1 inhibits Sirt3 expression and Parkin-dependent mitophagy, thereby exacerbating DCM; The absence of Sirt3 eliminated the effect of Mst1 on DCM, indicating that Sirt3 plays an important role in mitophagy in DCM [182]. Studies also found that increased expression of zinc transport protein 7 (ZIP7) in the heart, inhibition of PINK1/Parkin-mediated mitophagy, and exacerbation of cardiac insufficiency and fibrosis in mice were found in an HFD/STZ-induced mouse model, which was reversed by knockdown of ZIP7 [183]. In addition, in HFD-induced and palmitate (PA)-induced primary mouse cardiomyocyte models, increased expression of bromodomain protein 4 (BRD4) was found to inhibit PINK1/Parkin-mediated mitophagy, leading to impaired cardiac function, and the use of a BRD4 inhibitor (JQ1) was able to activate PINK1/Parkin-mediated mitophagy, thereby playing a therapeutic role in the treatment of DCM [184]. Mitochondrial aldehyde dehydrogenase 2 (ALDH2) has been shown to have a protective effect on the cardiovascular system. A recent study suggests that in an STZ-induced mouse model, it was found that ALDH2 exerts a protective effect on DCM through Parkin-dependent mitophagy [185].

However, the latest study differs from previous studies in that it exerts therapeutic effects on DCM by regulating mitochondrial quality control. This study found that H3 relaxin can reduce the expression of mitochondrial fission protein and mitophagy-related protein, and increase the expression of the mitochondrial fusion protein by activating the AMPK pathway in SD rats induced by HFD/STZ and H9C2 cell models induced by HG/PA, thereby exerting a certain therapeutic effect [186]. However, this study cannot directly confirm the therapeutic effect of improving mitophagy.

This section reviews the research progress on mitophagy in DCM. Unlike DKD, DR, and DPN, there is ample evidence to suggest that mitophagy has a positive effect on DCM (Figs. 2 and 6; Table 4), with only the latest research on H3 relaxin slightly conflicting. Mitophagy plays an important role in DCM, reducing lipid accumulation, improving diastolic dysfunction, promoting mitochondrial biogenesis, protecting myocardial cells, and improving myocardial function. Mitophagy provides new ideas and a theoretical basis for the prevention and

