The critical role of dysregulated autophagy in the progression of diabetic kidney disease

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Diabetic kidney disease (DKD) is one of the major public health problems in society today. It is a renal complication caused by diabetes mellitus with predominantly microangiopathy and is a major cause of end-stage renal disease (ESRD). Autophagy is a metabolic pathway for the intracellular degradation of cytoplasmic products and damaged organelles and plays a vital role in maintaining homeostasis and function of the renal cells. The dysregulation of autophagy in the hyperglycaemic state of diabetes mellitus can lead to the progression of DKD, and the activation or restoration of autophagy through drugs is beneficial to the recovery of renal function. This review summarizes the physiological process of autophagy, illustrates the close link between DKD and autophagy, and discusses the effects of drugs on autophagy and the signaling pathways involved from the perspective of podocytes, renal tubular epithelial cells, and mesangial cells, in the hope that this will be useful for clinical treatment.

KEYWORDS
diabetic kidney disease, autophagy, autophagosome, lysosome, podocytes, renal tubular epithelial cells

1 Introduction

Diabetes mellitus (DM) is a common and prevalent disease in recent years, characterized by chronic hyperglycaemia (Davidson et al., 2015). Diabetic kidney disease (DKD) is a serious microvascular complication of DM, which may present with a glomerular hyperfiltration state and microalbuminuria in the early stages, with disease progression to oedema and massive proteinuria and severe impairment of renal function (Reidy et al., 2014). According to reports, the number of people with DM will increase to 592 million by 2035 and about 35–40% of them will eventually progress to DKD, which is a major cause of end-stage renal disease (ESRD) and brings heavy...
psychological and financial burden to families and society (Cao and Cooper, 2011; Shi and Hu, 2014). Traditional treatments have focused on smoking cessation, diet control, weight loss, low protein diets, and lowering blood pressure and glucose and lipids to cope with the range of pathological changes caused by hyperglycemia (Lin et al., 2018). These methods provide some relief from DKD, but they cannot stop the progression of DKD to chronic kidney disease (McGrath and Edi, 2019). Therefore, new treatments for DKD are an urgent problem to be solved.

Autophagy is a conserved intracellular pathway that maintains cellular homeostasis by forming autolysosomes to degrade cytoplasmic components (Kitada and Koya, 2021). The term “autophagy” was first coined by Christian de Duve in 1967 as “self-eating” (Deter and De Duve, 1967). The degradation of mitochondria and other cellular components following glucagon stimulation in rats was observed and it was suggested that the autophagic process requires induction and activation of cyclic adenosine monophosphate (AMP) (Deter and De Duve, 1967). In recent years, autophagy has been intensively studied by many researchers and is considered to be a strictly cellular physiological regulatory process widely present in mammalian cells (Klionsky et al., 2021). And the molecular mechanisms associated with autophagy have been studied and discovered in yeast (Takeshige et al., 1992; Suzuki et al., 2001; Kim et al., 2002).

A growing number of studies have shown that the development of DKD is associated with a defect in autophagy in kidney (Deretic, 2021). Restoring autophagy can improve renal function, reduce the occurrence of oxidative stress, inhibit renal inflammation and fibrosis, and slow the progression of DKD, making it to be another important target for the treatment of DKD (Yang et al., 2018). But the literatures on the relationship between drugs and autophagy in DKD is currently poorly organized. Therefore, this review will discuss the important role of autophagy in DKD in terms of the two processes of autophagosome formation and autolysosome formation, in the hope of laying a theoretical foundation for the clinical treatment of DKD.

2 Autophagy

Three types of autophagy exist in mammalian cells: microautophagy, macroautophagy and chaperone-mediated autophagy (Li and Nakatogawa, 2022). Microautophagy is when proteins become trapped in vesicles formed by lysosomes and are subsequently degraded in the vacuolar lumen of lysosomes (Li and Nakatogawa, 2022). Chaperone-mediated autophagy is a highly specific form of protein catabolism mediated by the heat shock cognate 70 (Hsc70), which targets the lysosomal membrane directly into the lumen of the lysosome (Cuervo and Wong, 2014). In addition, mitophagy is a specific type of autophagy with a high degree of selectivity in its classification, which responds to organelle damage and pathogen invasion, and remove mitochondrial toxicity products (Bravo-San Pedro et al., 2017). This review focuses on the role of macroautophagy (hereafter referred to as autophagy) in DKD.

Autophagy is a highly dynamic process that includes several stages of initiation, extension, closure and degradation (Antonioli et al., 2017). Autophagy is primarily regulated by autophagy-associated proteins (ATG), which are encoded and modified by a set of highly conserved ATG genes (Levine and Kroemer, 2019). The mammalian target of rapamycin (mTOR) and AMP-activated kinase (AMPK) are two key molecules in the process of autophagy (Inoki et al., 2012). AMPK acts as an energy receptor and is activated when the AMP/ATP ratio increases in the absence of intracellular energy, while mTOR negatively regulates the process of AMPK activation and inhibits the onset of autophagy (Li and Chen, 2019). mTOR mainly works in two multi-protein complexes: mTORC1 and mTORC2 (Fantus et al., 2016). mTOR inhibits the activation of autophagy and promotes protein and nucleotide synthesis to facilitate cell growth, proliferation and differentiation, and also acts as an amino acid receptor (Kim and Guan, 2019). When cells are stimulated by amino acid signals, mTORC1 phosphorylates the downstream ribosomal protein S6 kinase (S6K) and the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) to promote protein synthesis (Yuan J. et al., 2020).

In the regulation of autophagy, AMPK is regulated by upstream calcium/calmodulin-dependent protein kinase 2 (CAMKK2, also called CAMKKβ) and serine/threonine-protein kinase stk11 (LKB1), while suppressing the expression of mTORC1 (Shaw et al., 2004; Hawley et al., 2005). Subsequently, AMPK phosphorylates the downstream Unc-51-like (ULK)1/2 complex (Alers et al., 2012). In mammals, ATG101 is an important component of the ULK1 complex and these components that make up ULK1 are responsible for inducing conformational changes to activate the ULK1 complex (Mercer et al., 2009; Lin and Hurley, 2016). The activation of ULK1 phosphorylates the downstream class III phosphatidylinositol 3 kinase (PI3K) complex (also known as VPS34 complex I), whose main target is Beclin-1. The complex is composed of the core protein PI3K, the autophagy-specific cofactor Beclin-1 and other important factors (Russell et al., 2013; Baskaran et al., 2014; Levine et al., 2015). Subsequently, the PI3K complex promotes the production of phosphatidylinositol-3-phosphate (PI3P), which recruits autophagy factors required for autophagosome formation and promotes the formation of omegasomes (omegasomes are derived from the part of the endoplasmic reticulum (ER) that is connected to other organelles) (Axe et al., 2008; Hayashi-Nishino et al., 2009; Lamb et al., 2013). In mammals, the
isolation membrane is supported by ER and may be connected by membrane tubules (Hayashi-Nishino et al., 2009; Ylä-Anttila et al., 2009). The simultaneous recruitment of the effect factors double FYVE zinc finger domain containing protein 1 (DCFP1) and WD repeat domain phosphoinositide-interacting protein (WIPI) contribute to the continuous extension of the phagophore (Dooley et al., 2014; Rogov et al., 2014). ATG2 and the transmembrane protein ATG9 are thought to be autophagosomal intermembrane and interfollicular lipid transport proteins, involved in the expansion of the phagophore (Noda, 2021) (Figure 1).

Subsequently, ATG16L1 acts as an E3 ligase, promotes ATG8 lipidation and successively binds to ATG5 and ATG12, forming an ATG12-ATG5-ATG16L1 ubiquitin-like binding complex (Popelka et al., 2021). Under starvation-induced conditions, WIPI binds to ATG16L1 and recruits the ATG12-ATG5-ATG16L1 complex allowing it to aggregate to the omegasome site of the phagophore (Dooley et al., 2014). Microtubule-associated proteins 1A/1B light chain 3B (LC3), a homologue of mammalian ATG8, is hydrolytically cleaved by ATG4 protein to produce LC3I, which is then activated by ATG7 and ATG3, followed by covalent binding of LC3I by phosphatidylethanolamine, and finally conversion of LC3 to LC3II (Sou et al., 2006; Glick et al., 2010). Researchers have identified the presence of LC3II on both the internal and external surfaces of phagophore, where it plays a role in membrane fusion and sorting of degraded cargo (Glick et al., 2010; Rogov et al., 2014), as well as controlling the size of autophagosomes (Nakatogawa et al., 2007) (Figure 1).

Finally, autophagosomes transports cargo into lysosomes through fusion with lysosomes to form autolysosome (Mizushima and Komatsu, 2011). The fusion of autophagosomes with lysosomes is regulated by the VPS34 complex II, which differs from the PI3K complex in that the subunit ATG14 has been replaced with UV radiation resistance associated (UVRAG) (Lamb et al., 2013). Ras-related protein 7 (Rab7) and ADP-ribosylation factor-like GTPase Arl8 play a key role in the localization of autophagosomes and lysosomes during the fusion process (Pu et al., 2016). They bind several motor junction proteins that link autophagosomes and lysosomes to cytoskeleton-
associated motor proteins that allow autophagosomes and lysosomes to move along microtubules (Garg et al., 2011; Pu et al., 2016). Homotypic fusion and vacuole protein sorting (multisubunit complex HOPS) are essential for autolysosome formation, which tether mobile vesicles along the cytoskeleton (Bröcker et al., 2012). Subsequently, the lipid component of autophagosomes regulates autophagosome-lysosome fusion, where the amount and ratio of PI(3)P and PI(3, 5)P2 regulates the formation of autolysosomes (Hasegawa et al., 2016). Finally, the lysosomes release the degraded products extracellularly in the form of cytosolic spit, facilitating the recycling of the degradation products (Buratta et al., 2020) (Figure 1).

Many clinical therapeutic agents for DKD have been shown to activate autophagy and induce the progression of DKD through different signaling pathways, including the classical drug for lowering sugar - metformin, the classic mTOR target inhibitor - rapamycin, and emerging therapeutic agents such as sodium-glucose cotransporter (SGLT)2 inhibitors and glucagon-like peptide 1 (GLP-1) activators (Gonzalez et al., 2021). In addition, in the ongoing research on Chinese herbal extracts, active ingredients such as resveratrol, hispidulin and berberine have shown renoprotective effects based on the induction of autophagy in kidney (which we will discuss in more detail in the following subsections) (Wang et al., 2019c).

3 DKD

The traditional pathogenesis of DKD is mainly associated with hyperglycaemia: elevated blood glucose promotes metabolic disturbances in DKD, like activating oxidative stress in the kidney, contributing to excessive production of reactive oxygen species (ROS) and reducing activity of antioxidant substances (Fang et al., 2012; Tuttle, 2017). The protein kinase C-α and polyol and hexosamine pathways are activated, upregulating ROS production and increasing the expression of the associated inflammatory factors interleukin (IL) 6, monocyte chemoattractant protein-1, tumour necrosis factor alpha and intercellular adhesion molecule-1 in DKD, accelerating the progress of DKD (Wu X. Q. et al., 2021; Dusabimana et al., 2021; Jha et al., 2022). In addition, imbalances in lipid metabolism, including increased lipid uptake or synthesis, are also important triggers for the development of DKD (Mitrofanova et al., 2021). In a hyperglycaemic environment, small arteries have abnormal systolic-diastolic function, endothelin-1 secretion is increased, promoting vascular dysfunction (Potenza et al., 2009; Tuttle, 2017). At the same time, genetic factors and activation of the renin-angiotensin-aldosterone system also contribute to the development of DKD (Vegter et al., 2012; Kato and Natarajan, 2019).

Controlling blood glucose, lipids and blood pressure are common methods in the treatment of DKD (Doshi and Friedman, 2017). Moreover, lifestyle changes such as: limiting protein and sodium intake, exercise, weight loss and smoking cessation, which can slow the progression of DKD and reduce the risk of cardiovascular events (Lin et al., 2018).

Proteinuria is a key indicator in the diagnosis of DKD and an important factor in the development of DKD (Colhoun and Marcovecchio, 2018). Coresh J et al. showed that changes in proteinuria were consistently associated with subsequent risk of ESRD through a cohort study (Coresh et al., 2019). Results from an 11-years observational cohort study from Japan showed that non-albuminuric DKD had a lower risk of mortality, cardiovascular events or abnormal kidney function compared with other DKD phenotypes (Yokoyama et al., 2020). Blood passes through the glomerular capillary network, passing through the glomerular filtration barrier to allow primary urine to enter the Bowman’s space, which is then reabsorbed by the renal tubules and finally excreted as a virtually protein-free urine (Mora-Fernández et al., 2014). Here, researchers have introduced an important concept: the glomerular filtration barrier (GFB), the disruption of which is an important cause of DKD proteinuria (Pavenstädt et al., 2003). It is a physiological barrier structure composed of glomerular endothelium, glomerular basement membrane (GBM) and podocytes and slit-diaphragm (SD) from the inside out, allowing a highly selective ultrafiltration of plasma components (Mora-Fernández et al., 2014; Lin and Susztak, 2016). The glyocalyx of the glomerular endothelium has specific molecular and charge properties and therefore constitutes a charge barrier for the glomerulus (Weinbaum et al., 2007). Thus, when endothelial cell dysfunction, GBM and podocyte damage occur, these lead to the production of proteinuria followed by glomerulosclerosis and a decrease in glomerular filtration (Jefferson et al., 2008).

