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Review article

A comprehensive insight into autophagy and its potential signaling pathways as a therapeutic target in podocyte injury

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ABSTRACT

As part of the glomerular filtration membrane, podocyte is terminally differentiated, structurally unique, and highly specialized in maintaining kidney function. Proteinuria caused by podocyte injury (foot process effacement) is the clinical symptom of various kidney diseases (CKD), including nephrotic syndrome. Podocyte autophagy has become a powerful therapeutic strategy target in ameliorating podocyte injury. Autophagy is known to be associated significantly with sirtuin-1, proteinuria, and podocyte injury. Various key findings in podocyte autophagy were reported in the past ten years, such as the role of endoplasmic reticulum (ER) stress in podocyte autophagy impairment, podocyte autophagy-related gene, essential roles of the signaling pathways: Mammalian Target of Rapamycin (mTOR)/ Phosphoinositide 3-kinase (PI3k)/ serine/threonine kinase 1 (Akt) in podocyte autophagy. These significant factors caused podocyte injury associated with autophagy impairment. Sirtuin-1 was reported to have a vital key role in mTOR signaling, 5′AMP-activated protein kinase (AMPK) regulation, autophagy activation, and various critical pathways associated with podocyte's function and health; it has potential value to podocyte injury pathogenesis investigation. From these findings, podocyte autophagy has become an attractive therapeutic strategy to ameliorate podocyte injury, and this review will provide an in-depth review on therapeutic targets he podocyte autophagy.

1. Background

1.1. Podocyte introduction

Podocytes cell from the glomerular filtration membrane is highly specialized in maintaining kidney function and has high basal autophagy activity to maintain their general health (Reiser, 2016; Hartleben et al., 2010). It is a critical element in the primary filtration barrier (Slit diaphragm), responsible for keeping the macro-molecule protein from leaving the body into urine unintentionally (Kawachi et al., 2006). Podocytes have a complex, unique cellular architecture that includes cell body and major foot processes described (Garg, 2018). The foot processes of podocytes are crucial in forming the interdigitating actin-based networks that enwrap the glomerular capillaries and are

Abbreviation: MCD, Minimal Change Disease; FSGS, Focal Segmental Glomerulosclerosis; ER, Endoplasmic reticulum; CKD, chronic kidney disease; PRR, Prorenin receptor; Atg, Autophagy related gene; 3-MA, 3-methyladenenine; mTOR, Mammalian target of rapamycin; ULK, Unc51-like autophagy-activating kinase 1; NHE-1, Na^+/ H^+ exchanger-1; ROS, Reactive oxygen species; Ang II, Angiotensin II; TRPC 6, Transcient receptor potential cation channel 6; MR, Mineralocorticoid receptor; Chop, CCAAT/ enhancer-binding protein (C/EBP) homologus protein; VEGF, Vascular endothelial growth factor; LPS, Lipopolysaccharide; FOXO, Forkhead-box transcription factor; AMPK, 5′-AMP-activated protein kinase; LC3II, Microtubule-associated protein 1-light chain 3; NF- κβ, Nuclear factor κβ; PPARγ, Peroxisome proliferator-activated receptor γ; PGC1α, Peroxisome proliferator-activated coactivator 1-α; GSK3, Glycogen synthase kinase 3; TSC, Tuberous sclerosis complex; PI3K, Phosphoinositide 3-kinase; Akt, Akt serine/threonine kinase 1; NR1, Notogensinoside R1; C1-Ten, Tensin 2; PTEN, Phosphatase and tensin homolog; PRAS40, Proline-rich AKT substrate 40 kDa; Wnt, Wingless-type MMTV integration site; TFEB, Nuclear translocation of transcription factor EB; TG, Tripterygium glycoside; PAN, Puromycin aminonucleoside; STIM1, Stromal interaction molecule 1; COX-2, Cyclooxygenase-2; ATF4, Activating transcription factor 4; HMGB1, High mobility group box 1; ADSC, Adipose-drive stem cell; NLRP3, Nucleotide-oligomerization domain-like receptor 3; TCM, Traditional Chinese medicine; RPF, Paecilomyces Cicadidae; LXR, Liver X receptor.

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bridged by a cell junction known as the slit diaphragm (Martin et al., 2018). The proximity of podocytes' foot processes with the slit diaphragm enables a mesh network of proteins to participate in podocyte signalling actively (Reiser, 2016). The optimum function of podocytes relies highly on the unique structure of their foot processes, and the exquisitely signaling in this microenvironment is vital. Hence, it is susceptible to any potential interfering agents that could disrupt the order of actin-cytoskeleton in podocyte foot processes and cause podocyte foot process effacement (Reiser, 2016).

1.2. Podocyte injury

Podocyte foot process effacement is also known as podocyte injury that is described as the reorganization of the actin cytoskeleton in podocyte foot processes. It could be observed through the changes of its foot process structure, such as thickening, spreading out, causing the kidney's loss of glomerular filtration function and disrupting the interdigitating networks (Garg, 2018). When podocytes were not functioning healthily, unfiltered macro-molecule enter urine and cause a condition called proteinuria. Proteinuria is well proven to be associated with podocyte effacement in Minimal Change Disease (MCD), Focal Segmental Glomerulosclerosis (FSGS), and Diabetic Nephropathy (DN) (Garg, 2018).

Podocytes are highly adaptable to physiological stresses at the same time to preserve function. As the podocyte cannot undergo a proper mitosis process, the lack of proliferation of podocytes causes the inability to restore podocytes' number after cell loss (Mundel, 2002). A novel mechanism of progressive podocyte loss known as "Podocyte Domino Effect" was suggested by finding in human CD25 chimeric mice (Matsusaka et al., 2011). Podocytes display a remarkable ability to recover from injury after effective pharmacological intervention (Muller-Deile and Schiffer, 2016). As long as the podocytes are not detached, they could recover in a short period (Muller-Deile and Schiffer, 2016). This phenomenon of podocytes recovery gives hope to various therapeutic approaches. The time duration between podocyte loss starting from injury is unknown; it would be ideal for letting the podocyte recover to its healthy state before the cell detachment occurs, known as podocytopenia, which is irreversible damage to the kidney.

1.3. MCD, FSGS & DN

FSGS & DN usually manifest more severe and long-lasting podocyte injury compared to MCD. Persistent podocyte injury could trigger the autophagy process instead of the transient podocyte injury in MCD. FSGS was reported to have a significantly lower percentage of autophagosome-positive and beclin-1 level in kidney podocytes than