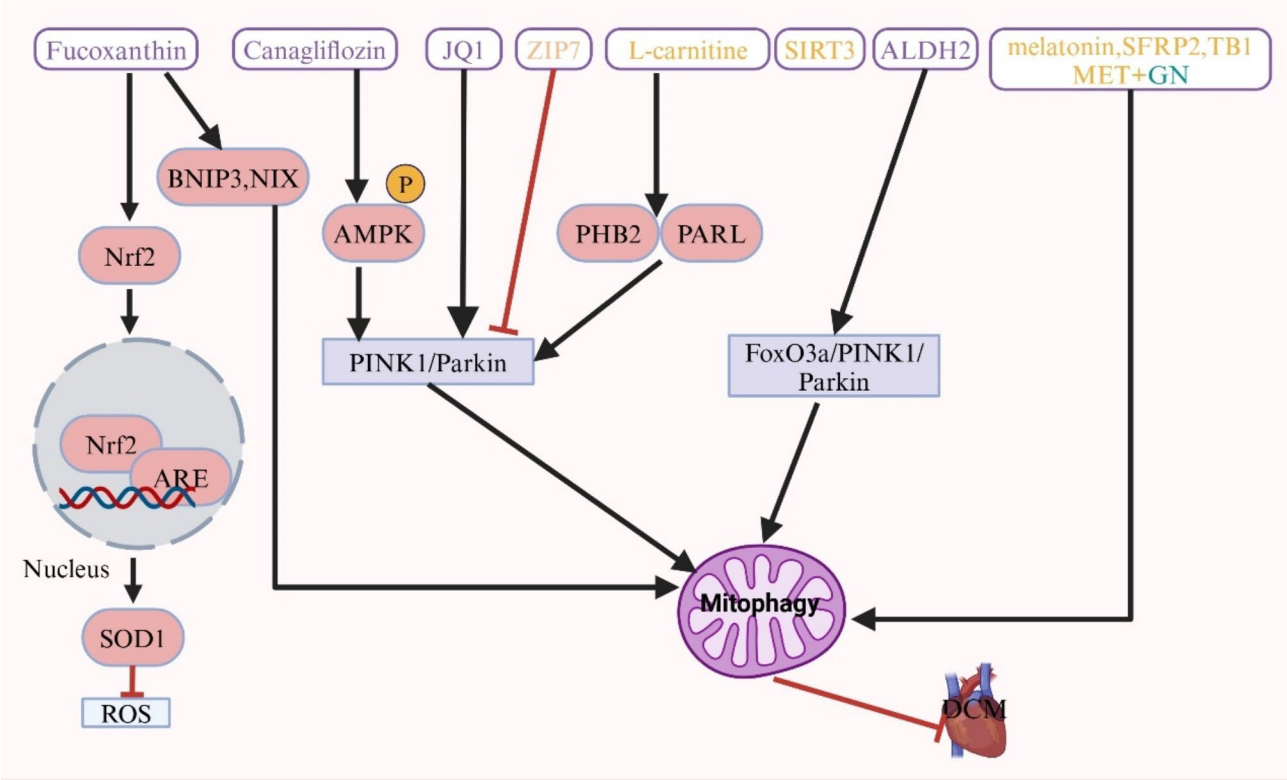

Fig. 6 The role of mitophagy in DCM. Purple font: compound; green font: Chinese medicine prescription or Chinese patent medicine; orange font: other types of substances. →: activation; ⟞: inhibition

treatment of DCM. In the future, in-depth research on the regulatory mechanism of mitophagy is expected to provide new targets and methods for the treatment of DCM.

Outlook and conclusions

In eukaryotic cells, mitochondria, as highly dynamic organelles, are essential for maintaining physiological balance within living organisms. Mitophagy eliminates surplus or malfunctioning mitochondria, regulating the quantity of mitochondria and preserving energy metabolism to preserve mitochondrial homeostasis. Dysregulated mitophagy leads to increased ROS, increased oxidative stress, increased apoptosis, and accelerated cellular senescence. Diabetic microangiopathy remains incurable. The primary therapies currently involve managing blood glucose levels, blood pressure, and blood lipid levels, diet, exercise therapy, and corresponding treatments depending on the site of microvascular complications. However, current treatments are not effective in preventing the occurrence of end-stage renal disease, blindness, disability, and other adverse outcomes, therefore, discovering new therapeutic targets is of utmost importance.

Above, we have summarized the existing research on mitophagy and microvascular complications in diabetes. Notably, we found that mitophagy can protect cells but may also lead to cell damage and cell death. Overactivation of mitophagy may result in the clearance of functionally normal mitochondria, leading to cell death, while excessive inhibition of mitophagy can prevent the timely removal of dysfunctional mitochondria, leading to the accumulation of damaged mitochondria and increased ROS production, which may trigger inflammatory responses and result in apoptosis, among other outcomes. Most studies tend to favor the activation of mitophagy to reduce oxidative stress, decrease inflammatory responses, and diminish apoptosis, thereby exerting a therapeutic effect. However, some studies indicate that excessive mitophagy can lead to cell damage in certain situations. The differences in research results may be attributed to several aspects: (1) Researchers have different research purposes and design different research schemes. Different research purposes use different induction methods to induce animals and cells and adopt different animal models and cell models according to different experimental purposes. These differences may lead to inconsistent results. (2) In addition, the differences in research purposes may also result in varying lengths of experimental periods. Changes in experimental periods will directly affect the speed and degree of disease progression, and different disease stages may

Table 4 The role of mitophagy in DCM

Drug/Targets	Models (Cells or Animals)	Influence pathways	Effects on mitophagy	Findings	Reference
Tat-Beclin1 (TB1)	HFD-induced Atg7 cKO mice and Parkin KO mice	---	Enhanced	Tat Beclin1 (TB1) can increase mitophagy and alleviate cardiac dysfunction	[174]
melatonin	HFD/STZ-induced diabetes rats	SIRT6-AMPK-PGC-1α-AKT	Enhanced	Melatonin treatment can activate the SIRT6-AMPK-PGC-1 α - AKT pathway, promote mitochondrial biosynthesis and enhance mitophagy, and delay the progression of DCM	[175]
melatonin	STZ-induced C57BL/6 mice and high glucose-induced primary mouse cardiomyocytes	---	Enhanced	Melatonin can promote mitophagy and improve myocardial damage	[176]
Canagliflozin	HG-induced rat cardiomyocytes (H9C2) and HFD/STZ induced C57BL/6J mice	PINK1/Parkin	Enhanced	Canagliflozin can increase AMPK phosphorylation and simultaneously activate PINK1/Parkin-dependent mitophagy, which can improve mitochondrial function and exert a certain therapeutic effect on DCM	[177]
SFRP2	H9C2 cells induced by glucose and lipid environment in rats and SD rats induced by HFD/STZ	---	Enhanced	SFRP2 can activate mitophagy and play a certain cardioprotective role	[178]
Ginseng Dingzhi Decoction and Metformin	HG-induced mouse cardiomyocytes	--	Enhanced	The combination therapy of Ginseng Dingzhi Decoction and Metformin can activate mitophagy, which has a certain protective effect on myocardial cells	[179]
L-carnitine	HG/FFA-induced human cardiac microvascular endothelial cells (HCMEC) and db/db mice	PINK1/Parkin	Enhanced	L-carnitine increases PINK1/Parkin-dependent mitophagy and reduces microvascular dysfunction in DCM through the CPT1a-PHB2-PARL pathway	[180]
Fucoxanthin	STZ-induced diabetes rats and HG-induced H9C2 cells	---	Enhanced	Fucoxanthin upregulates Bnip3/Nix, enhances mitophagy and reduces oxidative stress, improves myocardial fibrosis in diabetes rats, and reduces HG-induced H9C2 cell hypertrophy	[173]
Sirt3	STZ-induced Sirt3KO mice and primary neonatal mouse cardiomyocytes	Foxo3A-Parkin	Enhanced	Sirt3 exerts cardioprotective effects on DCM by activating Foxo3A Parkin-mediated mitophagy	[181]
Zinc transporter protein (ZIP7)	HFD/STZ induced mice	PINK1/Parkin	Inhibitory	Knocking out ZIP7 can increase mitophagy and improve cardiac function	[183]
JQ1	HFD-induced mouse and PA-induced primary mouse cardiomyocytes	PINK1/Parkin	Enhanced	BRD4 inhibitor (JQ1) can activate PINK1/Parkin-mediated mitophagy, thereby exerting a certain therapeutic effect on DCM	[184]
Mitochondrial aldehyde dehydrogenase 2 (ALDH2)	STZ-induced mouse model	---	Enhanced	ALDH2 exerts a protective effect on DCM through Parkin-dependent mitophagy	[185]