The foot-process is an essential component of the podocyte, with interlocking foot-process wrapping around the capillary bulb to form filtering slits that bridge with the electron-dense membrane-like structure SD (Huber and Benzing, 2005). High glucose-induced ROS production during DKD promotes podocyte detachment and apoptosis (Susztak et al., 2006). The non-renewable nature of the podocyte leads to a reduction in the number of podocytes, with subsequent disruption of the normal structure of the GFB and podocytes, weakened the connections between podocytes and finally the leakage of non-selective proteins (Susztak et al., 2006; Jefferson et al., 2008). Downregulation of nephrin expression, a key component of SD in the DKD environment, results in abnormal podocyte function (Doublier et al., 2003). The imbalance in activation of the small GTP-binding proteins Rac1 and Cdc42 (Cdc42 regulates the podocyte actin cytoskeleton), validates the link between podocyte injury and proteinuria as well as glomerulosclerosis at another level (Blattner et al., 2013). Autophagy deficiency is also an important participant in podocyte damage and will be discussed in the next section of the article.
In the course of DKD, damage to renal tubular epithelial cells has a greater correlation with kidney dysfunction (Carney, 2016). A series of inflammatory and oxidative stress responses generated by the massive protein leakage in DKD patients leads to morphological and functional dysfunction of the renal tubules, with epithelial mesenchymal transformation and cell detachment as well as apoptosis, ultimately leading to fibrosis (Chen et al., 2020). In addition to this, pathological changes in DKD glomeruli are often accompanied by proliferation and expansion of the mesangial matrix, and activation of mesangial cells driven by factors such as hyperglycaemia and dyslipidaemia, accelerating glomerulosclerosis (Ebefors et al., 2021). By reviewing the literatures, We have learned that advanced glycation end products (AGEs) are irreversible metabolites produced by hyperglycaemia and AGEs contribute to the production of ROS and mediate inflammatory processes (Matoba et al., 2020; Wu X. Q. et al., 2021; Jha et al., 2022). However, AGEs can be degraded by autophagy and inhibit the inflammatory response (Takahashi et al., 2017). A study of autophagy knockout followed by streptozotocin (STZ) induced DM showed severe microalbuminuria, podocyte and endothelial cell damage in the model mice compared to the control mice (Lenoir et al., 2015). And the renal pathological findings also showed extensive mesangium expansion and glomerulosclerosis, thus demonstrating the close relationship between DKD and autophagy (Lenoir et al., 2015).

4. DKD and autophagy

As mentioned previously, we have discussed the biological process of autophagy and its function in cellular metabolism (Kitada and Koya, 2021); and have argued for a close link between autophagy and DKD by reviewing the literatures (Lenoir et al., 2015). Therefore, we will explore how do drugs target autophagy for the treatment of DKD based on two processes, one is autophagosome formation and another is autolysosome formation, in the hope of enhancing the understanding of the relationship between autophagy and DKD.

4.1 The role of autophagosome formation in DKD

4.1.1 Role of autophagy in podocytes

In diabetic mice and murine podocyte cell (MPC-5) models, ruxolitinib or wogonin affected autophagy and delayed the progression of DKD through JAK/STAT and Bcl-2-mediated pathways (Chen D. et al., 2021; Liu et al., 2022). In another experimental study, overexpression of KLF4 (a zinc finger-containing transcription factor) showed that KLF4 could play a nephroprotective role by regulating the mTOR/S6K pathway to activate autophagy (Gong et al., 2019). Paecilomyces cicadae-fermented radix astragali played a role in activating autophagy by inhibiting the PI3K/AKT/mTOR signaling pathway, thereby alleviating the progression of DKD (Yang F. et al., 2020). In two experiments using db/db mice and MPC-5 cells as the primary targets, the calcium-sensitive receptor type II agonist cinacalcet worked by activating the CaMKKβ-LKB1-AMPK pathway, while the exosome generated by adipose-derived stem cells achieved therapeutic effects by inhibiting the Smad1/mTOR pathway (Lim et al., 2018; Jin et al., 2019). Similarly, sarsaapogenin (the main active ingredient in Anemarrhena asphodeloides Bunge) and spermine, both of which promoted autophagy by targeting GSK3β and AMPK/mTOR, respectively (Li et al., 2021; Zhang et al., 2021). In a podocyte model induced by high glucose, celestrol restored autophagy through an HO-1-mediated pathway while alleviating the inflammation and damage induced by high glucose in podocytes (Zhan et al., 2018). At the same time, in two additional experiments with high glucose induced podocytes, the expression of G-protein-coupled receptor 43 (GPR43) or sperm-associated antigen 5 (SPAG5), both of which promoted autophagy via the ERK/EGR1 and SPAG5/AKT/mTOR signaling pathways, were inhibited by GPR43 gene knockout or SPAG5 gene silencing, it could be used as potential therapeutic targets for DKD (Xu et al., 2020; Lu et al., 2022). In animal and cellular models of DKD, Astragaloside IV (AS-IV) induced autophagy by activating the AMPK pathway (Guo et al., 2017). In KK-Ay mice and podocyte models, treatment with apelin or AS-IV was administered and both were shown to play an important role in alleviating DKD by regulating the ERK/AKT/mTOR and SIRT1-NF-κB P65 signaling pathways (Liu et al., 2017; Wang X. et al., 2019). Interestingly, the use of hispidulin or berberine in DKD cell models, both of which promoted autophagy by inhibiting mTOR-related pathways (Wu et al., 2018; Li et al., 2020). Inhibition of mTOR and TFEB affected the formation and conversion of autophagy in DKD mice and cellular models, respectively (Zhao X. et al., 2018). Moreover, many researches have also revealed the effects of protein tyrosine phosphatase 1B, resveratrol, ursoodeoxycholic acid and 4-phenylbutyrate as well as histone deacetylase 4 on the autophagic process of podocytes in DKD models (Wang et al., 2014; Cao et al., 2016; Huang et al., 2017; Ito et al., 2017). Therefore, autophagy affects cell metabolism in podocytes through mTOR, AMPK, PI3K and other related pathways, inhibits inflammation and kidney damage, and delays the progress of DKD (Figure 2; Tables 1-3, Table.5).

4.1.2 Role of autophagy in renal tubular epithelial cells

In DKD mice and renal tubular epithelial cell models, treatment with LNA-anti-miR-214 or overexpression of
Klotho (an anti-aging factor expressed in the kidney) modulated the P53/miR-214/ULK1 and AMPK/ERK signaling pathways to exert nephroprotective effects (Ma et al., 2020; Xue et al., 2021). In a different study model, Korean red ginseng was shown to promote autophagy and thus reduced hyperglycaemia-induced renal inflammation and fibrosis, exerting a nephroprotective effect (Karunasagara et al., 2020). In a study using high glucose induced human proximal tubular cells (HK-2 cells) as a model, the investigators found that renal injury could be ameliorated by altering the expression of miR-155 and SIRT1, or by administering dapagliflozin and astilbin, respectively (Chen et al., 2018; Wang Y. et al., 2018; Xu et al., 2021). However, the difference between these two drugs was that dapagliflozin acted to suppress inflammation by regulating the AMPK/mTOR/NF-κB pathway, whereas astilbin worked on the PI3K/AKT signaling pathway to attenuate high glucose-induced autophagy and apoptosis (Chen et al., 2018; Xu et al., 2021). Carbon monoxide positively regulated autophagy via the Beclin-1-Bcl-2 pathway in the DKD model to protect the kidney from injury and aging; meanwhile, wogonin attenuated renal fibrosis by targeting PI3K/AKT/NF-κB to regulate renal inflammation and autophagic activity (Chen L. et al., 2021; Lei et al., 2021). In palmitic acid-induced HK-2 cells, alprostadil ameliorated renal tubular insulin resistance and restored autophagy via an autophagy-dependent fibroblast growth factor 21-associated pathway (Wei et al., 2018). Cyclocarya paliurus triterpenic acids or reduced expression of thioredoxin interacting protein (TXNIP) acted through mTOR or in combination with the AMPK pathway to induce autophagy (Huang et al., 2016; Zhang et al., 2019). In contrast, the Chinese herbal extract icariin from Epimedium restored autophagy and attenuated renal tubulointerstitial fibrosis by targeting miR-192-5p/GLP-1R (GLP-1 receptor) in a DKD model (Jia et al., 2021). At the same time, the overexpression of TXNIP (one of the factors of autophagy) induced by high glucose led to autophagy dysfunction and participated in the occurrence of DKD (Huang et al., 2014). Studies had shown that the drug empagliflozin or paricalcitol (an activated vitamin D analog) restored autophagy via AMPK-related pathways in DKD models (Lee et al., 2019; Li et al., 2022). Treatment with dencichine or Cathelicidin-BF peptide in DKD rats and cellular models showed that both positively regulated autophagy through an AMPK-mediated pathway and improved renal function by reducing oxidative stress and...
**TABLE 1 The role of autophagosome formation in DKD (drugs with clinical trials).**

| AMPK-mediated signaling pathway | Processing method | Modeling method (animal/cell) | Conclusion | References |
|---------------------------------|-------------------|-------------------------------|------------|-----------|
| Empagliflozin                    | STZ induced C57Bl/6j mice; HG induced human renal proximal tubular cells | Empagliflozin could reverse mitochondrial dynamics and autophagy so as to play the role of renal protection | Lee et al. (2019) |
| Berberine                       | HG-induced podocytes | Berberine activated podocyte autophagy by inhibiting the mTOR/P70S6K/4EBP1 signaling pathway, thereby alleviating podocyte apoptosis | Li et al. (2020) |
| Paricalcitol (an activated vitamin D analog) | STZ induced VDR-KO mice; HG induced HK-2 cells | VD-VDR could restore defective autophagy in the kidney of STZ-induced diabetic mice, which could be attributed to the activation of the Ca-CAMKK2-AMPK pathway in renal tubular epithelial cells | Li et al. (2022) |
| Metformin                       | HFD and STZ induced SD rats; HG cultured RMCs | Metformin alleviated oxidative stress and enhanced autophagy in diabetic kidney disease via AMPK/SIRT1-FOXO1 pathway | Ren et al. (2020) |
| Fenofibrate                     | HFD induced C57Bl/6j mice; PA induced mouse proximal tubule cells | Delayed treatment with fenofibrate had a therapeutic effect on HFD-induced kidney injury through the activation of AMPK and induction of subsequent downstream effectors: autophagy, fatty acid oxidation enzymes, and antioxidants | Sohn et al. (2017) |
| Calcium dobesilate              | HFD and STZ induced C57Bl/6 mice; HFD induced KK-Ay mice | Calcium dobesilate played a key role in protecting renal function and restoring autophagy by blocking VEGF/VEGFR2 and inhibiting the PI3K/AKT/mTOR signaling pathway | Wang et al. (2019b) |
| Metformin                       | High-glucose and high-fat diet and STZ induced SD rats; HG induced renal tubular epithelial cells | Metformin-induced AMPK significantly ameliorated renal autophagic function, inhibited the partial EMT of RTECs, and attenuated TIF, all of which effectively prevented or delayed the onset of DN. | Wang et al. (2021b) |
| Alprostadil (PGE1)              | PA induced HK-2 cells | The researchers demonstrated the potential protection of PGE1 on insulin resistance in renal tubules via autophagy-dependent FGF21 pathway in preventing the progression of DN. | Wei et al. (2018) |
| Dapagliflozin                   | HG induced HK-2 cells | In diabetic renal proximal tubular cells, dapagliflozin ameliorated HG-induced autophagic flux reduction, via increased AMPK activity and mTOR suppression; and inflammatory alterations due to NF-κB pathway suppression | Xu et al. (2021) |
| Liraglutide                     | SDT fatty rats | Liraglutide might exert a renoprotective effect via prevention of glomerular endothelial abnormality and preservation of autophagy in early-phase DKD, independent of blood glucose, and blood pressure levels | Yamada et al. (2021) |
| Dapagliflozin                   | ZDF rats; AGEs induced INS 1 cells | The renoprotective effect of the GLP-1 in DKD rats and the underlying mechanism that was independent of controlling glucose were illustrated | Yang et al. (2020b) |

DKD, diabetic kidney disease; AMPK, AMP-activated kinase; STZ, streptozotocin; HG, high glucose; mTOR, the mammalian target of rapamycin; P70S6K, ribosomal protein 70 S6 kinase; 4EBP1, 4E-binding protein 1; Ca-CAMKK2, calcium/calmodulin-dependent protein kinase kinase 2; HK-2, cells, human proximal tubular cells; VDR, Vitamin D receptor; SIRT1, sirtuin1; FOXO1, forkhead box transcription factor O1; HFD, high fat diet; SD, rats, Sprague-Dawley rats; RMCs, rat mesangial cells; PA, palmitic acid; VEGF, vascular endothelial growth factor; PI3K, phosphatidylinositol 3 kinase; AKT, protein kinase B; VEGF/R2, VEGF, receptor 2; EMT, epithelial mesenchymal transition; RTECs, renal tubular epithelial cells; TIF, tubulointerstitial fibrosis; DN, diabetic nephropathy; FGF21, fibroblast growth factor 21; NF-κB, nuclear factor-kappaB; eNOS, endothelial nitric oxide synthase; SDT, fatty rats, spontaneously diabetic torii fatty rats; ZDF, rats, Zucker diabetic fatty rats; AGEs, advanced glycation end products; GLP-1, glucagon-like peptide 1.