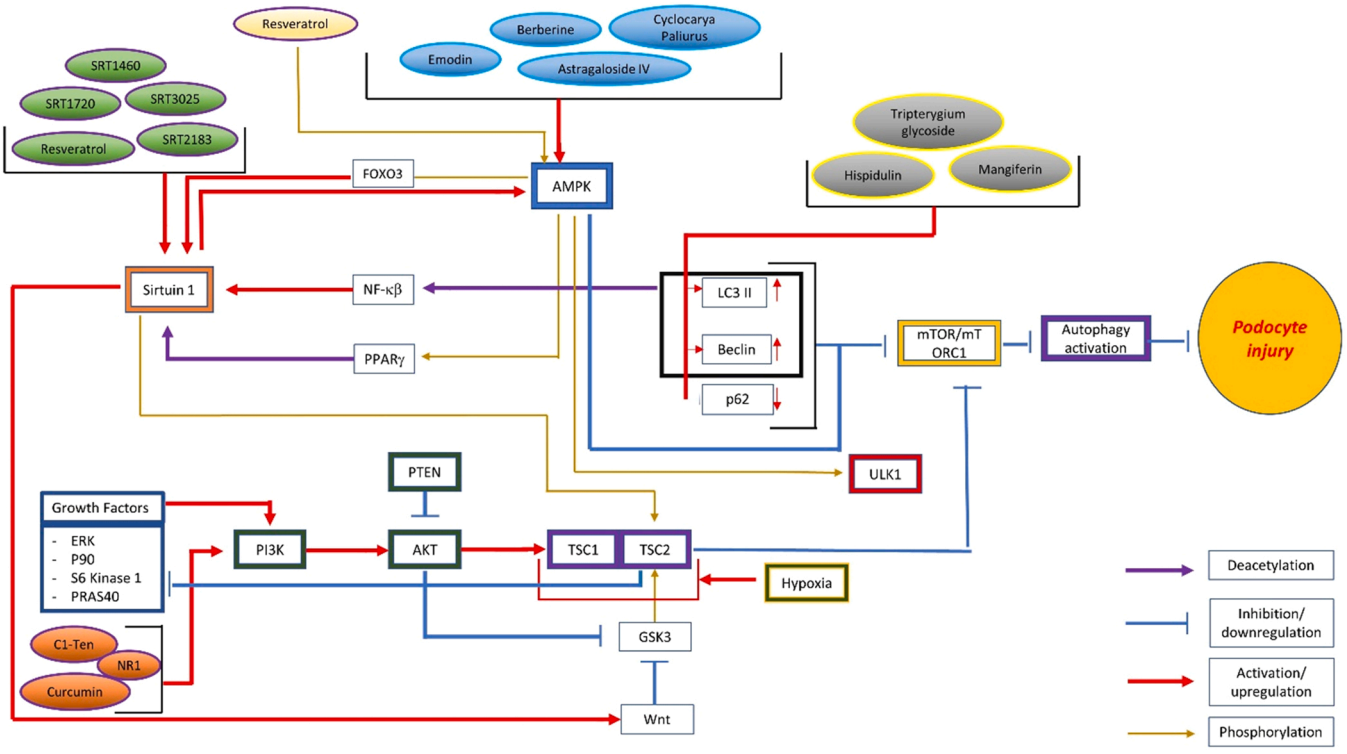

Fig. 1. Signaling pathways of main regulators that are involved in autophagy activation and suppression. Autophagy activation was mainly regulated by nutrient-sensing regulators such as mTOR, AMPK, and sirtuin1. AMPK could be activated by emodin, berberine, cyclocarya paliurus, and astragaloside IV that has phosphorylation directly to ULK1 and downregulates mTOR. Other natural active ingredients such as hispidulin, mangiferin, and tripterygium glycoside influenced LC3II, beclin, and p62. The elevation of LC3II and beclin together with suppression storage of p62 could downregulate mTOR, thus activating autophagy. The increased level of LC3II and beclin could deacetylate NF-κβ-p65 and activate sirtuin1. Sirtuin1 Grand AMPK could regulate each other via deacetylation and phosphorylation. AMPK deacetylated the downstream target of FOXO3 to activate sirtuin1, while during the low energy state, AMPK could negatively regulate mTORC1 due to sirtuin1. AMPK could deacetylate sirtuin1 by phosphorylating PPARγ, a coactivator sharing PGC1α. Resveratrol, SRT1460, SRT 1720, SRT3025, and SRT2183 are deemed as the potent sirtuin1 activators. The activated sirtuin 1 could phosphorylate TSC2 and promote Wnt, which had an inhibitory effect on GSK3. GSK3 could inhibit mTOR by phosphorylating TSC2 in a manner that depends on AMPK-phosphorylate TSC2. TSC1&2 are the mTOR inhibitors that could be activated during hypoxia conditions. The activated PI3K/Akt pathway from growth factors C1-Ten, NR1, and curcumin, could activate TSC1&2 to inhibit mTOR activities. mTOR: mammalian target of rapamycin, mTORC1: mammalian target of rapamycin complex 1, AMPK: 5′AMP-activated protein kinase, ULK1: unc51-like autophagy-activating kinase 1, LC3II: microtubule-associated protein 1-light chain 3, NF-κβ:Nuclear factor κβ FOXO3: forkhead-box transcription factor 3, PPARγ peroxisome proliferator-activated receptor γ, PGC1α peroxisome proliferator-activated coactivator 1-α GSK3: glycogen synthase kinase 3, TSC: tuberous sclerosis complex, PI3K: phosphoinositide 3-kinase, Akt: Akt serine/threonine kinase 1, NR1: notogensinoside R1, C1-Ten: Tensin 2, PTEN: phosphatase and tensin homolog, PRAS40: proline-rich AKT substrate 40 kDa, Wnt: Wingless-type MMTV integration site.

MCD (Zeng et al., 2014). The higher autophagic activities in MCD suggested that autophagy was impactful not to deteriorate MCD (Zeng et al., 2014). The activation of autophagy and the number of autophagic vacuoles were suggested to associate to podocytes foot process effacement and proteinuria in MCD (Tang et al., 2020; Ogawa-Akiyama et al., 2020). The signaling pathways and molecules in Fig. 1 are the relevant therapeutic targets towards podocyte injury that interplay with each other. In recent years of investigating the therapeutic approaches to ameliorate podocyte injuries and proteinuria in glomerular diseases, many biomarkers, metabolites, diagnosis, intervention, and development of new therapeutic targets for chronic kidney diseases had been reported and recently reviewed (W. Wang et al., 2019; Y. Wang et al., 2019; Y.-N. Wang et al., 2019). The exact pathogenesis of MCD, FSGS, and DN is still unknown, but they share a similar that was known so far and can be observed: podocyte injury. Podocyte injury is the most critical early event in the pathogenesis of proteinuria and progressive glomerulosclerosis in patients with MCD/ FSGS/ DN or other proteinuric kidney diseases (Sun et al., 2021).

1.4. Autophagy

This review focus on the potential mechanism and signalling pathways on podocyte autophagy. There are two intracellular degradative systems: ubiquitin proteasomal system (UPS) and ALP. The detailed mechanism, description, and impact of UPS and autophagy in podocytes have been thoroughly reviewed (Heintz and Meyer-Schwesinger, 2021). A growing body of evidence suggested that the homeostatic level of multiple podocyte-specific proteins such as nephrin, α-actinin 4, and synaptopodin are dependent on the UPS; nonetheless, the primary function of the UPS, in particular circumstances, tightly interplay with autophagy in maintaining a podocyte identity (Heintz and Meyer-Schwesinger, 2021).

There are three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy, as a different mode of transporting intracellular constituents to lysosomes (Liu et al., 2017). The significant common steps of autophagy include the following: initiation, elongation, maturation, fusion with lysosomes, and degradation (Clarke and Simon, 2019). The autophagy process occurs with several autophagy-related genes (ATG) combined to form molecular complexes that participate throughout the event in sequential order. The ULK1-ATG13-FIP200-ATG101 complex induces autophagosome formation and Beclin1 class III PI3K complex that generates PIP3, promoting nucleation. LC3-II becomes a reliable marker of autophagosomes because it remains attached to the lipid after the two conjugation systems involved in lipid phosphatidylethanolamine (PE) to form LC3-II (Heintz and Meyer-Schwesinger, 2021). There are a few well-studied autophagy receptors such as LC3 (ATG8 associated protein 1 A/1B light chain 3), sequestome 1 (SQSTM1/p62), and beclin 1 (core autophagy machinery) as indicators of the autophagy activities. Proper activation and completed each stage of the autophagy process influences the podocyte intracellular homeostasis and its high basal autophagy activities. The signaling pathways such as Mammalian Target of Rapamycin (mTOR), 5′AMP-activated protein kinase (AMPK), and Sirtuin have significant roles in activating and inhibiting the related components of autophagy.

Autophagy, also known as the autophagosomal lysosomal pathway (ALP), is essential for maintaining intracellular homeostasis and recycling the damaged protein (self-cleaning process) through degradation by lysosomes (Hartleben et al., 2010). The role of Autophagy in kidney cells was recently reported to slow down chronic kidney disease progression (CKD), leading to a protective effect (Gowd et al., 2020; Yoshibayashi et al., 2020), but the exact signaling pathways and mechanism remain largely unclear. In 2010, it was first discovered that induced autophagy was the key homeostasis mechanism that podocytes needed to maintain their integrity (Hartleben et al., 2010). The first detection of the presence of autophagy was in yeast along with the autophagy-related gene (Atg) that was further divided into 6 groups: Atg 1 kinase complex, Atg 9, Class III phosphoinositide 3-kinase complex (PI3KC3), PI3P-binding Atg2-Atg18 complex, and two ubiquitin-like conjugation systems (Atg12-Atg5 and Atg8 conjugation system) (Mizushima, 2010). Atg5 as podocyte-specific deletion of autophagy-related 5 protein was identified to lead to proteinuria and endoplasmic reticulum (ER) stress (Hartleben et al., 2010). In other words, autophagy could be a decisive factor to protect podocytes from injury, which inspired a new therapeutic direction. The discovery of Atg 5 by Hartleben et al. was later supported by other studies (Lenoir et al., 2015). Besides, Atg7-deficient podocytes were susceptible to the vulnerability of external stimuli known to target podocytes' health (Oliva Trejo et al., 2014; Yi et al., 2017). The neuron-like podocytes are often similar to neuron cells because both are terminally differentiated and similar in cell structure (Liebau et al., 2013)—the lack of ability to regenerate (Fries et al., 1989) but the excellent capacity to recover. The breakthrough discovery of autophagy in neurons inspired the investigation of autophagy in podocytes, in which a lot of interesting findings on how vital autophagy is to podocytes' function and structures (Fang et al., 2013).