lead to inconsistent results. (3) The diversity of intervention methods is also an important factor causing differences in results. Researchers may use traditional Chinese medicines, western medicines, proprietary Chinese medicines, and other drugs for treatment or select inhibitors or agonists of specific proteins for intervention and even employ advanced means such as gene intervention. These intervention methods have significant differences in terms of mechanism of action target selection and efficacy intensity and therefore may have completely different effects on research results. (4) Finally diabetic microvascular complications as a highly complex internal disease involve multiple aspects of pathogenesis including inflammatory responses oxidative stress endothelial cell dysfunction and other levels. These pathological processes interact and influence each other forming a complex network. This complexity in mechanism poses additional challenges for understanding research results. Currently, there are relatively more studies on mitophagy in DKD and DCM, but fewer studies on mitophagy in DR and DPN. More research is needed to elucidate the specific mechanisms of mitophagy in DKD, DR, DPN, and DCM.

Mitophagy is a complex and finely regulated process involving multiple signaling pathways and interactions of key molecules. However, the regulatory mechanisms

of these molecules are still unclear, making it difficult to precisely regulate mitophagy at specific targets in practical situations. In addition, due to the complexity of the mitophagy mechanism, it is difficult to achieve the desired therapeutic effect with a single intervention, and a combination of multiple means is required. Mitophagy activation and inhibition have different impacts on disease. In DKD, DPN, and DR, enhancing mitophagy may either improve the disease or lead to cellular damage and exacerbate the disease progression; in DCM, enhancing mitophagy can play a certain therapeutic role. This situation requires finding a personalized therapeutic strategy for rational use in clinical translation in response to disease progression, which is undoubtedly a major challenge. In terms of effectiveness, due to the differences in the regulation of mitophagy between individuals, such differences lead to different responses to the same treatment in different individuals, thus affecting the therapeutic efficacy. The purpose of this article is to summarize the existing research on mitophagy in diabetes microvascular disease, with a view to contributing to future clinical research work.

The contribution of mitophagy in diabetic microvascular complications is gradually being explored, but the specific molecular mechanisms and pathways of action remain unclear and elucidated. In addition to this, the current mitophagy-related strategies used for the treatment of DKD, DR, DPN, and DCM are all based on experimental animal and cellular models, which are still a long way from clinical studies. Therefore, it is important to understand the mechanism of action, identify effective therapeutic targets, and discover more mitophagy regulators.