**Pathway determination**

AMPK, AMP-activated kinase; mTOR, the mammalian target of rapamycin; P70S6K, ribosomal protein 70 S6 kinase; 4EBP1, 4E-binding protein 1; Ca-CAMKK2, calcium/calmodulin-dependent protein kinase kinase 2; HK-2, cells, human proximal tubular cells; VDR, Vitamin D receptor; SIRT1, sirtuin1; FOXO1, forkhead box transcription factor O1; HFD, high fat diet; SD, rats, Sprague-Dawley rats; RMCs, rat mesangial cells; PA, palmitic acid; VEGF, vascular endothelial growth factor; PI3K, phosphatidylinositol 3 kinase; AKT, protein kinase B; VEGF/R2, VEGF, receptor 2; EMT, epithelial mesenchymal transition; RTECs, renal tubular epithelial cells; TIF, tubulointerstitial fibrosis; DN, diabetic nephropathy; FGF21, fibroblast growth factor 21; NF-κB, nuclear factor-kappaB; eNOS, endothelial nitric oxide synthase; SDT, fatty rats, spontaneously diabetic torii fatty rats; ZDF, rats, Zucker diabetic fatty rats; AGEs, advanced glycation end products; GLP-1, glucagon-like peptide 1.

**Antioxidant via the AMPK pathway**

Lee et al. (2019). In addition, researchers have experimentally demonstrated that the use of therapeutic agents and approaches such as mitoQ (mitochondria-targeted antioxidant) and NSC697923 inhibitor and t-AUCB (an inhibitor of soluble epoxide hydrolase) can slow down the progression of DKD by improving autophagy (Xiao et al., 2017; Pontrelli et al., 2021).

**References**

Huang et al. (2020); Liu et al. (2020). However, experiments in which metformin treated DKD rats and renal tubular epithelial cells models, metformin exerted therapeutic effects through an AMPK-mediated pathway (Wang F. et al., 2021). To investigate the specific mechanism of fenofibrate on the DKD model, researchers found that fenofibrate induced autophagy and acted as an antioxidant via the AMPK pathway (Sohn et al., 2017).
### TABLE 2 The role of autophagosome formation in DKD (drugs without clinical trials).

| Signaling pathway | Processing method | Modeling method (animal/cell) | Conclusion | References |
|--------------------|-------------------|-----------------------------|------------|------------|
| RAGE/mTOR signaling pathway | Paoniforin | AGEs induced HBZV-1 cells | Paoniforin inhibited AGEs induced autophagy and cell injury in HBZV-1 through activating mTOR and inhibiting RAGE | Chen et al. (2017) |
| PI3K/Akt signaling pathway | Astilbin | HG induced HK-2 cells | Astilbin attenuated HG-induced autophagy and apoptosis in HK-2 cells through the PI3K/Akt pathway | Chen et al. (2018) |
| JAK/STAT signaling pathway | Ruxolitinib | STZ induced C57BL/6 J mice, HG induced MPC-5 | JAK/STAT pathway promoted the progression of diabetic kidney disease via autophagy in podocytes | Chen et al. (2021a) |
| Beclin-1-Bcl-2 complex mediated signaling pathway | Carbon monoxide (CO) | HFD and STZ induced C57BL/6 mice; HG induced HBZV-1 cells, HK-2 cells and HPC. | CO protected DN mice from renal senescence and function loss via improving autophagy partly mediated by dissociating Beclin-1-Bcl-2 complex, which was possibly ascribed to the degradation of SASP. | Chen et al. (2021c) |
| ULK1-mediated signaling pathway | Genapocide | Unx, HFD and STZ induced C57BL/6 mice | Genapocide enhancedULK1-mediated autophagy and reduced oxidative stress, inflammation, and fibrosis | Sasaibama et al. (2021) |
| AMPK/mTOR signaling pathway | Ethyl acetate | STZ induced Wistar albino rats | Phenolic-rich fraction had a protective effect against diabetic nephropathy presumably via enhancing autophagy and prevention of apoptosis | Ezzat et al. (2021) |
| AMPK-mediated signaling pathway | Astragaloside IV (AS-IV) | STZ induced C57BL/6 mice, HG induced podocytes | AS-IV prevented the progression of DN, which was mediated at least in part by SRECA2-dependent ER stress attenuation and AMPK-promoted autophagy induction | Guo et al. (2017) |
| AdipoR1/AMPK signaling pathway | AdipoRon | DKD patients, db/db mice, HG induced HK-2 cells | Autophagy-mediated lipophagy deficiency played a critical role in the ectopic lipid deposition and lipid-related renal injury of DN. | Han et al. (2021) |
| AMPK signaling pathway | Dencichine | HFD and STZ induced SD rats, hydrogen peroxide induced HK-2 cells | Dencichine ameliorated renal injury by improving oxidative stress, apoptosis, and fibrosis in diabetic rats | Huang et al. (2020) |
| Smad1/mTOR signaling pathway | Jiedu Tongluo Baoshen formula | HFD and STZ induced rats | Jiedu Tongluo Baoshen formula enhanced podocyte autophagy to reduce podocyte damage, thereby effectively treating DKD proteinuria and protecting kidney function | Jin et al. (2019) |
| NF-kB/iNOS signaling pathway | Valproic acid (VPA) | STZ induced SD rats | VPA treatment ameliorated the podocyte and renal injuries mainly by facilitating the autophagy and inactivation of NF-kB/iNOS signaling | Khan et al. (2015) |
| mTORC1 signaling pathway | Very-low-protein diet | Wistar fatty rats | A very-low-protein diet improved advanced diabetic renal injuries, including tubulointerstitial damage, by restoring autophagy through the suppression of the mTORC1 pathway | Kitada et al. (2016) |
| PI3K/Akt/NF-kB signaling pathway | Wogonin | STZ induced mice; HG induced HK-2 cells | Wogonin could mitigate tubulointerstitial fibrosis and renal tubular cell injury via regulating PI3K/Akt/NF-kB signaling pathway-mediated autophagy and inflammation | Lei et al. (2021) |
| mIR-141-3p/PTEN/Akt/mTOR signaling pathway | Triptolide | HFD and STZ induced SD rats; HG induced human mesangial cells | Triptolide alleviated fibrosis by restoring autophagy through the miR-141-3p/PTEN/Akt/mTOR pathway | Li et al. (2017) |
| GSK3β signaling pathway | Sarsasapogenin (Sar) | STZ induced rats, HG induced podocytes | Sar meliorated experimental DN through targeting GSK3β signaling pathway and restoring podocyte autophagy | Li et al. (2021) |
| CaMKKβ-LKB1-AMPK signaling pathway | Cinacalcet | db/db mice, HG induced HGEs, and murine podocytes | Cinacalcet increased intracellular Ca2+ followed by an activation of CaMKKβ-LKB1-AMPK signaling in HGEs and podocytes in the kidney, and then modulated apoptosis and autophagy | Lim et al. (2018) |
| ERK/Akt/mTOR signaling pathway | Apelin | KKAy mice, HG induced podocytes | Increased apelin concentration in plasma inhibited podocyte autophagy, which would lead to podocyte apoptosis and renal dysfunction in diabetes | Liu et al. (2017) |
| AMPK signaling pathway | Cathelicidin-RF peptide | STZ induced rats; hydrogen peroxide induced HK-2 cells | Cathelicidin-RF peptide ameliorated renal fibrosis and podocyte autophagy | Liu et al. (2020) |

(Continued on following page)
In summary, autophagy plays an important role in maintaining the homeostasis and function of renal tubular epithelial cells. If autophagy is imbalanced, it leads to intracellular metabolic changes and accelerates the onset and progression of disease, but these could be restored with drugs such as metformin and empagliflozin (Figure 2; Table.1-3, Table.5).

**TABLE 2 (Continued) The role of autophagosome formation in DKD (drugs without clinical trials).**

| Signaling pathway | Processing method | Modeling method (animal/cell) | Conclusion | References |
|-------------------|-------------------|-------------------------------|------------|-----------|
| Bcl-2-mediated signaling pathway | Wogonin | STZ induced C3HBL/6 J mice; HG induced MPC-5 | Wogonin protected glomerular podocytes by targeting Bcl-2-mediated autophagy and apoptosis in diabetic kidney disease | Liu et al. (2022) |
| signaling pathway | Caffeic acid | HFD and STZ induced Wistar rats | Caffeic acid modulated autophagy pathway through inhibition of autophagy regulatory miRNAs, and then played a role in anti-diabetic nephropathy | Matholi et al. (2017) |
| AMPK-mTOR-ULK1 signaling pathway | Mangiferin | STZ induced SD rats | Mangiferin delayed the progression of DN and protected the podocytes by enhancing autophagy under diabetic conditions via the AMPK-mTOR-ULK1 pathway | Wang et al. (2018a) |
| SIRT1-NF-κB signaling pathway | AS-IV | KK-Ay mice; HG induced mesangial cells | AS-IV ameliorated renal function and morphology by inducing autophagy and inhibiting mesangial cell activation through the SIRT1-NF-κB signaling pathway | Wang et al. (2018b) |
| SIRT-NE-fx-P65 signaling pathway | AS-IV | KK-Ay mice; HG induced podocytes | AS-IV exerted its effects on podocyte EMT through modulation of the SIRT1-NF-κB signaling pathway and autophagy activation | Wang et al. (2019a) |
| GPER/Keap1/Nrf2 signaling pathway | Icarin | STZ induced SD rats; HG induced human mesangial cells | The therapeutic effects of icarin on type 1 diabetic nephropathy were demonstrated in rats via GPER mediated P62-dependent Keap1 degradation and Nrf2 activation | Wang et al. (2020) |
| Nrf2/PINK signaling pathway | MitQR (mitochondria-targeted antioxidant) | db/db mice; HG induced HK-2 cells | MitQR exerted beneficial effects on tubular injury in DKD via mitophagy and that mitochondrial quality control was mediated by Nrf2/PINK. | Xiao et al. (2017) |
| PI3K/AKT/mTOR signaling pathway | Paclitaxel/cis-ceramide-fermented Radix astragali (RPF) | HFD and STZ induced C3HBL/6 mice; HG induced podocytes | RPF enhanced autophagy in podocytes and delayed DN probably by inhibiting the PI3K/AKT/mTOR signaling pathway | Yang et al. (2020a) |
| AMPK/mTOR signaling pathway | Erlotinib | STZ induced C3H8KLKS/ j mice (eNOS−/− mice) | Inhibition of EGFR with erlotinib attenuated the development of diabetic nephropathy in type 1 diabetes, which was mediated at least in part by inhibition of mTOR and activation of AMPK, with increased autophagy and inhibition of ER stress | Zhang et al. (2014) |
| AMPK-mTOR signaling pathway | Cyclocarya paliurus triterpenic acids (CPT) | STZ induced SD rats; HG induced HK-2 cells | CPT might be a desired candidate against diabetes, potentially through AMPK-mTOR-regulated autophagy pathway | Zhang et al. (2019) |
| AMPK-mediated signaling pathway | Huang Gui Solid Dispersion (HGSD) | HFD and STZ induced Wistar rats, db/db mice | HGSD protected against diabetic kidney dysfunction by inhibiting glomerular mesangial matrix expansion and activating autophagy | Zhang et al. (2020) |
| AMPK/mTOR signaling pathway | Spermine | STZ induced Wistar rats, HG induced podocytes | Spermine might have the potential to prevent diabetic kidney injury in rats by promoting autophagy via regulating the AMPK/mTOR signaling pathway | Zhang et al. (2021) |
| CaMKK2-AMPK-p-mTOR signaling pathway | Juhiobose A (JuA) | HFD and STZ induced SD rats | JuA protected against type 1 diabetic nephropathy through inhibiting oxidative stress and apoptosis mediated by mitochondria and ER stress. In addition, autophagy and mitophagy were enhanced by JuA | Zhang et al. (2022) |