Between the two central intracellular degrading systems, autophagy appears to be highly relevant to podocyte homeostasis in the aspect of aging and stress instead of UPS. Currently, evidence that suggests that UPS is activated during the early course of autophagy impairment is still limited; more studies need to elucidate this suggestion (Heintz and Meyer-Schwesinger, 2021). However, UPS and autophagy are considered two independent protein degrading systems with frequent crosstalk in podocytes (Heintz and Meyer-Schwesinger, 2021). The crosstalk between UPS and autophagy is mediated by unfolded protein response (UPR) and eventually induces autophagy by activating AMPK (Heintz and Meyer-Schwesinger, 2021). However, the crosstalk and compensation of two systems towards each other are still not absolute, and it was suggested that it is highly dependent on the type of podocyte stress. The role and contribution of UPS in podocyte aging are entirely unknown. The dysfunction of the autophagy activities was reported to contribute to the damage of podocytes, which induced autophagy could be a primary protective mechanism against podocyte aging and injury (Hartleben et al., 2010).

2. Sirtuin and aging

Sirtuin (SIRT), a silent information regulator protein, has a decisive role in inducing autophagy (Kong et al., 2015). Vast evidence confirmed the role of sirtuin in aging (Polak-Jonkisz et al., 2013; Morris, 2021). Aging is recently being seen as a disease since the discovery of the sirtuin gene that has gruesome consequences in our body, leading to multiple current daunting diseases such as cardiovascular disease, diabetes mellitus, brain-related disease, cancer, and kidney diseases (Kong et al., 2015). Histone acetylation and histone deacetylation in various conditions via acetyltransferases are the central roles of sirtuin as a critical modulator of metabolism responses adapted to stress and multiple signaling events that had a close association with aging-related diseases (Morigi et al., 2018). The discovery of sirtuin as a longevity gene was exciting for various researchers to view the current diseases with aging. Recent studies in sirtuin allow the authors to connect some findings in podocyte autophagy studies.

The expression of PGC1α was induced under cold exposure and exercise via AMPK, calorie restriction, and oxidative stress via sirtuin 1 (Clark and Parikh, 2021). These signalling pathways critically regulate podocyte autophagy and maintain protein homeostasis in the healthy podocyte. PGC1α is a master regulator of mitochondria biogenesis (Clark and Parikh, 2021; Ploumi et al., 2017), and due to the human kidneys' functions, which require a dense number of mitochondria (Gujarati et al., 2020) to supply the required amount of ATP as energy to process filtration, reabsorption, and secretion; PGC1α becomes a vital component to healthy kidneys when mitochondria must fulfill the

energy supply (Clark and Parikh, 2021). AMPK inhibits mTOR by deactivating Raptor to enable autophagy by directly activating ULK1 (Clark and Parikh, 2021). AMPK acts as a cellular energy monitor and protector that works closely with sirtuin and transcription factor EB (TFEB) translocation. Sirtuin interplays with AMPK have been shown to protect against aging, fibrosis, diabetic kidney disease, acute kidney disease (Clark and Parikh, 2021).

Sirt1 and Sirt3, as the most studied sirtuin, are the key molecules in cellular energy metabolism in podocytes that have significant roles in the pathogenesis of various kidney diseases in the aspect of podocyte injuries and aging. The overexpression of Sirtuin 3 was reported to promote autophagy, upregulate AMPK and downregulate mTOR (Peasley et al., 2021). Wakino et al. had reviewed multiple factors that sirtuin 1 regulates (Wakino et al., 2015); more factors were discovered closely related to sirtuin, and aging was reviewed in detail by Morris et al. Morris (2021). Detailed roles of sirtuins, AMPK, and PGC1α pathways in kidney diseases were recently reviewed by Clark et al. Clark and Parikh (2021).

The decline of kidney functions that could potentially compromise the ability to recover from podocyte injury and endurance to the susceptibility of damage is closely related to aging. Autophagy in kidney aging was reviewed by Tang et al., that sirtuin 1 was noticeably lower in older mice than the younger mice (Tang et al., 2020). Autophagy signalling pathways might share common regulatory molecules with apoptosis, enabling them to regulate and modify each other too effectively.

Another prominent characteristic feature of general aging related to sirtuin 1 is the shortening of the telomere that protects the ends of chromosomes (Morris, 2021). They shorten after each cell replication event, and the shortening of telomere was well associated with a decline of stem cells and premature aging (Morris, 2021). The shortening of telomere was also associated with cellular senescence (Camici et al., 2011), a permanent cell cycle arrest that will release senescence-associated proteins and other factors which the accumulation of it can cause damage to the surrounding cells (Shankland et al., 2021). Studies revealed many senescence-associated genes in aged podocytes were identified, and classic inflammation-associated genes and components of the inflammasome pathway significantly increased in aged podocytes that indicated glomerular aging (Shankland et al., 2021).

3. mTOR: a critical signaling pathway to regulate autophagy

The mammalian target of Rapamycin (mTOR) is a serine-threonine kinase that regulates cell growth, proliferation, survival, autophagy, and metabolism (Ma et al., 2018). The increased activation of mTOR activities acted as a negative regulator of autophagy in association with chronic kidney diseases (Ma et al., 2018). A signaling pathway known as ULK1 was revealed for its role in podocytes' autophagy for the first time by Wu et al., that rapamycin, also known as sirolimus, could inhibit the mTOR-ULK1 pathway to increase autophagy level hence reducing podocytes injury (Wu et al., 2013). Wu et al. also confirmed that autophagy plays a vital role in maintaining the homeostasis of podocytes while noticing that rapamycin treatment could reduce podocyte injury and increase autophagy by downregulating the mTOR signaling pathway (Wu et al., 2013; Xiao et al., 2014). In 2013, Fang et al. reported high glucose-induced stress that could interrupt autophagy (Fang et al., 2013). 3-methyladenenine (3-MA) or by Beclin-1 siRNA was a detrimental factor in maintaining podocyte structure and could inhibit the basal autophagy activities of podocytes under high-glucose conditions. The inhibited autophagy activities by 3-MA could be alleviated by rapamycin (Fang et al., 2013). The 3-MA role in podocytes' autophagy was later supported by Chen et al. (2015) (Cheng et al., 2015) and Tan et al. (2016) (Tan et al., 2016). On the other hand, a critical protein expressed by podocytes known as nephrin could be affected by the mTOR complex 1 activity. Hence, the reduced activation of mTOR complex 1 was seen as a potential therapeutic strategy to prevent diabetes nephropathy (Inoki et al., 2011). The beneficial role of rapamycin was supported by a later study in 2016 by Tan et al. Tan et al. (2016) and Jin et al. (2018) (Jin et al., 2018).

4. The essential role of ER stress in autophagy and the role of mitochondria in apoptosis

The endoplasmic reticulum (ER) is where the secreted membrane proteins are translocated to be covalently modified into a proper folding confirmation by the enzymes and chaperones. The loss of balance in protein loading and folding capacity is known as ER stress(Inagi et al., 2005). During ER stress, the unfolded protein response (UPR) will trigger an adaptive signaling pathway activated by the misfolded proteins to maintain protein homeostasis (Inagi et al., 2005; Navarro-Betancourt et al., 2020). In podocytes well-terminally-develop structures, it comprises an abundance of mitochondria, Golgi system, lysosomes, and rough and smooth ER to perform the high anabolic and catabolic workload. Riediger et al. provided evidence for the first time that Prorenin receptor (PRR) in podocytes was essential for podocytes autophagy and its survival (Riediger et al., 2011). PRR plays an essential role in maintaining intravascular acidification in which PRR deficiency could result in intensified ER stress and the massive amount of unprocessed protein that is eventually causing podocyte death (Riediger et al., 2011).