Abbreviations

DKD	Diabetic kidney disease
DR	Diabetic retinopathy
DPN	Diabetic peripheral neuropathy
DCM	Diabetic cardiomyopathy
DM	Diabetes Mellitus
ROS	reactive oxygen species
UB	Ubiquitin
PINK1	PTEN-induced putative kinase 1
MTS	Mitochondrial targeting sequence
UBL	Ubiquitin-like
RING0	A truly interesting new gene 0
TIM23	Translocase of inner mitochondria membrane
PARL	Presenilin-associated rhomboid protein
OMM	Outer mitochondrial membrane
VDAC1	Voltage-dependent anion channel protein 1
MFN1	Mitochondrial fusion 1
MFN2	Mitochondrial fusion 2
ATG8	Autophagy-related protein 8
LC3	Microtubule-associated protein 1 light chain 3
P62/SQSTM1	Sequitosome-1
OPTN	Optineurin
TAX1BP1	T-cell leukemia virus type I binding protein 1
NBR1	Neighbor of BRCA1 gene 1
LIR	LC3 Interaction region
SMURF1	Smad ubiquitination regulator-1
MUL1	Mitochondrial E3 ubiquitin protein ligase 1
GP78	Glycoprotein 78
Drp1	Dynamin-related protein 1
MFF	Mitochondrial fission factor
FUNDC1	FUN14 structural domain-containing protein-1
NIX	Nip3-like protein X
BNIP3	BCL2-interacting protein 3
Ser13	Serine at position 13
PGAM5	Phosphoglycerate mutase family member 5
ULK1	Unc-51-like kinase 1
Ser17	Serine at position 17
Ser24	Serine at position 24
Bcl-2	B-cell lymphoma-2
CL	Cardiolipin
PHB2	Prohibitin 2
OPA1	Optic atrophy protein 1
FIS1	Fmitochondrial fission protein 1is1
MAMs	Mitochondria-associated endoplasmic reticulum membranes
BAX	BCL-2-associated X protein
Bcl-xL	B-cell lymphoma-extra large
NETs	Neutrophil extracellular trapping nets
AMPK	Adenylate-activated protein kinase
HG	High glucose
Arfip2	ADP-ribosylation factor 2-interacting protein
STZ	Streptozotocin
PGRN	Progranulin
MPC5	Mouse renal podocytes
FoxO1	Forkhead box protein O1
HK-2	Human renal proximal tubule cells
HFD/STZ	High-fat diet-fed combined streptozotocin
TXNIP	Thioredoxin-interacting protein
CERS6	Ceramide synthase 6
HIF-1α	Hypoxia-inducible factor-1α
PACS-2	Phosphorolytic acidic cluster sorting protein 2
RTEC	Renal tubular epithelial cell
HRGEC	Human glomerular endothelial cells
TSF	Tangshen formula
JCYSTL	JinChan YiShen TongLuo formula
QRXZYQ	Qing-Re-Xiao-Zheng-Yi-Qi formula
HKC	Huangkui Capsules
SHYS	San-Huang-Yi-Shen Capsule
DOP	Dendrobium officinale polysaccharide
ICA	Icariin
AS II	Astragaloside II
WJ-39	A novel aldose reductase inhibitor
VDR	Vitamin D receptor
FIN	Finerenone
PP2A	Protein phosphatase
Nrf2	Nuclear factor erythroid 2-related factor 2
SFN	Sulforaphane
DIO	Diosgenin
EPO	Erythropoietin
JuA	Jujubeoside A
P-MSCs	Placental-derived mesenchymal stem cells
HDD	Huangqi Danshen decoction
AS-IV	Astragaloside IV
NAC	N-acetyl-L-cysteine
PAA	Fuling acid A
ARPE-19	Human retinal pigment epithelial cell line
RPE	Retinal pigment epithelial
rMC-1	Rat retinal Müller cell
NGR1	Panax ginseng saponin R1 (NGR1)
TGR5	Membrane G protein-coupled bile acid receptor 5 (TGR5)
RMEC	Retinal endothelial cells
TIN2	TERF1 Interacting Nuclear Factor 2
ARPE-19	Human retinal pigment epithelial cell
SBN	Silymarin
N2A	Mouse neuroblastoma cells
PCN	Picrotoxin
KO	Knockout
RSC96	Rat Schwann cell line
TB1	Tat-Beclin1
H9C2	HG-induced rat cardiomyocytes

SFRP2	Secreted frizzled-related protein 2
GN	Ginseng Dingzhi Decoction
MET	Metformin
HG/FFA	High glucose and free fatty acid
HCMEC	Human cardiac microvascular endothelial cell
FX	Fucoxanthin
ZIP7	Zinc transporter protein 7
PA	Palmitate
BRD4	Bromodomain protein 4 (BRD4)

Acknowledgements
All figures were created with Figdraw.com, Microsoft PowerPoint, and BioRender.com.

Author contributions
WQ, XW designed this idea. XH and JL wrote the manuscript. XH, JL, YZ, LX reviewed literature, and created tables and charts. WQ and WX have revised the manuscript. All authors have read and approved the final manuscript.

Funding
This work was supported by the Jilin Provincial Development and Reform Commission (No. 2024C012-1) and the Science and Technology Development Plan Project of Jilin Province (Grant No. YDZJ202301ZYTS153).

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 13 December 2024 / Accepted: 23 February 2025
Published online: 04 March 2025

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