RAGE, the receptor for advanced glycation end-products; HBZY-1, cells, rat mesangial cells; JAK/STAT, the Janus kinase (JAK)/signal transducers and the transcription (STAT); MPC-5, murine podocyte MPC-5; cells; Bcl1-1, mammalian ortholog of the yeast autophagy-related gene 6 (Atg6) and Bcl1-1, in the Caenorhabditis elegans nematode; Bcl-2, B cell lymphoma-2; SASSP, senescence-related secretory phenotype; Unx, unilateral nephrectomy; ULK1, unc-51-like kinase 1; ER, endoplasmic reticulum; SERCA2, sarco(endo)plasmic reticulum Ca(2+) ATPase, 2, Adipor1, adiponectin receptor 1; Smad1, Smad family member 1; ADSCs, adipose-derived stem cells; ADSCs-Exo, ADSCs-derived exosome; iNOS, inducible nitric oxide synthase; mTORC1, the mechanistic target of rapamycin complex 1; PTEN, phosphatase and tensin homolog; GSK3β, glycogen synthase kinase 3β; LBK1, liver kinase B1; HGFECs, human glomerular endothelial cells; ERK, extracellular signal-regulated kinase; GPER, G-protein-coupled estrogen receptor; Keap1/Nrf2, the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2 related factor 2; PINK, tissin homolog (PTEN)-induced putative kinase; EGFR, epidermal growth factor receptor;

et al., 2018; Jiang et al., 2020; Han et al., 2021; Liang et al., 2021; Zheng et al., 2021). In summary, autophagy plays an important role in maintaining the homeostasis and function of renal tubular epithelial cells. If autophagy is imbalanced,
4.1.3 Role of autophagy in glomerular mesangial cells

Treatment of induced rat mesangial cells and animals with metformin and paeoniflorin showed that metformin alleviated oxidative stress and enhanced autophagy via the AMPK/SIRT1-FOXO3a pathway (Ren et al., 2020). In contrast, paeoniflorin showed that metformin alleviated oxidative stress and enhanced autophagy via the AMPK/SIRT1-FOXO3a pathway (Ren et al., 2020). In addition to this, metformin alleviated oxidative stress and enhanced autophagy via the AMPK/SIRT1-FOXO3a pathway (Ren et al., 2020). In DKD patient-derived mesangial cells, it was demonstrated that metformin alleviated oxidative stress and enhanced autophagy via the AMPK/SIRT1-FOXO3a pathway (Ren et al., 2020). In DKD patient-derived mesangial cells, it was demonstrated that metformin alleviated oxidative stress and enhanced autophagy via the AMPK/SIRT1-FOXO3a pathway (Ren et al., 2020).

**TABLE 3** The role of autophagosome formation in DKD (low or high expression of a certain target).

| Signaling pathway | Processing method | Modeling method (animal/cell) | Conclusion | References |
|-------------------|-------------------|-----------------------------|------------|-----------|
| Akt/mTOR signaling pathway | LncRNA SOX2OT overexpression | STZ induced C57BL/6J mice; HG induced mouse mesangial cells | LncRNA SOX2OT alleviated the pathogenesis of DN via regulating Akt/mTOR-mediated autophagy | Chen et al. (2021b) |
| AKT/SIRT1-FOXO3a signaling pathway | P2Y2R knockout | Unx, HFD and STZ induced C57BL/6 mice | P2Y2R contributed to the pathogenesis of DN by impairing autophagy and served as a therapeutic target for treating DN. | Dusabemana et al. (2020) |
| FOXO1/STAT1 signaling pathway | Loss of TIMP3 | TIMP3(−/−) mice; HG induced mesangial cells | Reduction of TIMP3 caused a concomitant STAT1-dependent and compartment-specific loss of FOXO1 activity, which in turn diminished the expression of protective autophagy genes to fuel glomerular damage in a mouse model | Fiorentino et al. (2013) |
| mTOR/S6K signaling pathway | KLF4 overexpression | db/db mice, DKD mice serum induced podocytes | KLF4 ameliorated DKD by activating autophagy via the mTOR pathway | Gong et al. (2019) |
| mTOR signaling pathway | Reduce the expression of TXNIP | DKD patients, STZ induced rats, HG induced HK-2 cells | Hyperglycemia-induced TXNIP contributed to the dysregulation of tubular autophagy and mitophagy in DN through activation of the mTOR signaling pathway | Huang et al. (2016) |
| ERK/EGFR signaling pathway | Gene knockdown of GPR43 | HG induced podocytes | GPR43 activation-mediated lipotoxicity contributed to podocyte injury in DN by modulating the ERK/EGF pathway | Lu et al. (2022) |
| P53/miR-214/ULK1 signaling pathway | LNA-anti-miR-214 | STZ induced C57BL/6J and Akita mice; HG induced proximal tubule cells | Autophagy impairment was instigated by the downregulation of ULK1 via P53-mediated induction of miR-214 | Ma et al. (2020) |
| HDAC4-STAT1 signaling pathway | pGLV3-shRNA2-HDAC4 | Unx and STZ induced SD rats, db/db mice; HG, AGES or TGF-β induced podocytes | HDAC4 contributed to podocyte injury and was one of critical components of a signal transduction pathway that linked renal injury to autophagy in diabetic nephropathy | Wang et al. (2014) |
| P53/miR-155-SIRT1 signaling pathway | Change the expression of miR-155 and SIRT1 | HG induced HK-2 cells | The signaling axis of P53, miR-155-5p, and SIRT1 in autophagic process might be a critical adapting mechanism for diabetic kidney injury | Wang et al. (2018c) |
| SPAG5/AKT/mTOR signaling pathway | Silencing SPAG5 | HG induced human podocytes | SPAG5 antisense RNA1 inhibited autophagy and exacerbated apoptosis of podocytes via SPAG5/AKT/mTOR pathway | Xu et al. (2020) |
| mTOR/TFEB signaling pathway | Inhibit the activity of mTOR and TFEB | db/db mice, AGES induced podocytes | AGES inhibited the formation and turnover of autophagosomes in podocytes by activating mTOR and inhibiting the nuclear translocation of TFEB. | Zhao et al. (2018a) |
| EGR1 signaling pathway | CIDEC silencing | Unx and STZ induced SD rats, HG induced NRK-52E cells | CIDEC gene silencing might delay the progression of DN by restoring autophagy activity and inhibiting apoptosis with the participation of GFR1 and ATGL | Zheng et al. (2021) |

LncRNA SOX2OT, LncRNA SOX2 overlapping transcript; P2Y2R, purinergic receptors; TIMP3, tissue inhibitor of metalloproteinase three; KLF4, Krüppel-like factor 4; TXNIP, thioredoxin-interacting protein; EGR1, early growth response factor 1; GPR43, G-protein-coupled receptor 43; HDAC4, histone deacetylase 4; TGF-β, transforming growth factor-beta; SPAG5, sperm-associated antigen 5; TFE3, transcription factor EB; CIDEC, cell death-inducing DFF45-like effector C; NRK-52E, renal tubular epithelial cell.

4.1.3 Role of autophagy in glomerular mesangial cells

Treatment of induced rat mesangial cells and animals with metformin and paeoniflorin showed that metformin alleviated oxidative stress and enhanced autophagy via the AMPK/SIRT1-FOXO3a pathway (Ren et al., 2020). In contrast, paeoniflorin reduced LC3II/LC3I expression through the RAGE/mTOR pathway, decreased the number of autophagosomes and inhibited AGES-induced autophagy (Chen et al., 2017). To investigate the role of LncRNA SOX2OT and tissue inhibitor of metalloproteinase 3 (TIMP3) in the progression of DKD, overexpression or gene deletion was used in treated mice and mouse mesangial cells, suggesting that the overexpression of LncRNA SOX2OT (SOX2 overlapping transcript) restored autophagy via Akt/mTOR, while TIMP3 deletion led to reduced FOXO1 expression of the autophagy key factor and increased expression of the FOXO1 transcriptional repressor STAT1, driving renal function to deteriorate in DKD patients and mice (Fiorentino et al., 2013; Chen K. et al., 2021). In addition to this, AS-IV induced autophagy and inhibited activation of mesangial cells in the SIRT1-NF-κB pathway, alleviating mesangial matrix expansion and proliferation in the KK-Ay mouse model (Wang et al., 2018b). In DKD rat and HMC models, icariin promoted G-protein-coupled estrogen...
TABLE 4 The role of autolysosome formation in DKD.

| Signaling pathway | Processing method | Modeling method (animal/cell) | Conclusion | References |
|-------------------|-------------------|-------------------------------|------------|------------|
| PI3K/Akt-GSK3β- | Hepatocyte growth factor (HGF) | STZ induced DBA/2J mice; HG induced MPC-5 | HGF protected against diabetic nephropathy through restoring podocyte autophagy, which at least partially involved PI3K/Akt-GSK3β-TFEB axis-mediated lysosomal function improvement | Hou et al. (2020) |
| TFEB signaling pathway | | DKD patients; AGEs induced HK-2 cells | Lyosomal membrane permeabilization and lysosomal dysfunction were triggered by AGEs, which induced autophagic inactivation in renal tubular epithelial cells from patients with DN. | Liu et al. (2015) |
| | Resveratrol plus vitamin E | DKD patients; AGEs induced podocytes | Lyosomal membrane permeabilization induced lysosomal dysfunction, which was a key node of insufficient autophagy of podocytes in DKD. | Liu et al. (2019) |
| Vaspin/HSPA1L-mediated signaling pathway | Vaspin knockout | Obesity related kidney disease and DN patients; high fat-high sucrose diet induced C57BL/6j mice | Vaspin maintained PTCs through ameliorating ER stress, autophagy impairment, and lysosome dysfunction in DKD via vaspin/HSPA1L-mediated pathways | Nakatsuka et al. (2021) |
| TFEB-mediated | ATG5 knockout | STZ induced Atg5/F KAP mice; HG induced PTECs | Autophagy inhibited the accumulation of AGES by promoting lysosomal biogenesis and function in the kidney proximal tubules | Takahashi et al. (2017) |
| signaling pathway | Inhibit the expression of Smad3 | d/hb mice; AGE-BSA induced HK-2 cells | Smad3 promoted lysosome depletions via the inhibition of TFEB-dependent lysosome biogenesis | Yang et al. (2021a) |
| Smad3-mediated | Keluoxin | High-fat and high-sugar diet and STZ induced SD rats | Keluoxin could regulate autophagy via improving the lysosomal degradation function and alleviating podocyte injury, alleviated kidney injury in rats with DN, and had a protective effect on renal function | Yang et al. (2021b) |
| signaling pathway | MScs injection and TFEBS | STZ induced BALB/c mice; cultured primary MScs | Mesenchymal stem cells restored lysosomal function and activated autophagy, and then suppressed inflammatory response and alleviated renal injuries in DN mice via TFEB-dependent Mφ switch | Yuan et al. (2020b) |
| TFEB-mediated | RNAi transfection | STZ induced BALB/c mice; cultured primary MScs | Mesenchymal stem cells restored lysosomal function and activated autophagy, and then suppressed inflammatory response and alleviated renal injuries in DN mice via TFEB-dependent Mφ switch | Yuan et al. (2020b) |
| signaling pathway | High dose vitamin E | DN patients; STZ induced SD rats; AGES induced HK-2 cells | High dose vitamin E attenuated DN via improvement of lysosomal function and alleviation of autophagic stress | Zhao et al. (2018b) |

HSPA1L, heat shock protein family A member 1 like; PTCs, proximal tubular cells; ATG, autophagy-related genes; PTECs, proximal tubular epithelial cells; MScs, mesenchymal stem cells.

receptor-mediated P62-dependent Keap1 degradation as well as Nrf2 activation, and played a therapeutic role in the progression of type 1 DKD in rats (Wang et al., 2020). Similarly, triptolide targeted the miR-141-3p/PTEN/AKT/mTOR pathway to induce autophagy and protect renal function (Li et al., 2017). By summarizing the above literature, we found that autophagy exists in glomerular mesangial cells. Oxidative stress and inflammation inhibit autophagy in mesangial cells, but the application of drugs such as AS-IV and Icariin can upregulate the occurrence of autophagy by regulating autophagy-related pathways (Figure 2; Tables 1-3, Table 5).