Kidneys require vast energy to filter 180 liters of blood daily. Mitochondria are essential to supply the energy through ATP generation to sustain the workload of filtering blood and carrying out essential functions such as waste removal, reabsorption of nutrients, fluid homeostasis, and electrolyte maintenance (Gujarati et al., 2020). The imbalance of mitochondria homeostasis was reported to contribute to the development and progression of various glomerular diseases (Navarro-Betancourt et al., 2020). In addition, mitochondria were also reported to participate in cell apoptosis induction (Gujarati et al., 2020).

PGC1α was known for its potent effect on mitochondrial autophagy (mitophagy); its overexpression could be toxic and exacerbate renal injury if its downstream mediators were inhibited, eliminating the positive protective effect of mitophagy (Clark and Parikh, 2021). The overexpression of PGC1α using $PPAR_{\gamma}$ could protect podocytes from oxidative damage and glomerulosclerosis. The signaling pathway of PGC1α needs more studies to find out the specific connection in podocyte injury because direct transgenic overexpression was detrimental to podocytes, but indirect PGC1α stimulation through upstream regulators activation was a protective effect on podocytes (Clark and Parikh, 2021). A decrease in PGC1α could lead to dysfunction of telomere maintenance, thus activating p53 associated with apoptosis (Morris, 2021).

Podocytes' high level of catabolic, anabolic activities, and transcapillary pressure during the filtration process (Nagata, 2016), indicate an adaptable characteristic but sensitive to cell stress (mechanical, oxidative, and immunological). Therefore, podocyte loss leads to glomerulosclerosis and kidney diseases (Inagi et al., 2005). Inositol requiring enzyme-1α (IRE1α), a UPR transducer could facilitate autophagy by activating PI3K and increasing Beclin-1 (Navarro-Betancourt et al., 2020). Studies reported that UPR is interrelated with mitochondrial function while IRE1α is abundant in mitochondria as an essential component of the podocyte in protein homeostasis network and fine-tuning autophagy (Navarro-Betancourt et al., 2020). IRE1α was reported to have a role in maintaining podocyte structural integrity as mice age, podocyte homeostasis, and injury (Kaufman et al., 2017). It enables the likelihood of targeting the IRE1α pathway to improve protein homeostasis in chronic glomerular disease (Navarro-Betancourt et al., 2020).

In 2014, there was more evidence to associate autophagy with ER stress mentioned in Fang et al., studies. Understanding cell death crosstalk with autophagy was not well known until Fang et al. reported the ER stress as an essential mechanism of apoptosis and autophagy

(Fang et al., 2014). It was reported that SIRT1 could regulate apoptosis by exerting renoprotective effects to protect against oxidative stress-induced apoptosis through deacetylation of FOXO3 (Wang et al., 2015). Besides that, Sirtuin activator 1720 that activates Sirtuin 1 was suggested to inhibit p53-dependent transcription during cellular stress by reducing the deacetylation of p53 to regulate apoptosis, oxidative stress, and inflammation (Kim et al., 2019).

Yuan et al. supported ER stress role in podocytes, leading to podocyte injury induced by aldosterone, and the injury was inhibited by mineralocorticoid receptor (MR) (Yuan et al., 2015). Studies strikingly reported the independent role of aldosterone in podocyte injury and CKD progression (Shavit et al., 2012) and highlighted CCAAT/enhancer-binding protein (C/EBPα) homologous protein known as Chop, which could be critical in ER stress-induced apoptosis. Aldosterone is among the vital factors that cause podocyte injury (Yuan et al., 2015). The mechanism model suggested by Yuan et al. indicated that ER stress-induced podocyte injury is directly connected with Chop and Reactive Oxygen Species (ROS) (Yuan et al., 2015). The role of ROS as mediator and trigger factor of the podocytes autophagy was further studied in 2016 by Bai et al. Bai et al. (2016), and later on, in Miaomiao et al., that the increased ROS level was found to contribute to cell death (Miaomiao et al., 2016). Chop-dependent apoptosis and autophagy were reported as the result of ER stress caused by aldosterone that mediates its action through MR to induce podocyte injury's coping mechanism, but the mechanism of aldosterone and MR remain elusive (Yuan et al., 2015).

5. The role of VEGF, FOXO 1 in podocyte autophagy

Vascular endothelial growth factor (VEGF) has a primary binding site and production site in podocytes to maintain renal function. Overexpression of VEGF was reported in 2016 that had a significant association with diabetes caused podocytes injury, which could be ameliorated by rapamycin-induced autophagy activity (Liu et al., 2017; Miaomiao et al., 2016). Miaomiao et al. were the first to report that podocyte autophagy could negatively regulate VEGF expression that caused podocyte injury in diabetic mice. It was supported by other studies that podocyte autophagy impairment could impact the secretion of VEGF, which is necessary for glomerular structure maintenance (Kaufman et al., 2017). FOXO1 (also known as forkhead in rhabdomyosarcoma, or FKHR) was first noticed by Wang et al., which interacted with Atg 7, promoting autophagy activity (Wang et al., 2016). It was reported that FOXO1 promotes Sirt1 expression and functions synergistically to increase cell survival (Morris, 2021).

6. The role of PI3K pathway in podocyte foot process effacement

PI3K pathway was supported by a growing body of evidence on the role of controlling the remodeling of the actin cytoskeleton in podocytes. Actin cytoskeleton's disorganization in podocyte injury is associated with PI3K. Huang et al. provided evidence that the PI3K/Akt pathway was inactivated after podocyte injury, but Notoginsenoside R1 (NR1) treatment could reactivate it (Huang et al., 2017). In 2017, astragaloside IV was discovered as a potential therapeutic strategy that could prevent the progression of diabetes nephropathy by Guo et al. Guo et al. (2017). The beneficial effect of astragaloside IV was associated with the expression of AMP-activated protein kinase α (AMPKα) phosphorylation (Guo et al., 2017). NR1 was reported to have a protective effect in podocytes for the first time by Huang et al. Huang et al. (2017). The PI3K/Akt/mTOR pathway activation was involved in the protective effects induced by NR1.

7. The therapeutic effects of natural products in podocyte injury associated with autophagy

In 2018, Chen et al. revealed that amino acid starvation could promote podocyte autophagy in a short duration because amino acid was a crucial component in podocyte autophagy induction (Chen et al., 2018). The nuclear TFEB, a core regulator of autophagy, would block amino acid starvation-induced autophagy when inhibited (Chen et al., 2018). Tripterygium glycoside (TG), an active ingredient from the herb Tripterygium wilfordii Hook F, protects podocytes from puromycin aminonucleoside (PAN)-induced podocyte injury by autophagy activation via PI3K-dependent pathway (Gong et al., 2018) and protects against podocyte injury induced by high-glucose serum (Zhan et al., 2019). Evidence supported TG to have immunosuppressive and anti-inflammatory effects towards chronic kidney disease (Gong et al., 2018). Following TG, a bioactive triterpenoid isolated from the roots of Tripterygium wilfordii known as celastrol was reported to have a few critical protective features towards high-glucose condition podocyte injury (Zhan et al., 2018). According to Zhan et al. (2018), celastrol could restore high-glucose-induced deficiency of the autophagy pathway and restore podocyte viability (Zhan et al., 2018). High-glucose murine podocytes reported that hispidulin could induce autophagy and inhibit apoptosis, potentially therapeutic in future development (Wu et al., 2018). Another natural product, iridoid glycoside compound known as catalpol, was derived from traditional Chinese medicinal herb Rehmannia glutinosa, which could ameliorate renal function and proteinuria in diabetic nephropathy hence providing a protective effect to stabilize podocyte cytoskeleton and improve podocyte autophagy impairment (Chen et al., 2019). Mangiferin, a polyphenol with antioxidant, anti-tumor, anti-bacterial, antiviral, was recently discovered that delayed diabetes nephropathy progression and protected podocytes through the AMPK-mTOR-ULK1 pathway that enhance autophagy (M. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; X. Wang et al., 2018).