4.1.4 Other studies on autophagosome formation in DKD

The use of GLP-1 in Zucker diabetic fatty rats and AGES induced Ins 1 cells model showed that GLP-1 showed renoprotective effects independent of hypoglycaemia (Yang S. et al., 2020). Using liraglutide in an animal model of spontaneously diabetic tori fatty rats, it was concluded that liraglutide protected the kidney and activated autophagy in early DKD via the AMPK/eNOS pathway independent of reductions in blood glucose and blood pressure (Yamada et al., 2021). Caffeic acid, ethyl acetate or Huang-Gui Solid Dispersion (HGSD) was used in a model of Wistar rats with established DM, and it was ultimately concluded that all three drugs could activate autophagy through AMPK-mediated pathways, switching on of key downstream genes (Matboli et al., 2017; Zhang et al., 2020; Ezzat et al., 2021). Purinergic receptors P2Y2R knockout impaired autophagy via the AKT/SIRT-1/FOXO3a signaling pathway in an experiment using unilateral nephrectomy combined with high fat diet and STZ (Dusabimana et al., 2020). However, in two other studies using the same animal model, the use of the drug geniposide or Abelmoschus manihot activated autophagy, reduced fibrosis and inflammation, as a result slowed the progression of DKD (Kim et al., 2018; Dusabimana et al., 2021). Meanwhile, erlotinib, Cordyceps militaris polysaccharides, and calcium dobesilate were used in STZ-induced mice as a model to demonstrate that erlotinib activated AMPK, inhibited mTOR activity and thus epidermal growth factor receptor, and played a role in the renal protective mechanism (Zhang et al., 2014). And another
# TABLE 5 The role of autophagosome formation in DKD (supplementary material).

| Signaling pathway | Processing method | Modeling method (animal/cell) | Conclusion | References |
|-------------------|-------------------|-------------------------------|------------|------------|
| - Ursodeoxycholic acid (UDCA) and 4-phenylbutyrate (4-PBA) | db/db mice; HG induced podocytes | UDCA and 4-PBA prevented HG-induced podocyte apoptosis by alleviating ER stress and restoring autophagy | Cao et al. (2016) |
| - Cordyceps militaris polysaccharides (CMP) | STZ induced C57BL/6 mice | CMP exerted a protective effect on DN in STZ-treated mice possibly via activation of autophagy | Chen et al. (2019) |
| TXNIP-mediated signaling pathway | Reduce TXNIP overexpression | STZ induced C57Bl/6 mice; HG induced proximal tubular cells | HG-induced overexpression of TXNIP might contribute to the dysfunction of tubular autophagy in diabetes | Huang et al. (2014) |
| miR-383-5p-mediated signaling pathway | Resveratrol | db/db mice; HG induced podocytes | Resveratrol effectively attenuated high glucose-induced apoptosis via the activation of autophagy in db/db mice and podocytes, which involved miR-383-5p | Huang et al. (2017) |
| - Protein tyrosine phosphatase 1B (PTP1B) disruption | HFD and STZ induced C57BL/6 mice (Ptpn1fl/fl mice); HG induced podocytes | Podocyte PTP1B deficiency attenuated hyperglycemia-induced renal damage | Ito et al. (2017) |
| miR-192-5p/GLP-1R signaling pathway | Icariin | High-sugar and high-fat diet and STZ-induced SD rats; HG induced HK-2 and NRK-49F cells | Icariin alleviated tubulointerstitial fibrosis by restoring autophagy through the miR-192-5p/GLP-1R pathway | Jia et al. (2021) |
| - t-AUCB (an inhibitor of sEH) | db/db mice; HG induced HK-2 cells | t-AUCB played a protective role in hyperglycemia-induced proximal tubular injury and that the potential mechanism of t-AUCB-mediated protective autophagy was involved in modulating mitochondrial function and ER stress | Jiang et al. (2020) |
| - Korean red ginseng | STZ induced SD rats; HG induced HK-2 cells | Korean red ginseng attenuated hyperglycemia-induced renal inflammation and fibrosis via accelerated autophagy and protected against diabetic kidney disease | Karunasagara et al. (2020) |
| - Abelmoschus manihot | Unx, HFD and STZ induced C57BL/6 mice | Supplementation of Abelmoschus manihot ameliorated diabetic nephropathy and hepatic steatosis by activating autophagy in mice | Kim et al. (2018) |
| - IL-17A knockout | STZ induced C57BL/6 mice (IL-17A KO mice) | IL-17 deficiency aggravated of STZ-induced DN via attenuation of autophagic response | Kim et al. (2021) |
| ATF4-mediated signaling pathway | Inhibit the expression of ATF4 | STZ induced ATF4 ± heterozygous mice; HG induced NRK-52E cells | ATF4 promoted renal tubulointerstitial fibrosis by suppressing autophagy in diabetic nephropathy | Liang et al. (2021) |
| - Isorhamnetin | HFD and STZ induced Wistar rats | Isorhamnetin improved fasting blood glucose, renal and lipid profiles with increased autophagosomes in renal tissues, and suppressed miRNA regulation of autophagy genes, finally played a renal protective role | Mathé et al. (2021) |
| - NSC697923 inhibitor | DN Patients; HG induced HK-2 cells | Prolonged hyperglycemia in diabetic patients could impair autophagy as a consequence of Lys63-Ub protein accumulation, thus promoting intracellular autophagic vesicles increase, finally leading to tubular cell death in DN. | Pontrelli et al. (2018) |
| - SCO-792 (enteropeptidase inhibitor) | WF rats | SCO-792-induced therapeutic efficacy was likely to be independent of glycemic control and mediated by the regulation of AAs and autophagy, so as to improve the condition of DKD patients | Sugama et al. (2021) |
| VDR/Atg3 signaling pathway | Paricalcitol (Vitamin D receptor agonist (VDRA)) | STZ induced SD rats; db/db mice | VDR/Atg3 axis deficiency resulted in SD-TJ transition and foot processes effacement via blocking the P62-mediated autophagy pathway in DN. | Wang et al. (2021a) |
| HO-1-mediated signaling pathway | Celestrol | HG induced podocytes | Celestrol might protect against HG-induced podocyte injury, inflammation and insulin resistance by restoring HO-1-mediated autophagy pathway | Zhan et al. (2018) |

GLP-1R, GLP-1, receptor; NRK-49F, rat kidney fibroblasts; sEH, soluble epoxide hydrolase; IL-17A, interleukin 17A; Lys63-Ub, lysine 63 ubiquitination; WF, rats, Wistar fatty rats; SD-TJ, slit diaphragm-tight junction; HO-1, heme oxygenase.
drug calcium dobesilate restored autophagy by blocking the VEGF/P13K/akt/mTOR cascade reaction and exerted nephroprotective effects together with Cordyceps militaris polysaccharides (Wang et al., 2019b; Chen et al., 2019). In a DKD rat model, mangiferin increased the number of autophagosomes in DKD rat podocytes and reduce proteinuria in diabetic rats, and this result was achieved by upregulating phosphorylated AMPK and ULK1 as well as downregulating mTOR phosphorylation (Wang et al., 2018a). Similarly, in a study on jujuboside A (JuA), it was demonstrated that JuA also promoted autophagy and mitophagy by activating CaMKK2, an upstream regulator of AMPK, alleviating the hyperglycaemic state and reducing various indicators of renal function (Zhong et al., 2022). The Chinese herbal formula Jiedu polysaccharides (Wang et al., 2019b; Chen et al., 2019). In a separate study, a group of STZ-induced male BALB/c mice were injected with mesenchymal stem cells (MSCs) via tail vein while primary MSCs were extracted from BALB/c mice for culture and then transfected with TFEB RNA. The results demonstrated that MSCs shifted the M2 phenotype from M1/M2 to macrophages and produce a nephroprotective effect, which was mediated by TFEB (Yuan Y. et al., 2020).

In experiments with DKD patients and AGEs-induced podocytes, researchers found that AGEs did not induce autophagy in podocytes, but increased LC3-II and P62-positive vacuoles, demonstrating that the autophagic degradation pathway was disrupted. This was caused by increased lysosomal membrane permeability inducing lysosomal dysfunction; however, therapeutic measures of resveratrol plus vitamin E could improve this situation (Liu et al., 2019). In db/db mice and AGE-BSA-induced HK-2 cells, restoration of Smad3 expression promoted TFEB-dependent lysosomal biogenesis (Yang C. et al., 2021). AGEs was able to induce an increase in the number of autophagosomes, the accumulation of sequestosome 1 protein and a decrease in the number of autolysosomes in AGEs-induced HK-2 cells. Therefore, this experiment concluded that AGEs was able to cause inactivation of autophagy, accelerate increased lysosomal permeability and dysfunction in HK-2 cells (Liu et al., 2015). Hepatocyte growth factor was used on high glucose-induced MPC-5 and STZ-induced mice, which regulated the P13K/akt-GSK3β-TFEB signaling pathway, improved lysosomal function and increased autophagic activity (Hou et al., 2020). In the ATG5 knockout mouse model and proximal tubular epithelial cells model, defective autophagy downregulated lysosomal biogenesis and promote the accumulation of AGEs, leading to DKD progression (Takahashi et al., 2017). In a study using STZ-induced Sprague-Dawley rats after high-glucose and high-fat model, the drug Keluoxin improved biochemical indicators, reduce podocyte damage and modulate lysosomal function in DKD rats, mitigating the progression of DKD (Yang X. et al., 2021).

In experiments using only animals as research models, researchers have found that drugs can activate autophagy, regulate autophagy-related pathways and key autophagy factors, and exert nephroprotective effects (Figure 2; Table.1-3, Table.5).

### 4.2 The role of autolysosome formation in DKD

In experiments with DKD patients and AGEs-induced podocytes, researchers found that AGEs did not induce autophagy in podocytes, but increased LC3-II and P62-positive vacuoles, demonstrating that the autophagic degradation pathway was disrupted. This was caused by increased lysosomal membrane permeability inducing lysosomal dysfunction; however, therapeutic measures of resveratrol plus vitamin E could improve this situation (Liu et al., 2019). In db/db mice and AGE-BSA-induced HK-2 cells, restoration of Smad3 expression promoted TFEB-dependent lysosomal biogenesis (Yang C. et al., 2021). AGEs was able to induce an increase in the number of autophagosomes, the accumulation of sequestosome 1 protein and a decrease in the number of autolysosomes in AGEs-induced HK-2 cells. Therefore, this experiment concluded that AGEs was able to cause inactivation of autophagy, accelerate increased lysosomal permeability and dysfunction in HK-2 cells (Liu et al., 2015). Hepatocyte growth factor was used on high glucose-induced MPC-5 and STZ-induced mice, which regulated the P13K/akt-GSK3β-TFEB signaling pathway, improved lysosomal function and increased autophagic activity (Hou et al., 2020). In the ATG5 knockout mouse model and proximal tubular epithelial cells model, defective autophagy downregulated lysosomal biogenesis and promote the accumulation of AGEs, leading to DKD progression (Takahashi et al., 2017). In a study using STZ-induced Sprague-Dawley rats after high-glucose and high-fat model, the drug Keluoxin improved biochemical indicators, reduce podocyte damage and modulate lysosomal function in DKD rats, mitigating the progression of DKD (Yang X. et al., 2021).

In experiments using only animals as research models, researchers have found that drugs can activate autophagy, regulate autophagy-related pathways and key autophagy factors, and exert nephroprotective effects (Figure 2; Table.1-3, Table.5).

### 5. Discussion

Defective autophagy is present in the pathophysiology of many diseases and has been studied in the fields of oncology, neurodegenerative diseases, metabolic diseases and renal diseases,
where it is closely related to the pathological process of DKD (Mizushima and Levine, 2020).

AMPK activation by upstream kinases rapidly phosphorylates the ULK-1 complex while inhibiting the activation of mTOR (Alers et al., 2012). Subsequent phosphorylation of downstream Beclin-1 activates the PI3K complex, and promotes the synthesis of PI3P (Axe et al., 2008; Russell et al., 2013; Baskaran et al., 2014). Then PI3P recruits autophagy factors, inducing the formation of omegasomes which work as the initial part of the phagophore (Lamb et al., 2013). Subsequently, omegasomes are continuously extended by the action of DCFP1 and WIPI (Lamb et al., 2013). In parallel, two downstream ubiquitin complexes (ATG12-ATG5-ATG16L1 and LC3-II) are formed and then recruited to the phagophore upon induction of WIPI and ATG16L1 (Sou et al., 2006; Dooley et al., 2014; Popelka et al., 2021). Subsequently, the autophagosome wrapped around the cargo fuses with the lysosome and is regulated by the VPS34 complex II and the HOPS complex as well as Rab7 (Bröcker et al., 2012; Lamb et al., 2013; Pu et al., 2016). It is eventually degraded by the lysosome and excreted from the cell in the form of exocytosis for subsequent recycling and use (Buratta et al., 2020).

Hyperglycaemia stimulates the production of metabolites such as ROS and AGEs, which promote oxidative stress, inflammation and impair autophagy, while drugs can slow the progression of DKD by inducing or restoring autophagy (Zheng et al., 2020; Winiarska et al., 2021). In recent years relevant reports have discussed drugs that target autophagy in the treatment of DKD, such as the herbal extracts, the emerging GLP-1 activators and SGLT2 inhibitors and so on, all of which have been shown to modulate the autophagic process and improve renal function (Huang et al., 2017; Wang et al., 2018b; Winiarska et al., 2021; Yamada et al., 2021).

Autophagy acts as a reactive protective mechanism in the kidney in order to protect cells from stressors, and mTOR is generally inhibited in this situation (Kim et al., 2011). However, the inhibition of autophagy that results from mTOR activation does not imply cell damage, but rather promotes cell proliferation and contributes to kidney repair (Xie et al., 2015; Viana et al., 2018). Similarly, in a separate study, autophagy was found to have a possible role in promoting renal fibrosis: in severe acute kidney injury, tubular cells undergo arrest in the G2/M phase, leading to the secretion of pro-fibrotic factors that promotes the progression of renal fibrosis, accompanied by the emergence of TOR-autophagic spatially coupled compartments structures (distinct cytoplasmic compartments rich in mTORC1) (Yang et al., 2010; Canaud et al., 2019; Tang et al., 2020). In addition, side effects associated with the mTOR inhibitor rapamycin for DKD, such as hyperglycaemia, insulin resistance and dyslipidaemia, have also been reported, which may be related to the metabolic profile of the pancreas and other insulin-resistant tissues, including the liver and muscle (Viana et al., 2018). Therefore, the existence of autophagy is therefore like a double-edged sword.

However, there are many questions about autophagy that have not been clearly described. Three types of autophagy are known, namely microautophagy, macroautophagy and chaperone-mediated autophagy, and have been described and studied in details (Li et al., 2012; Feng et al., 2014; Dash et al., 2019). However, it is not clear whether there is an interconnection among the three of them, and the specific triggering mechanism of autophagy in them is also lacking. Further discoveries are needed about the specific mechanisms by which autophagy produces stress responding to human metabolites. On the other hand, there are no extensive experimental studies on the exact mechanism of autophagosome-lysosome fusion regulation and degradation and a large body of evidence is lacking to support this view. In addition, the exact mechanism of action of drugs targeting autophagy is still unclear, which has prevented the translation of some drugs from animal studies to human clinical studies for the time being, and therefore lacks theoretical support for human clinical studies. We have now affirmed the positive role of autophagy for the treatment of DKD and it can be one of the key directions for the future treatment of DKD (Ding and Choi, 2015). However, autophagy also has side effects, so how to manipulate autophagy is an important issue for researchers today. The above issues will need to be refined over time with further research.

6 Conclusion

Activation of autophagy protects renal function, while impaired autophagy is involved in DKD progression. Although drugs targeting autophagy are still being investigated and some have already been used clinically, the incidence of DKD is still on the rise, so maintaining autophagy in the kidney’s intrinsic cells is now an urgent issue in the medical field. By reviewing the physiological process of autophagy and the roles of DKD therapeutic agents as well as related pathways, we hope to provide new perspectives and inspiration for the clinical treatment of DKD.

Author contributions

ZZ, YS, JX, DJ, XL, DZ designed the idea, checked the literature, made tables and figures. ZZ and YS wrote the
manuscript. FL, WQ and XT modified the manuscript. All authors have read and approved the final manuscript.

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References

Alers, S., Löffler, A. S., Wesseldorp, S., and Stork, B. (2012). Role of AMPK-mTOR:URI2/ in the regulation of autophagy: Cross talk, shortcuts, and feedbacks. Mol. Cell. Biol. 32 (1), 2–11. doi:10.1128/mcb.01519-11

Antonioli, M., Di Rienzo, M., Pacentini, M., and Fimia, G. M. (2017). Emerging mechanisms in initiating and terminating autophagy. Trends Biochem. Sci. 42 (1), 28–41. doi:10.1016/j.tibio.2016.09.008

Axe, E. L., Walker, S. A., Manufiia, M., Chandra, P., Roderick, H. L., Habermann, A., et al. (2008). Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum. J. Cell Biol. 182 (4), 685–703. doi:10.1083/jcb.200803137

Baskaran, S., Carlson, L. A., Stepanovic, G., Young, L. N., Grob, P., et al. (2014). Architecture and dynamics of the autophagic phosphatidylinositol 3-kinase complex. Elife 3, e05115. doi:10.7554/e1.e05115

Blattner, S. M., Hodgkin, J. B., Nishio, M., Wylie, S. A., Saha, J., Soofi, A. A., et al. (2013). Divergent functions of the rho GTPases Rac1 and Cdc42 in podocyte injury. Kidney Int. 84 (5), 920–930. doi:10.1038/ki.2013.175

Bravo-San Pedro, J. M., Kroemer, G., and Galluzzi, L. (2017). Autophagy and mitophagy in cardiovascular disease. Circ. Res. 120 (11), 1812–1824. doi:10.1161/ cirecirc.117.311082

Brocker, C., Kuhle, A., Gatsogiannis, C., Balderhaar, H. J., Hönscher, C., Engelbrecht-Vandré, S., et al. (2012). Molecular architecture of the multisubunit homotypic fusion and vacuole protein sorting (HOPS) tethering complex. Proc. Natl. Acad. Sci. U. S. A. 109 (6), 1991–1996. doi:10.1073/pnas.1117791109

Buratta, S., Tancini, B., Gagini, K., Delo, F., Chiaradia, E., Urbanelli, L., et al. (2020). Lysosomal exocytosis, exosome release and secretory autophagy: The individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol. 7 (2), 115–127. doi:10.1016/s2213-8587(18)30313-9

Cuervo, A. M., and Wong, E. (2014). Chaperone-mediated autophagy: Roles in disease and aging. Cell Prolif. 53 (3), e12763. doi:10.1111/cpr.12763

Ding, Y., and Choi, M. E. (2015). Autophagy in diabetic nephropathy. J. Cell Mol. Med. 19 (1), 96–101. doi:10.1111/jcmm.12318

Deter, R. L., and De Duve, C. (1967). In “The Cell: A Molecular View.”

Dooley, H. C., Razi, M., Polson, E. H., Girardin, S., Wilson, M. I., and Tooze, S. A. (2014). WIP1 links LC3 conjugation with PI3P, autophagosome formation, and pathogen clearance by recruiting Atg12-5-16L1. Mol. Cell 55 (2), 238–252. doi:10.1016/j.molcel.2014.05.021

Conflict of interest

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Doshi, S. M., and Friedman, A. N. (2017). Diagnosis and management of type 2 diabetic kidney disease. Clin. J. Am. Soc. Nephrol. 12 (8), 1366–1373. doi:10.2215/ CIN.11111016

Doublier, S., Salvidio, G., Lupia, E., Ruotsalainen, V., Verzola, D., Deferrari, G., et al. (2003). Nephrin expression is reduced in human diabetic nephropathy: Evidence for a distinct role for glycated albumin and angiotensin II. Diabetes 52 (4), 1023–1030. doi:10.23736/S0012-186X.03.04103-X

Dusabimana, T., Kim, S. R., Park, E. J., Je, J., Jeong, K., Yun, S. P., et al. (2020). P2Y2R contributes to the development of diabetic nephropathy by inhibiting autophagy response. Mol. Metab. 10, 101089. doi:10.1016/j.molmet.2020.101089

Dusabimana, T., Park, E. J., Je, J., Jeong, K., Yun, S. P., Kim, H. J., et al. (2021). Geniposide improves diabetic nephropathy by enhancing ULK1-mediated autophagy and reducing oxidative stress through AMPK activation. J. Cell Biochem. 22 (4), 1651. doi:10.3390/jcbi202100165

Ebeors, K., Bergwall, L., and Nystrom, J. (2021). The glomerulus according to the mesangium. Front. Med. (Lausanne) 8, 740572. doi:10.3389/fmed.2021.740572

Ezzat, S. M., Abdallah, H. M. I., Yassen, N. N., Radwan, A. R., Mostafa, E. S., Salama, M. M., et al. (2021). Phenolics from Physalis peruviana fruits ameliorate streptozotocin-induced diabetes and diabetic nephropathy in rats via induction of autophagy and apoptosis regression. Biomed. Pharmacother. 142, 111948. doi:10.1016/j.biopha.2021.111948

Fang, D., Wan, X., Deng, W., Guan, H., Ke, W., Xiao, H., et al. (2012). Fuxing Xue Baoshen formula enhances podocyte autophagy and reduces proteinuria in diabetic nephropathy. Exp. Ther. Med. 4 (5), 871–876. doi:10.3892/etm.2012.680

Fanus, D., Rogers, N. M., Grahammer, F., Huber, T. B., and Thomson, A. W. (2016). Roles of mTOR complexes in the kidney: Implications for renal disease and transplantation. Nat. Rev. Nephrol. 12 (10), 587–609. doi:10.1038/nrneph.2016.108

Feng, Y., He, D., Yao, Z., and Klionsky, D. J. (2014). The machinery of lysosomal trafficking and cell killing are controlled by the Akt-like GTPase Inhibit. Immunity 35 (2), 182–193. doi:10.1016/j.immuni.2011.06.009

Glick, D., Barth, S., and Macleod, K. F. (2010). Autophagy: Cellular and molecular mechanisms. J. Pathol. 221 (1), 3–12. doi:10.1002/path.2597

Gong, J., Zhan, H., Li, Y., Zhang, W., Jin, J., and He, Q. (2019). Kripped-like factor 4 ameliorates diabetic kidney disease by activating autophagy via the mTOR pathway. Mol. Med. Rep. 20 (4), 3240–3248. doi:10.3892/mmr.2019.10585

González, C., Carro Negueruela, M., Nicora Santamarina, C., Resnik, R., and Jeaffreson, J. (2017). Lipophagy deficiency exacerbates ectopic lipid accumulation and tubular cells injury in diabetic kidney disease. Cell Death Dis. 8 (11), 1031. doi:10.1038/s41419-021-04326-y

Huang, C., Cheng, L., Feng, X., Li, X., and Wang, L. (2020). Dencichine ameliorates renal injury by improving oxidative stress, apoptosis and fibrosis in diabetic rats. Life Sci. 258, 118146. doi:10.1016/j.lfs.2020.118146

Huang, C., Lin, M. Z., Cheng, D., Braet, F., Pollok, C. A., and Chen, X. M. (2014). Thiorodxin-interacting protein mediates dysfunction of tubular autophagy in diabetic kidneys through inhibiting autophagic flux. Lab. Invest. 94 (3), 309–320. doi:10.1038/labinvest.2014.2

Huber, T. B., and Benzing, T. (2005). The slit diaphragm: A signaling platform to regulate podocyte function. Curr. Opin. Nephrol. Hypertens. 14 (3), 211–216. doi:10.1097/01.mnh.0000168585.85003.a8

Inoki, K., Kim, J., and Guan, K. L. (2012). AMPK and mTOR in cellular energy homeostasis and drug targets. Annu. Rev. Pharmacol. Toxicol. 52, 381–400. doi:10.1146/annurev-pharmtox-010611-134537

Ito, Y., Hsu, M. F., Betteaieb, A., Koike, S., Mello, A., Calvo–Rubio, M., et al. (2017). Protein tyrosine phosphatase 1B deficiency in podocytes mitigates hyperglycemia-induced renal injury. Metabolism 76, 56–69. doi:10.1016/j. metabol.2017.07.009

Jefferson, J. A., Shankland, S. J., and Pichler, R. H. (2008). Proteinuria in diabetic kidney disease: A mechanistic viewpoint. Kidney Int. 74 (1), 22–36. doi:10.1038/annrheumdis.2008.128

Jia, Z., Wang, K., Zhang, D., Yuan, D., Xiao, K., Liu, S., et al. (2021). Icarin ameliorates diabetic renal tubulointerstitial fibrosis by restoring autophagy via regulation of the miR-192-5p/GLP-1R pathway. Front. Pharmacol. 12, 720387. doi:10.3389/fphar.2021.720387

Jiang, X. S., Xiang, X. Y., Chen, X. M., He, J. L., Liu, T., Gan, H., et al. (2020). Inhibition of soluble epoxide hydrolase attenuates renal tubulointerstitial dysfunction and ER stress by restoring autophagic flux in diabetic nephropathy. Cell Death Dis. 11 (5), 385. doi:10.1038/s41419-021-2594-x

Jin, D., Liu, F., Yu, M., Zhao, Y., Yan, G., Xue, J., et al. (2022). Jiedu Tongluo Baoshen formula enhances podocyte autophagy and reduces proteinuria in diabetic kidney disease by inhibiting PI3K/Akt/mTOR signaling pathway. J. Ethnopharmacol. 293, 115246. doi:10.1016/j.jep.2022.115246