On the other hand, trehalose is a natural ingredient with protective effects found in yeast, bacteria, fungi, and invertebrates (Kang et al., 2014). It was suggested to be a safer therapeutic strategy for glomerular disease because of its autophagy induction, alleviating podocyte injury, apoptosis, and actin cytoskeleton changes (Kang et al., 2014). The therapeutic effect of trehalose to improve apoptosis and autophagy condition was discovered in 2014 by Kang et al., that trehalose could induce podocytes autophagy without imposing reactive oxygen species (ROS) in the mTOR independent manner (Kang et al., 2014). ROS plays a vital role in promoting oxidative stress and activates ER stress (Tang et al., 2017). In another study, the anti-apoptotic effects of trehalose directly correlated with autophagic reflux and selective induction of autophagy (Tang et al., 2017).

8. The active ingredients (BBR, MFSD, RPF) and LXR in various signaling pathways

In 2020, Dai et al. pointed out various studies that reported that wnt/ß-catenin, a common signaling pathway for cell proliferation and a key role in autophagy, was associated with podocyte injury when it was being activated abnormally (Dai et al., 2020). Wnt/ß-catenin will further enhance podocyte injury by inhibiting podocyte autophagy, but this could be ameliorated by combining natural products known as Mahuang Fuzi ShenZhuo decoction (MFSD) treatment with clinical results (Dai et al., 2020). Various studies supported compelling evidence that many crude extracts and a combination of natural products could inhibit the wnt/ ß-catenin signaling pathway in chronic kidney disease (W.J. Liu et al., 2019; D. Liu et al., 2019; Wang et al., 2018).

Berberine (BBR) is the active ingredient of coptis with multiple pharmacological effects such as antioxidant, anti-inflammatory, and anti-diabetes, making it an exciting treatment option for podocytes (Li et al., 2020). BBR successfully demonstrated the therapeutic effect by inhibiting the mTOR/ P70S6K/ 4EBP1 signaling pathway, thus increasing podocyte autophagy and reducing apoptosis (Li et al., 2020). An exciting treatment from the fermentation method of Traditional Chinese Medicine (TCM) known as Radix astragali and Paecilomyces

Cicadidae (RPF) was studied (Yang et al., 2020). The studies' evidence showed that RPF could enhance autophagy and protect podocytes from various signaling pathways such as PI3K/ AKT/ mTOR (Yang et al., 2020). A critical active ingredient known as curcumin has potent effects in affecting podocyte autophagy activities. It was involved in various signaling pathways such as PI3k/ Akt/ mTOR pathway (Tu et al., 2019) and proteins such as Beclin1/ UVRAG/ Bcl2 (Z. Zhang et al., 2020; P. Zhang et al., 2020) that exerted therapeutic effects in podocyte autophagy.

A new perspective about the Liver X receptor (LXR) directly associated with podocyte autophagy activities, its activation will inhibit the formation of autophagosomes in podocytes, which leads to podocyte injury (P. Zhang et al., 2020; Z. Zhang et al., 2020). LXR was found to inhibit the AMPK signaling pathway, and LXR activation contributed to mTOR activation (P. Zhang et al., 2020; Z. Zhang et al., 2020). LXR's relationship with AMPK and the mTOR signaling pathway provided a new perspective in podocyte injury's pathogenesis (P. Zhang et al., 2020; Z. Zhang et al., 2020). Table 1 shows the relevant factors in podocyte autophagy, and Table 2 highlights the crucial signaling pathway involved in podocyte autophagy.

9. Discussion

Autophagy is an integral part of maintaining the podocyte's optimum function to provide general health of the kidney (Huber et al., 2012), and there were various vital factors associated with podocyte autophagy that was tabulated in Table 1. The induction of autophagy in selective podocyte injury methods such as puromycin amino nucleoside (PAN) was noticed declining again over time. This could suggest that autophagy may have a threshold for the "self-cleaning" process while the UPS role in the setting is not known. Without an effective, long-lasting autophagy process to maintain the homeostasis of podocytes, increased podocyte apoptosis occurs. This observation was reported from FSGS, but MCD could reference the result because selective podocyte injury (PAN) is commonly used in MCD (Heintz and Meyer-Schwesinger, 2021). Interestingly, it is unclear that UPS and autophagy transcript upregulation is absent in MCD but not FSGS and DN. MCD was potentially described as the pre-stage of FSGS because, under the light microscope, it appears as usual without scarring. One speculation is that the intensity of injury for MCD is not as severe and persistent as FSGS and DN; hence, in MCD, the podocyte injury mainly was transient, and the UPS and autophagy were not noticeably observed (Beeken et al., 2014). Nonetheless, in frequent-relapse MCD, podocyte injury is persistent; therefore, further autophagy studies are crucial to explore in MCD, such as the signaling pathways of autophagy, the UPS, and ALP activation in frequent relapse MCD.

The impairment of autophagy in podocytes was positively associated with ER stress in various injury methods (High glucose-induced injury, PAN-induced injury, and LPS induced injury), which should be thoroughly compared and studied to elucidate the autophagy process in association with ER stress from different podocyte injuries methods. Most studies in diabetic nephropathy (Table 2) did not discuss the role of ER stress with podocyte injury, autophagy, and the signaling pathways involved. Tables 2 and 3 summarized different podocyte injury approaches and their therapeutic targets in different signaling pathways in diabetic and non-diabetic kidney disease, respectively, which could be the potential target for investigating podocyte autophagy. Various factors in Table 1 could cause the interruption of podocyte autophagy activities worthy of further investigation. The UPR during ER stress transiently attenuates degradation of misfolded proteins (autophagy) and on a set of apoptosis (Inagi et al., 2005). Mitochondria were reported to participate in cell apoptosis induction (Gujarati et al., 2020). The impairment of autophagy and mitophagy that involves PGC1α activating p53 associated with apoptosis could be inhibited by the activation of Sirt1 during cellular stress. Sirt1 has a decisive role in regulating apoptosis by targeting p53, PGC1α, and FOXO3 (Peasley et al., 2021). The apoptosis of podocyte cells will deteriorate kidney condition. However, more studies are needed to elucidate further this connection and the indirect protective role of PGC1α.

Podocytes are insulin-sensitive kidney cells with non-dividing characteristics (Rogacka et al., 2020), explaining the injury associated with diabetes. Most podocyte autophagy studies investigated diabetic nephropathy, but it is sporadic in minimal change disease. Table 3 summarises the studies reported on non-diabetic kidney diseases. Nonetheless, it was reported that podocyte autophagy impairment was significantly associated with foot process effacement, proteinuria, and hypoalbuminemia in minimal change disease nephrotic syndrome, but the detailed mechanism is still far from clear (Ogawa-Akiyama et al., 2020). FSGS, MCD, and DN share the same pathological outcome of podocyte injury (with different severity) and proteinuria; it is hypothesized that signaling pathways of podocyte autophagy in diabetic nephropathy might be relevant in other glomerulopathies, especially MCD and FSGS. Studies showed that autophagy occurred earlier than apoptosis; if autophagy were inhibited, it would increase apoptosis. If autophagy-mediated repair could happen early before apoptosis, it would inhibit podocyte injury induced by Puromycin Aminonucleoside (PAN) (Yu et al., 2020).

As a therapeutic approach, podocyte autophagy is still relatively new to non-diabetic chronic kidney diseases such as MCD, the most common cause of the nephrotic syndrome, and it was encouraged to investigate podocyte autophagy in minimal change disease (Ogawa-Akiyama et al., 2020). Based on emerging evidence to support autophagy's significant role in podocyte injury, podocyte autophagy could be the promising research target in minimal change disease. Nonetheless, the current DN evidenced podocyte autophagy studies may not be entirely fit to study for idiopathic minimal change disease because of the minimal change disease's multifactorial nature. Non-high glucose-induced podocyte injury in vitro with autophagy studies could reveal if autophagy were beneficial for other podocyte injury diseases such as MCD or FSGS. The therapeutic approach for MCD and FSGS could benefit significantly from investigating in-depth in autophagy, ER stress, AMPK signaling pathway, and sirtuin signaling pathway to elucidate further the unclear pathogenesis of minimal change disease. Evidence harvested from podocyte autophagy in diabetic nephropathy studies shall be referenced to investigate MCD. Unfortunately, the challenge remains to induce the MCD-specific podocyte injury model.