Jin, J., Shi, Y., Gong, J., Zhao, L., Li, Y., He, Q., et al. (2019). Euxos secreted from adipose-derived stem cells attenuates diabetic nephropathy by promoting autophagy flux and inhibiting apoptosis in podocyte. Stem Cell Res. Ther. 10 (1), 95. doi:10.1186/s13287-019-1177-1

Karunasagar, S., Hong, G. L., Park, S. R., Lee, N. H., Jung, D. Y., Kim, T. W., et al. (2020). Korean red ginseng attenuates hyperglycemia-induced renal inflammation and fibrosis via accelerated autophagy and protects against diabetic kidney disease. J. Ethnopharmacol. 254, 112693. doi:10.1016/j.jep.2020.112693

Kato, M., and Natarajan, R. (2019). Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat. Rev. Nephrol. 15 (6), 327–345. doi:10.1038/nrneph.2019.11536

Kh, S., Jena, G., Tickoo, K., and Kumar, V. (2015). Valproate attenuates the proteinuria, podocyte and renal injury by facilitating autophagy and inactivation of NF-κB/INOS signaling in diabetic rat. Biochem. 110, 1–16. doi:10.1016/j.biochem.2014.12.015

Kim, H., Dusabimana, T., Kim, S. R., Je, J., Jeong, K., Kang, M. C., et al. (2018). Supplementation of Abelmoschus manihot ameliorates diabetic nephropathy and hepatic steatosis by activating autophagy in mice. Nutrients 10 (11), 1703. doi:10.3390/nu10111917

Kim, J., and Guan, K. L. (2019). mTOR as a central hub of nutrient signalling and cell growth. Nat. Cell Biol. 21 (1), 63–71. doi:10.1038/s41556-018-0205-1

Kim, J., Huang, W. P., Stromhaup, P. E., and Klionsky, D. J. (2002). Convergence of multiple autophagy and cytoplasme to vacuole targeting components to the pericarval membrane compartment prior to de novo vacuole formation. J. Biol. Chem. 277 (1), 763–773. doi:10.1074/jbc.M101934200

Kim, J., Kundu, M., Viollet, B., and Guan, K. L. (2011). AMPK and mTOR regulate autophagy through direct phosphorylation of ULK1. Nat. Cell Biol. 13 (2), 132–141. doi:10.1038/ncb2152
Khim, K. H., Hong, G. L., Jung, D. Y., Karunasagar, S., Jeong, W. I., and Jung, J. Y. (2021). IL-17 deficiency aggravates the streptozotocin-induced diabetic nephropathy through the reduction of autophagosome formation in mice. Mol. Med. 27 (1), 25. doi:10.1007/s10020-021-00285-4

Kitada, M., and Koya, D. (2021). Autophagy in metabolic disease and ageing. Nat. Rev. Endocrinol. 17 (11), 647–661. doi:10.1038/s41574-021-00531-9

Kitada, M., Ogura, Y., Sursuki, T., Sen, S., Lee, S. M., Kanasaki, K., et al. (2016). A very low-sodium diet ameliorates advanced diabetic nephropathy through autophagy induction by suppression of the mTORC1 pathway in Wistar fatty rats, an animal model of type 2 diabetes and obesity. Diabetes 59 (6), 1307–1317. doi:10.2337/db15-0125-016R-3R2-4

Klionsky, D. J., Petroni, G., Amaravadi, R. K., Baehrecke, E. H., Ballabio, A., Boya, P., et al. (2021). Autophagy in major human diseases. Embo J. 49 (19), e108633. doi:10.15252/embj.2021108863

Lamb, C. A., Yoshimori, T., and Tuzzo, S. A. (2013). The autophagosome: Origins unknown, biogenesis complex. Nat. Rev. Mol. Cell Biol. 14 (12), 759–774. doi:10.1038/nrm3696

Lee, Y. H., Kim, S. H., Kang, J. M., Heo, J. H., Kim, D. J., Park, S. H., et al. (2019). Empagliflozin attenuates diabetic tubulopathy by improving mitochondrial fragmentation and autophagy. Am. J. Physiol. Ren. Physiol. 317 (4), F767–F780. doi:10.1152/ajpren.00565.2018

Lei, L., Zhao, J., Liu, X. Q., Chen, J., Qi, X. M., Xia, L. L., et al. (2021). Wogonin alleviates kidney tubular epithelial injury in diabetic nephropathy by inhibiting PI3K/Akt/NIK-NF-kB signaling pathways. Drug Des. Dev. Ther. 15, 3131–3150. doi:10.2147/dddt.s130882

Lenoir, O., Jasiek, M., Hénique, C., Guyonnet, L., Hartleben, B., Bork, T., et al. (2015). Endothelial cell and podocyte autophagy synergistically protect from diabetes-induced glomerulosclerosis. Autophagy 11 (7), 1130–1145. doi:10.4161/aut.39542.2015.1049799

Levine, B., and Kroemer, G. (2019). Biological functions of autophagy genes: A cell biology perspective. Cell 176 (1-2), 11–42. doi:10.1016/j.cell.2018.09.048

Levine, B., Liu, R., Dong, X., and Zhong, Q. (2015). Beclin orthologs: Integrative functions in the regulation of autophagy. Front. Pharmacol. 6, 1–17. doi:10.3389/fphar.2015.00254

Li, A., Yi, B., Han, H., Yang, S., Hu, Z., Zheng, L., et al. (2022). Vitamin D-VDR signaling activates autophagy genes related to diabetic nephropathy by modulating the miR-214/ULK1 axis in renal tubular epithelial cells. J. Cell Death. 117918. doi:10.1177/1942059721104729

Matboli, M., Eissa, S., Ibrahim, D., Hegazy, M. G. A., Islam, S. S., and Habib, E. K. (2017). Caffeic acid attenuates diabetic kidney disease via modulation of autophagy in a high-fat diet/streptozotocin-induced diabetic rat. Pathol. Res. Pract. 213 (7), 646–649. doi:10.1016/j.prp.2017.04.008

Matboli, M., Ibrahim, D., Hasanin, A. H., Hassan, M. K., Habib, E. K., Bekht, M. M., et al. (2021). Epigenetic modulation of autophagy genes linked to diabetic nephropathy by administration of isorhamnetin in Type 2 diabetes mellitus rats. Epigenomics 13 (13), 187–202. doi:10.2217/epi-2020-0353

Matsuda, T., Takeda, Y., Nagai, Y., Yokota, T., Utsunomiya, K., and Nishimura, R. (2020). Targeting redox imbalance as an approach for diabetic kidney disease. Biomedicines 8 (2), 40. doi:10.3390/biomedicines8020040

Mccrath, K., and Edi, R. (2019). Diabetic kidney disease: Diagnosis, treatment, and prevention. Am. Fam. Physician 99 (12), 751–759.

Mercer, C. A., Kalapappan, A., and Dennis, P. B. (2009). A novel human Atg13 binding protein, Atg101, interacts with ULK1 and is essential for macroautophagy. Autophagy 5 (5), 649–662. doi:10.4161/auto.5.5.8249

Mistrafovan, A., Burke, G., Menzler, S., and Fornoni, A. (2021). New insights into renal lipid dysmetabolism in diabetic kidney disease. World J. Diabetes 12 (5), 524–540. doi:10.4239/wjd.v12.i.5.524

Mizushima, N., and Komatsu, M. (2011). Autophagy: Renovation of cells and organelle stress in diabetic kidney disease. Mol. Cell. 43 (1), 96–108. doi:10.1016/j.molcel.2011.07.017

Mizushima, N., and Levine, B. (2020). Autophagy in human diseases. N. Engl. J. Med. 383 (16), 1564–1576. doi:10.1056/NEJMr1220774

Mora-Fernández, C., Domínguez-Pimentel, V., de Fuentes, M. M., Górriz, J. L., Pavenstädt, H., Kriz, W., and Kreitler, M. (2003). Cell biology of the glomerular podocyte. J. Physiol. 552, 61–80. doi:10.1113/jphysiol.2002.048924

Matsuda, T., Takeda, Y., Nagai, Y., Yokota, T., Utsunomiya, K., and Nishimura, R. (2020). Targeting redox imbalance as an approach for diabetic kidney disease. Biomedicines 8 (2), 40. doi:10.3390/biomedicines8020040

McCrath, K., and Edi, R. (2019). Diabetic kidney disease: Diagnosis, treatment, and prevention. Am. Fam. Physician 99 (12), 751–759.

Mizushima, N., and Komatsu, M. (2011). Autophagy: Renovation of cells and organelle stress in diabetic kidney disease. Mol. Cell. 43 (1), 96–108. doi:10.1016/j.molcel.2011.07.017

Mizushima, N., and Levine, B. (2020). Autophagy in human diseases. N. Engl. J. Med. 383 (16), 1564–1576. doi:10.1056/NEJMr1220774

Mora-Fernández, C., Domínguez-Pimentel, V., de Fuentes, M. M., Górriz, J. L., Pavenstädt, H., Kriz, W., and Kreitler, M. (2003). Cell biology of the glomerular podocyte. J. Physiol. 552, 61–80. doi:10.1113/jphysiol.2002.048924

Nakagawa, H., Ichimura, Y., and Ohsumi, Y. (2007). Atg8, a ubiquitin-like protein required for autophagosome formation, mediates membrane tethering and hemifusion. Cell 130 (1), 165–178. doi:10.1016/j.cell.2007.05.021

Nakatsuka, A., Yamaguchi, S., Eguchi, J., Sakuta, S., Iwakura, Y., Sugiyama, H., et al. (2021). A Vaspin-HSPA1L complex protects proximal tubular cells from reganelle stress in diabetic kidney disease. Commun. Biol. 4 (1), 373. doi:10.1038/s42003-021-01902-y

Noda, N. (2021). Atg2 and Atg9 Intermembrane and interleaflet lipid transporters driving autophagy. Biochim. Biophys. Acta Mol. Cell. Biol. Lipids 1866 (8), 15956. doi:10.1016/j.bbalip.2021.15956

Pavenstädt, H., Kriz, W., and Kreitler, M. (2003). Cell biology of the glomerular podocyte. Physiol. Rev. 83 (1), 253–307. doi:10.1152/physrev.00202.2002

Pontrelli, P., Oranger, A., Barozzino, M., Idelva, C., Conserva, F., Fiore, M. G., et al. (2018). Derogulation of autophagy under hypoglycemic conditions is dependent on increased lysine 60 ubiquitination: A candidate mechanism in the
progression of diabetic nephropathy. J. Mol. Med. Biol. 96 (7), 645–659. doi:10.1007/s00108-019-1665-3

Popelka, H., Reinharz, E. F., Metur, S. P., Leary, K. A., Ragusa, M. J., and Klionsky, D. J. (2021). Membrane binding and homodimerization of Artg16 via two distinct protein regions is essential for autophagy in yeast. J. Mol. Biol. 433 (5), 166809. doi:10.1016/j.jmb.2021.166809

Potenza, M. A., Gagliardi, S., Nacci, C., Carratu, M. R., and Montagnani, M. (2009). Endothelial dysfunction in diabetes: From mechanisms to therapeutic targets. Curr. Med. Chem. 16 (1), 94–112. doi:10.2174/092986709787082853

Pu, J., Guardia, C. M., Keren-Kaplan, T., and Bonifacino, J. S. (2016). Mechanisms and functions of lysosome positioning. J. Cell Sci. 129 (23), 4329–4339. doi:10.1242/jcs.196287

Reidy, K., Kang, H. M., Hostetter, T., and Szutzkat, K. (2014). Molecular mechanisms of diabetic kidney disease. J. Clin. Invest. 124 (6), 2333–2340. doi:10.1172/JCI72721

Ren, H., Shao, Y., Wu, C., Ma, X., Lv, C., and Wang, Q. (2020). Meformin alleviates oxidative stress and enhances autophagy in diabetic kidney disease via AMPK/SIRT1-FoxO1 pathway. Mol. Cell Endocrinol. 500, 110628. doi:10.1016/j.mce.2019.110628

Roger, V., Döttch, V., Johansen, T., and Kirkini, V. (2014). Interactions between autophagy receptors and ubiquitin-like proteins form the molecular basis for selective autophagy. Mol. Cell 53 (2), 167–178. doi:10.1016/j.molcel.2013.12.014

Russell, R. C., Tian, Y., Yuan, H., Park, H. W., Chung, Y. Y., Kim, J., et al. (2013). UK1 induces autophagy by phosphorylating Beclin 1 and activating VPS34 lipid kinase. Nat. Cell Biol. 15 (7), 741–750. doi:10.1038/ncb2757

Shaw, R. J., Kosmatska, M. D., Bardeesy, N., Hurley, R. L., Witters, L. A., DePinho, R. A., et al. (2004). The tumor suppressor LKB1 kinase directly phosphorylates and activates AMPK. Cell 117, 77–88. doi:10.1016/j.cell.2004.05.014