Among the autophagy studies, the best-studied regulatory mechanisms that mediate autophagy are energy-nutrient sensing status signaling pathways: AMP-activated protein kinase (AMPK), mTOR, and Sirtuin (Y.-N. Wang et al., 2019; W. Wang et al., 2019; Y. Wang et al., 2019). Intermittent fasting (calories-restriction) was believed to increase the Sirtuin-1 activity, thus increasing autophagy activities (Abas and Sabry, 2020), but it is still controversial about its feasibility and efficacy in clinical settings (Lee et al., 2020). Nonetheless, the involvement of sirtuin in molecular research had tremendous discoveries in recent years. Calories restriction could significantly reduce insulin activity because podocytes are insulin-sensitive kidney cells (Rogacka et al., 2020), and it was reported that a calories restriction diet could activate the longevity gene: Sirtuin-1, which provided other renoprotective features (Kong et al., 2015; Lee et al., 2020).

Fig. 1 showed the relationship between sirtuin, AMPK, mTOR, and autophagy with potential therapeutic substances and targets. Various substances could activate autophagy by upregulating AMPK signaling pathway activities and downregulating mTORC1 activities with the involvement of sirtuin-mediating factors. Hispidulin (Wu et al., 2018), mangiferin (M. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; X. Wang et al., 2018), and tripterygium glucoside (Gong et al., 2018) share a similar pathway in activating autophagy by increasing beclin 1 and LC3II expression and suppressing the storage of p62 which effectively downregulate the mTOR signaling pathway. The increased beclin1 and LC3II were reported to deacetylate NF-κB-p65, leading to sirtuin activation (Y.-N. Wang et al., 2019; W. Wang et al.,

Table 1
Podocyte autophagy relevant significant focus.

Protein	Gene	Signaling Pathway	Other targets (molecule/ receptor/ inhibitor/ enzyme)
High mobility group box 1 (HMGB1) (Kang et al., 2011; Jin et al., 2019)	Atg5 (Hartleben et al., 2010; Yoshibayashi et al., 2020; Lenoir et al., 2015; Bai et al., 2016)	Mammalian target-of-rapamycin complex 1 (mTORC1) (Yi et al., 2017; Liebau et al., 2013; Xiao et al., 2014; Inoki et al., 2011; Wang et al., 2016; Huang et al., 2017; Chen et al., 2018; Kang et al., 2014; Tu et al., 2019; P. Zhang et al., 2020; Z. Zhang et al., 2020; Yasuda-Yamahara et al., 2015; Tagawa et al., 2016)	prorenin receptor (PRR) (Riediger et al., 2011)
NALP3 (Nakahira et al., 2011)	ATG-7 siRNA (Oliva Trejo et al., 2014; Yi et al., 2017; Wang et al., 2016; Feng et al., 2014)	Mammalian target-of-rapamycin complex 2 (mTORC2) (Wu et al., 2013)	mineralocorticoid receptor (MR) (Yuan et al., 2015; Shavit et al., 2012)
FK506-binding protein (FKBP12) (Wu et al., 2013)	Arrb 1 / Arrb 2 (Liu et al., 2016)	ULK pathway (Wu et al., 2013)	3-methyladenenine (3-MA) (Fang et al., 2013, 2014; Cheng et al., 2015; Tan et al., 2016; Bai et al., 2016; Wang et al., 2016)
Angiotensin II (Shengyou and Li, 2015)	Notch 2 gene (Zhang et al., 2017)	PI3K/Akt/mTOR pathway (Huang et al., 2017; Gong et al., 2018; Yang et al., 2020; Tu et al., 2019; Feng et al., 2014; Mao et al., 2016; Zheng et al., 2020)	Salubrinal/Tauroursodeoxycholic acid (TUDCA) (Fang et al., 2013)
CCAAT/ enhancer-binding protein (C/EBP) homologous protein (Chop) (Yuan et al., 2015)	Long non-coding (Inc) RNA (GM5524 & GM15645) (Feng et al., 2018)	HDAC4–STAT1 pathway (Wei and Dong, 2014)	α-galactosidase (Liebau et al., 2013)
Beclin-1 (Fang et al., 2013; Bai et al., 2016; Wang et al., 2016)	Gene of Stromal Interaction Molecule 1 (STIM1) (Jin et al., 2018)	NF-kB/ iNOS signaling pathway (Khan et al., 2015)	Adipose-derived stem cells (ASCs) (Zhang et al., 2013; Jin et al., 2019)
P62 (Bai et al., 2016; Wang et al., 2016)	NUP160 (M. Wang et al., 2018; X. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018)	AMPK signaling pathway (Guo et al., 2017; P. Zhang et al., 2020; Z. Zhang et al., 2020; Mao et al., 2016)	human glial cell line-derived neurotrophic factor (GDNF) (Zhang et al., 2013)
Light chain 3 (LC3) (Bai et al., 2016; Wang et al., 2016)		PTEN-mediated autophagy signaling (Zheng et al., 2020; Sun et al., 2017)	Na^+/H^+ exchanger-1 (NHE-1) (Feng et al., 2014)
ß-arrestin1/ ß-arrestin 2 (Liu et al., 2016)		Notch signaling pathways (Zhang et al., 2017; Zheng et al., 2020)	PI3-kinases inhibitor (Feng et al., 2014)
Ubiquitin-like protein: ATG 7, ATG5, ATG12–5 (Liu et al., 2016)		Amino acid signaling/ Amino acid upstream signals (Chen et al., 2018)	Trehalose (mTOR inducer)(Kang et al., 2014)
forkhead in rhabdomyosarcoma, (FOXO 1) (Wang et al., 2016)		mTOR/P70S6K/4EBP1 signaling pathway (Jin et al., 2018; Li et al., 2020; Mao et al., 2016)	Histone deacetylases (HDACs) (Wei and Dong, 2014; Khan et al., 2015)
Cyclooxygenase-2 (Jin et al., 2018)		Wnt/ ß-catenin pathway (Dai et al., 2020; W.J. Liu et al., 2019; D. Liu et al., 2019; Wang et al., 2018)	N-acetyl cysteine (NAC) (Yuan et al., 2015; Bai et al., 2016)
Connexin 43 (Cx43) (Ji et al., 2019)		TGFß/Smad pathways (X. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; M. Wang et al., 2018; Jin et al., 2019)	Ginsenoside Rg1(Bai et al., 2016;Mao et al., 2016)
		AMPK-mTOR-ULK1 pathway (M. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; X. Wang et al., 2018)	vascular endothelial growth factor (VEGF) (Miaomiao et al., 2016; Liu et al., 2016)
		Pim1-p21-mTOR signaling axis (Wu et al., 2018)	Chloroquine (Wang et al., 2016)
		AKT/mTOR signaling pathway (Jin et al., 2019)	sarcoendoplasmic reticulum Ca2 + ATPase 2b (SERCA2b)(Guo et al., 2017)
		Smad1/mTOR signaling pathway (Jin et al., 2019)	Advanced glycation end products (AGEs)(Takahashi et al., 2017;D. Liu et al., 2019; W.J. Liu et al., 2019)
		PGRN-CAMKK-AMPK pathway (Zhou et al., 2019)	g-secretase inhibitor (DAPT)(Zhang et al., 2017)
		SIRT1 signaling pathway (P. Zhang et al., 2020; Z. Zhang et al., 2020)	nuclear translocation of transcription factor EB (TFEB)(Chen et al., 2018)
			Tripterygium glycoside (TG) (Gong et al., 2018; Zhan et al., 2019)
			Mangiferin (1, 3, 6,7-tetrahydroxyxanthone-C2-β-D glucoside) (M. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; X. Wang et al., 2018)
			Hispidulin (Wu et al., 2018)
			Celastrol (Zhan et al., 2018)
			Catalpol (iridoid glycoside) (Chen et al., 2019)
			Curcumin (Tu et al., 2019; Zhang et al., 2020)
			Progranulin (PGRN) (Zhou et al., 2019)
			nucleotide-oligomerization domain-like receptor 3 (NLRP3) (Hou et al., 2020)
			Berberine (Li et al., 2020)
			Paecilomyces cicadidae (RPF) (Yang et al., 2020)
			Liver X receptor (LXRs) (P. Zhang et al., 2020; Z. Zhang et al., 2020)
			P66Shc protein adaptor (Zheng et al., 2020)

Table 2
Highlight findings of the various signaling pathway involved in podocyte autophagy in Diabetic Nephropathy (DN).