Sohn, M., Kim, K., Uddin, M. J., Lee, G., Hwang, I., Kang, H., et al. (2017). Delayed treatment with fenofibrate alleviates oxidative stress and enhances autophagy in diabetic kidney disease via AMPK/SIRT1-FoxO1 pathway. Mol. Cell Endocrinol. 500, 110628. doi:10.1016/j.mce.2019.110628

Shi, Y., and Hu, F. B. (2014). The global implications of diabetes and cancer. Lancet 383 (9933), 1947–1948. doi:10.1016/S0140-6736(14)60886-2

Suzuki, K., Kirisako, T., Kamada, Y., Mizushima, N., Noda, T., and Ohsumi, Y. (2003). The ‘intranuclear’ organelles Autophagy receptors LC3, GABARAP, and GATE-16. EMBO J. 16 (1), 94. doi:10.1093/emboj/20.21.5971

Tang, C., Livingston, M. J., Liu, Z., and Dong, Z. (2020). Autophagy in kidney disease. Kidney Int. 97, 110628. doi:10.1016/j.kint.2020.09.0559

Wang, B., Qian, J. Y., Tang, T. T., Lin, L. L., Yu, N., Guo, H. L., et al. (2021a). VDR/Ang3 Axis regulates slit diaphragm to tight junction transition via p62-mediated autophagy pathway in diabetic nephropathy. Diabetes 70 (11), 2639–2651. doi:10.2337/db21-0205

Wang, F., Sun, H., Zuo, B., Shi, K., Zhang, X., and Chang, C. (2012b). Metformin attenuates renal tubulointerstitial fibrosis via upgrading autophagy in the early stage of diabetic nephropathy. Sci. Rep. 11 (1), 16362. doi:10.1038/s41598-021-95825-7

Wang, K., Zheng, X., Pan, Z., Yao, W., Gao, X., Wang, X., et al. (2020). Icariin prevents extracellular matrix accumulation and ameliorates experimental diabetic kidney disease by inhibiting oxidative stress via GPerox mediated p62-dependent Keap1 degradation and Nrf2 activation. Front. Cell Dev. Biol. 8, 559. doi:10.3389/fcell.2020.00559

Wang, X., Gao, L., Lin, H., Song, J., Wang, J., Yin, Y., et al. (2018a). Mangiferin prevents diabetic nephropathy progression and protects podocyte function via autophagy in diabetic rat glomeruli. Eur. J. Pharmacol. 824, 170–178. doi:10.1016/j.ejphar.2018.02.009

Wang, X., Gao, Y., Tian, N., Wang, T., Shi, Y., Xu, J., et al. (2019a). Atragoside IV inhibits glucose-induced epithelial-mesenchymal transition of podocytes through autophagy enhancement via the SIRT-NF-kB p65 axis. Sci. Rep. 9 (1), 323. doi:10.1038/s41598-018-36911-1

Wang, X., Gao, Y., Tian, N., Zha, Z., Wang, T., Xu, J., et al. (2018b). Atragoside IV represses high glucose-induced mesangial cells activation by enhancing autophagy via SIRT1 deacetylation of NF-kB p65 subunit. Drug Des. Deliv. Ther. 12, 2971–2980. doi:10.2478/ddt-2014-0111

Wang, X., Liu, J., Zhen, J., Zhang, C., Wang, Q., Liu, J., et al. (2014). Histone deacetylase 6 selectively contributes to podocyte injury in diabetic nephropathy: Kidney Int. 86 (4), 712–725. doi:10.1038/ki.2014.111

Wang, Y., Lu, Y. H., Tang, C., Xue, M., Li, X. Y., Chang, P., et al. (2019b). Calcium depended restores autophagy by inhibiting the VEGF/PI3K/AKT/mTOR signaling pathway. Front. Pharmacol. 10, 886. doi:10.3389/fphar.2019.00886

Wang, Y., Zhao, H., Wang, Q., Zhou, X., Lu, X., Liu, T., et al. (2019c). Chinese herbal medicine in ameliorating diabetic kidney disease via activating autophagy. J. Diabetes Res. 2019, 9030893. doi:10.1155/2019/9030893

Xie, Y., Kang, R., Sun, X., Zhong, M., Huang, J., Klionsky, D. J., et al. (2015). Endoplasmic reticulum stress induces autophagy in murine podocytes and podocyte depletion in mice: The possible role of AMPK autophagy. Am. J. Physiol. Ren. Physiol. 312 (2), F323–F334. doi:10.1152/ajprenal.00596.2015

Xiao, L., Xu, X., Zhang, F., Wang, M., Xu, Y., Tang, D., et al. (2017). The anti-inflammatory and antidiabetic effects of Astragalus membranaceus extract on rat models of DM2. Int. J. Mol. Sci. 18(11), 2639–4339. doi:10.3390/ijms18112639

Yamamoto, T., et al. (2017). Autophagy inhibits the accumulation of diabetes. Diabetes 66 (5), 1359–1372. doi:10.2337/db16-0056

Yamamoto, T., Takabatake, Y., Kimura, T., Maejima, I., Namba, T., and Wang, Q. (2020). Metformin alleviates oxidative stress and enhances autophagy in diabetic kidney disease via AMPK/SIRT1-FoxO1 pathway. Mol. Cell Endocrinol. 500, 110628. doi:10.1016/j.mce.2019.110628

Zhang et al. 10.3389/fphar.2022.977410

Zhao, Y., Wang, X., Gao, L., Lin, X., Xue, M., et al. (2018). Mangiferin alleviates oxidative stress and enhances autophagy in diabetic kidney disease. Oxid. Med. Cell Longev. 2018, 8634. doi:10.1155/2018/8634
Autophagy. *Acta Diabetol.* 58 (10), 1413–1423. doi:10.1007/s00592-021-01736-4

Yamada, S., Tanabe, J., Ogura, Y., Nagai, Y., Sugaya, T., Ohata, K., et al. (2021). Renoprotective effect of GLP-1 receptor agonist, liraglutide, in early-phase diabetic kidney disease in spontaneously diabetic Torii fatty rats. *Clin. Exp. Nephrol.* 25 (4), 365–375. doi:10.1007/s10157-020-02007-2

Yang, C., Chen, X. C., Li, Z. H., Wu, H. L., Jing, K. P., Huang, X. R., et al. (2021a). SMAD3 promotes autophagy dysregulation by triggering lysosome depletion in tubular epithelial cells in diabetic nephropathy. *Autophagy* 17 (9), 2325–2344. doi:10.1080/15548627.2020.1824694

Yang, D., Livingston, M. J., Liu, Z., Dong, G., Zhang, M., Chen, J. K., et al. (2018). Autophagy in diabetic kidney disease: Regulation, pathological role and therapeutic potential. *Cell Mol. Life Sci.* 75 (4), 669–688. doi:10.1007/s00018-017-2659-1

Yang, F., Qu, Q., Zhao, C., Liu, X., Yang, P., Li, Z., et al. (2020a). Faelciclymases cicadae-fermented Radix astragali activates podocyte autophagy by attenuating PI3K/AKT/mTOR pathways to protect against diabetic nephropathy in mice. *Biomed. Pharmacother.* 129, 110479. doi:10.1016/j.biopha.2020.110479

Yang, L., Beschetnova, T. Y., Brooks, C. R., Shah, J. V., and Bonventre, J. V. (2010). Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. *Nat. Med.* 16 (5), 535–543. doi:10.1038/nm.2144

Yang, S., Lin, C., Zhuo, X., Wang, J., Rao, S., Xu, W., et al. (2020b). Glucagon-like peptide-1 alleviates diabetic kidney disease through activation of autophagy by regulating AMP-activated protein kinase-mammalian target of rapamycin pathway. *Am. J. Physiol. Endocrinol. Metab.* 319 (6), E1019–E1030. doi:10.1152/ajpendo.00195.2019

Yang, X., Han, X., Wen, Q., Qiu, X., Deng, H., and Chen, Q. (2021b). Protective effect of Keluoxin against diabetic nephropathy in type 2 diabetic mellitus models. *Evid-Based Complementary Altern. Med.* 2021, 8455709. doi:10.1155/2021/8455709

Yla-Anttila, P., Vihinen, H., Jokitalo, E., and Eskelinen, E. L. (2009). 3D tomography reveals connections between the phagophore and endoplasmic reticulum. *Autophagy* 5 (8), 1180–1185. doi:10.4161/aut.5.8.10274

Yokoyama, H., Araki, S. I., Kawai, K., Yamazaki, K., Shirabe, S. I., Sugimoto, H., et al. (2020). The prognosis of patients with type 2 diabetes and nonalbumpuric diabetic kidney disease is not always poor: Implication of the effects of coexisting reticulum. *Diabetes Care* 43 (5), 1102–1110. doi:10.2337/dc19-2049

Yuan, J., Dong, X., Yap, J., and Hu, J. (2020a). The MAPK and AMPK signalings: Interplay and implication in targeted cancer therapy. *J. Hematol. Oncol.* 13 (1), 115. doi:10.1186/s13045-020-00949-4

Yuan, Y., Li, L., Zhu, L., Liu, F., Tang, X., Liao, G., et al. (2020b). Mesenchymal stem cells elicit macrophages into M2 phenotype via improving transcription factor EB-mediated autophagy to alleviate diabetic nephropathy. *Stem Cells* 38 (5), 639–652. doi:10.1002/stem.3144

Zhan, X., Yan, C., Chen, Y., Wei, X., Xiao, J., Deng, L., et al. (2018). Celastrol antagonizes high glucose-evoked podocyte injury, inflammation and insulin resistance by restoring the HO-1-mediated autophagy pathway. *Med. Immunol.* 104, 61–68. doi:10.1016/j.medi.2018.10.021

Zhang, M., Zhang, Y., Xiao, D., Zhang, J., Wang, X., Guan, F., et al. (2020). Highly bioavailable berberine formulation ameliorates diabetic nephropathy through the inhibition of glomerular mesangial matrix expansion and the activation of autophagy. *Eur. J. Pharmacol.* 873, 172955. doi:10.1016/j.ejphar.2020.172955

Zhang, M. Z., Wang, Y., Pauksukaitis, P., and Harris, R. C. (2014). Epidermal growth factor receptor inhibition slows progression of diabetic nephropathy in association with a decrease in endoplasmic reticulum stress and an increase in autophagy. *Diabetes* 63 (6), 2063–2072. doi:10.2337/db13-1279

Zhang, X. X., Jhang, C. H., Liu, Y., Lou, D. X., Huang, Y. P., Gao, M., et al. (2019). *Cyclocarya palustris* triterpenic acids fraction attenuates kidney injury via AMPK-mTOR-regulated autophagy pathway in diabetic rats. *Phytomedicine* 64, 153060. doi:10.1016/j.phymed.2019.153060

Zhang, X., Zhang, L., Chen, Z., Li, S., Che, B., Wang, N., et al. (2021). Exogenous spermine attenuates diabetic kidney injury in rats by inhibiting AMPK/mTOR signaling pathway. *Int. J. Mol. Med.* 47 (3), doi:10.3892/ijmm.2021.4860

Zhao, X., Chen, Y., Tan, X., Zhang, L., Zhang, H., Li, Z., et al. (2018a). Advanced glycation end-products suppress autophagic flux in podocytes by activating mammalian target of rapamycin and inhibiting nuclear translocation of transcription factor EB. *J. Pathol.* 245 (2), 235–248. doi:10.1002/path.5077

Zhao, Y., Zhang, W., Jia, Q., Feng, Z., Guo, J., Han, X., et al. (2018b). High dose vitamin E attenuates diabetic nephropathy via alleviation of autophagic stress. *Front. Physiol.* 9, 139. doi:10.3389/fphys.2018.01393

Zheng, D., Tao, M., Liang, X., Li, Y., Jin, J., and He, Q. (2020). p66shc regulates podocyte autophagy in high glucose environment through the Notch-PTEN-PI3K/Akt/mTOR pathway. *Histol. Histopathol.* 35 (4), 405–415. doi:10.14670/hh-18-178

Zheng, G. S., Tan, Y. M., Shang, Y. Y., Liu, Y. P., Hu, B. A., Wang, D., et al. (2021). CIDEc silencing attenuates diabetic nephropathy via inhibiting apoptosis and promoting autophagy. *J. Diabetes Investig.* 12 (8), 1336–1345. doi:10.1111/jdi.13534

Zhong, Y., Luo, R., Liu, Q., Zhu, J., Lei, M., Liang, X., et al. (2022). Jujuboside A ameliorates high fat diet and streptozotocin induced diabetic nephropathy via suppressing oxidative stress, apoptosis, and enhancing autophagy. *Food Chem. Toxicol.* 159, 112697. doi:10.1016/j.fct.2021.112697