Signaling pathways	Studies	Disease	Inhibitors/ Therapeutic target	Main finding	Induce methods
mTOR	Inoki et al. 2011 (Inoki et al., 2011)	Diabetic nephropathy	Potentially chemical chaperons such as PBA	mTORC1 activation is critical to induce Diabetic nephropathy	Generated mice with *Tsc1* deletion specifically in podocytes (PcKOTsc1)
mTOR	Xiao et al. 2014 (Xiao et al., 2014)	Diabetic nephropathy	Rapamycin	Rapamycin can ameliorate renal injury by increasing autophagy activity and inhibiting apoptosis of podocytes	Streptozotocin (STZ)-induced type 1 diabetic mice
mTOR	Yasuda et al. 2015 (Yasuda-Yamahara et al., 2015)	Diabetic nephropathy	None	mTORC1 is a nutrient-sensing signaling complex that inhibits autophagy.	High-fat diet-induced diabetic mice with podocyte-specific autophagy deficiency
mTOR	Tagawa et al. 2016 (Tagawa et al., 2016)	Diabetic nephropathy	None	Huge, damaged lysosomes were found in HFD-fed, podocyte-specific autophagy-deficient mice.	Developed podocyte-specific autophagy-deficient mice in a high-fat diet-induced (HFD) diabetic model
PI3k/Akt/ mTOR	Huang et al. 2017 (Huang et al., 2017)	Diabetic nephropathy	Notoginsenoside R1 (NR1)	Treatment with NR increased mTOR, PI3K, and Akt phosphorylation levels, leading to activation of the PI3K/Akt/mTOR signaling pathway in podocytes. The first NR1 study in vitro indicated the protective effects of NR1 in a signaling pathway.	High-glucose-induced podocyte apoptosis
PI3k/Akt/ mTOR	Tu et al. 2019 (Tu et al., 2019)	Diabetic nephropathy	Curcumin	Curcumin protects podocytes through PI3k/ Akt/mTOR pathway.	Streptozotocin (STZ) and high-fat sugar diet-induced DN in mice.
PI3K/Atk/ mTOR	Yang et al. 2020 (Yang et al., 2020)	Diabetic nephropathy	Radix astragali and Paecilomyces cicadae (RPF)	RPF could enhance autophagy by inhibiting PI3K/Atk/mTOR pathway to protect podocytes.	The high-glucose-induced podocyte injury model
Notch-PTEN-PI3K/Atk/ mTOR	Zheng et al. 2020 (Zheng et al., 2020)	Diabetic nephropathy	P66Shc protein adaptor	P66Shc inhibits podocyte autophagy and induce apoptosis through Notch-PTEN-PI3K/ Akt/mTOR	STZ-induced mice
AMPK	Guo et al. 2017 (Guo et al., 2017)	Diabetic nephropathy	Astragaloside IV	Astragaloside IV prevented the progression of diabetic nephropathy and AMPK regulated autophagy induction.	STZ-induced mice
HDAC4-STAT 1	Wei et al. 2014 (Wei and Dong, 2014)	Diabetic nephropathy	None	HDAC4 contributed to podocyte injury specifically by suppressing autophagy via STAT1 deacetylation	STZ-induced mice
NF-kB/ iNOS signaling pathway	Khan et al. 2015 (Khan et al., 2015)	Diabetic nephropathy	Valproic acid (VPA)	VPA treatment ameliorates podocytes' injury by inactivation of NF-kB/iNOS signaling and facilitating autophagy.	STZ-induced mice
PTEN	Sun et al. 2017	Diabetic nephropathy	miR-217 inhibition	The inhibition of miR-217 exerts a protective effect in high-glucose-induced podocyte damage by restoring the autophagy pathway via targeting PTEN.	High-glucose-induced injury
mTOR/ P70S6K/ 4EBP1	Li et al. 2020 (Li et al., 2020)	Diabetic nephropathy	Berberine	Berberine could attenuate high-glucose-mediated inhibition of autophagy and restore podocyte viability.	High-glucose-induced podocyte injury
Wnt/ ß-catenin	Dai et al. 2020 (Dai et al., 2020)	Diabetic nephropathy	Mahuang Fuzi and Shenzhuo decoction (MFSD)	MFSD treatment can inhibit the activation of the Wnt/ ß-catenin pathway, which inhibits autophagy.	High-glucose-induced podocyte injury
AMPK-mTOR-ULK1	Wang et al. 2018 (M. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; X. Wang et al., 2018)	Diabetic nephropathy	Mangiferin	Mangiferin could delay the progression of diabetic nephropathy and protect podocytes by enhancing autophagy via the AMPK-mTOR-ULK1 pathway.	STZ-induced diabetic rats
Pim1-p21-mTOR	Wu et al. 2018 (Wu et al., 2018)	Diabetic nephropathy	Hispidulin	Hispidulin induced autophagy and inhibited apoptosis, associated with Pim1 inhibition and the Pim1-p21-mTOR signaling axis regulation.	High-glucose-induced-mice
PGRN-CAMKK-AMPK	Zhou et al. 2019 (Zhou et al., 2019)	Diabetic nephropathy	Progranulin (PGRN)	PGRN could induce autophagy via PGRN-CAMKK-AMPK pathway activation, the new therapeutic modalities for diabetic nephropathy treatment.	High-glucose-induced-mice and podocyte

2019; Y. Wang et al., 2019). Resveratrol was reported to have a role in activating sirtuin via AMPK phosphorylation; the upregulated NAD+ level regulates sirtuin will have the counter effect in regulating the AMPK via liver kinase B1 (LKB1). AMPK was reported to deacetylate downstream target of FOXO3 further to activate sirtuin (Y.-N. Wang et al., 2019; W. Wang et al., 2019; Y. Wang et al., 2019). $PPAR_{\gamma}$ is a coactivator that, shared with PGC1α could be phosphorylated by AMPK to deacetylate sirtuin (Y.-N. Wang et al., 2019; W. Wang et al., 2019; Y. Wang et al., 2019). In short, AMPK could regulate sirtuin activities and be regulated by sirtuin activities, thus affecting mTOR activities either with direct communication by phosphorylating ULK or phosphorylating TSC2 (Y.-N. Wang et al., 2019; W. Wang et al., 2019; Y. Wang et al., 2019). Findings indicated that AMPK had the inhibitory effect of mTORC1 on podocyte autophagy in a short-term adaptive response, which made AMPK the central regulatory pathway in regulating podocyte autophagy (Bork et al., 2020). AMPK agonist known as AICAR can increase AMPK. 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), an activator of AMPK, was reported to improve renal function by restoring mitochondrial SIRT3 expression and activity hence reducing renal injury by increasing transcript levels of nicotinamide phosphoribosyltransferase (Nampt) (Morigi et al., 2015).

Studies reported the critical role of the mTOR signaling pathway in

Table 3
Highlight findings of the various signaling pathway involved in podocyte autophagy in non-diabetic kidney diseases.

Signaling pathways	Studies	Disease	Inhibitors/ Therapeutic target	Main finding	Induce methods
mTOR	Liebau et al. 2013 (Liebau et al., 2013)	Fabry's disease	a-galactosidase A-deficient podocytes	a-galactosidase A-deficient podocytes may cause deficient mTOR kinase activity	Transfection conditionally immortalized human podocyte
mTOR	Kang et al. 2014 (Kang et al., 2014)	Minimal Change nephrotic syndrome	Trehalose	Trehalose treatments decrease podocyte apoptosis and show cytoprotective effects. Trehalose induced podocyte autophagy in an mTOR independent way.	Porumycin aminonucleoside (PAN)-treated podocytes
mTOR	Yi et al. 2017 (Yi et al., 2017)	Not specified	Rapamycin	Activation of rapamycin led to the suppression of adriamycin-induced apoptosis.	Adriamycin-induced nephropathy
mTOR	Chen et al. 2018 (Chen et al., 2018)	Not specified	Amino acid signaling regulates autophagy at the transcriptional level through transcription factor EB	Amino acid starvation promoted TFEB activity and caused podocyte autophagy, mTOR suppression, and TFEB activation may mediate amino acid starvation-induced autophagy in the podocyte.	Amino acid deprivation medium to culture podocytes in vitro
mTOR/ AMPK/ STIR1	Zhang et al. 2020 (P. Zhang et al., 2020; Z. Zhang et al., 2020)	Not specified	None	Liver X receptor activation could inhibit autophagic flux by blocking autophagosome formation in podocytes by affecting the mTOR, AMPK, and SIRT1 signaling pathways.	STZ-induced diabetic mice
mTOR-ULK1	Wu et al. 2013 (Wu et al., 2013)	Not specified	Rapamycin	Rapamycin could reduce podocyte injury by increasing the autophagy level via mTOR-ULK1 pathway inhibition.	PAN-induced podocyte injury
PI3k/Akt	Feng et al. 2014	Not specified	Na+ /H+ exchanger-1 (NHE-1)	NHE-1 exerts a protective effect by activating autophagy via the PI3k/Akt pathway to reduce ER stress injury.	Induce mice with passive Heymann Nephritis with rabbit anti-Fx1A IgG antibody
AMPK	Mao et al. 2016 (Mao et al., 2016)	Not specified	Ginsenoside Rg1	Rg1 was effective in attenuating autophagy via AMPK/mTOR/PI3K pathway.	Angiotensin II-induced podocyte injury
PI3k	Gong et al. 2018 (Gong et al., 2018)	Not specified	Tripterygium glycoside (TG)	TG protected podocytes from PAN-induced injury by activation of autophagy mainly via the PI3k-dependent pathway.	PAN-induced podocyte injury
Notch	Zhang et al. 2017 (Zhang et al., 2017)	Not specified	Rapamycin	Rapamycin reduces injury by involving in Notch signaling during podocyte differentiation and kidney development	g-secretase inhibitor (DAPT) treated cells
mTOR/ P70S6K/ 4EBP1	Jin et al. 2018 (Jin et al., 2018)	Idiopathic membranous nephropathy	Rapamycin	Rapamycin could activate podocyte autophagy by effectively inhibiting mTOR/ P70S6K/4EBP1, reducing podocyte apoptosis.	PAN-induced podocyte injury
Wnt/ ß-catenin	Wang et al. 2018 (X. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; M. Wang et al., 2018)	Tubulo-interstitial fibrosis	Secolanostane tetracyclic triterpenoids	Secolanostane tetracyclic triterpenoids could be novel inhibitors that simultaneously target multiple renin-angiotensin systems, blocking smad3 phosphorylation in vitro and in vivo, inhibiting Wnt activation/ ß-catenin pathway.	Angiotensin II treated HK-2 cells

negatively regulating podocyte autophagy, thus causing podocyte injury. The central signaling hub for autophagy, is mTOR signaling pathway, was critically associated with Sirtuin-1 (Y.-N. Wang et al., 2019; Y. Wang et al., 2019; W. Wang et al., 2019). Table 2 summarizes the studies in different signaling pathways, the effective inhibitor/ therapeutic molecule that successfully regulate the mTOR activities shall be investigated further about their mechanisms in ameliorated podocyte injury in detail. Evidence is building up to support the activation of mTOR contributes to immune-mediated glomerular disease via the upstream signaling of phosphoinositide 3-kinase/ AKT and mitogen-activated protein kinase pathways (Ma et al., 2018); besides, various growth factors, energy status, and amino acids involve deeply with the cellular growth, metabolism, the negative regulation of autophagy (P. Zhang et al., 2020; Z. Zhang et al., 2020). Growth factors such as extracellular signal-regulated kinase (ERK), p90, S6 kinase 1, Akt-mediated phosphorylation of PRAS40 (Gui and Dai, 2020) can activate mTORC1 via PI3k/Akt pathway. Besides, Notoginsenoside R1 (Huang et al., 2017) and C1-Ten (Lee et al., 2017) also shared the same PI3k/Akt pathway for autophagy activation. The activated Akt inhibits mTOR via its inhibitors TSC1&2 and through AMPK in combination with liver kinase B1 (LKB1)(Clarke and Simon, 2019; Ma et al., 2018). Furthermore, the activated Akt and Wnt (Gui and Dai, 2020) inhibit GSK3 by phosphorylating TSC2 via AMPK-phosphorylate TSC2 manner (Clarke and Simon, 2019) to inhibit mTOR. The wnt/ ß-catenin pathway, there was limited evidence supporting the explanation that MFSD treatment relies heavily on inhibiting wnt/ ß-catenin signaling pathway, future studies are needed to develop a more in-depth mechanism (Dai et al., 2020). Under hypoxia conditions, TSC1&2 will be activated to inhibit mTOR via the Redd1 gene by promoting TSC2 dissociation from 14-3-3 protein (Gui and Dai, 2020). On the other hand, overexpression of Connexin43 (transmembrane protein) negatively regulates autophagy while decreased expression would suppress the mTOR pathway, but the role of Connexin43 in the signaling pathways remain unknown; studies of Connexin43 with TSC1&2, AMPK and sirtuin may be a potential therapeutic direction (Ji et al., 2019).

Recent studies reported that manipulation of long-term genetic mTOR activities did not influence high basal autophagy in podocytes (Bork et al., 2020). Instead, AMPK was suggested to be the main decisive factor of autophagy activation. Atg5 knockout mice are an excellent animal model of autophagy impairment, ER stress, and aging-related glomerulosclerosis (Huber et al., 2012), while the use of mTOR inhibitor usually increases the autophagy activities. However, the direct effect of mTOR inhibitor on podocyte-specific atg5 deletion is rare. Surprisingly, studies suggested that mTOR appears to independently regulate autophagy from observing podocyte-specific deletion of atg5 consequences (Shankland et al., 2021; Huber et al., 2012). However, atg5 and mTOR are both closely associated with sirtuin (Y.-N. Wang et al., 2019; Y. Wang et al., 2019; W. Wang et al., 2019). The presence of atg5 is essential for autophagy activation, but mTOR is unnecessary for the high basal autophagy activities in the podocyte. However, the high mTORC1 activity in podocytes might suggest a unique mechanism requiring mTORC1 and autophagy. It was reported that TOR-autophagy spatial

coupling compartment (TASCC) could be the reason. Further studies of understanding mTOR-independent autophagy regulation will strengthen podocyte autophagy's current mechanism findings.

The health span and lifespan of the kidney rely heavily on the expression of sirtuin. The loss of sirtuin expression was observed in aging kidneys, while its upregulation was associated with longevity. AMPK, as the master regulator of autophagy in podocytes that relies heavily on sirtuin expression to maintain its autophagy activities, this observation matches the description of aging in kidney disease, which is specific to podocyte injury for most of the glomerular diseases. The reduction of sirtuin leads to the reduction of autophagy with less activation of AMPK by sirtuin. Autophagy impairment will interfere with podocyte homeostasis and eventually lead to podocyte injury if persistent. The investigation of sirtuin in glomerular diseases is still in its infancy and requires more disease-specific studies to establish the role of sirtuin in pathogenesis.

Natural ingredients from hispidulin, mangiferin, tripterygium glycoside, and resveratrol can activate sirtuin possess huge therapeutic interests for podocyte injury. Sirtuin1 activators such as SRT1720, SRT2183, SRT3025, SRT2104, and SRT1460 were believed to be structurally unrelated to resveratrol but still can be a 1000-fold potent activator of sirtuin than resveratrol (WangA et al., 2021; Bonkowski and Sinclair, 2016). 3-MA was known to inhibit autophagy and further enhance ROS production, but rapamycin reduces the ROS at the cellular level, which is connected to mTOR. Studies revealed that 3-MA and Atg5 short hairpin RNA reversed resveratrol's effect, reducing sirtuin activation and inhibiting autophagy activation (Y.-N. Wang et al., 2019; W. Wang et al., 2019; Y. Wang et al., 2019). 3-MA and Atg5 were also reported to affect an active ingredient known as triptolide by decreasing the expression of fibronectin and collagen IV (Y.-N. Wang et al., 2019; W. Wang et al., 2019; Y. Wang et al., 2019). Other natural products such as curcumin, berberine, radix astragali, triptolide, and paecilomyces cicadidae were involved in PI3K/ Akt/ mTOR pathway, but their molecular activities with sirtuin remain unclear. Nevertheless, various natural products were reported to exert a renoprotective effect on chronic kidney diseases patients required more clinical studies to support the beneficial effects (Wen et al., 2017; Wang et al., 2018). In contrast, the above-mentioned natural products and their active ingredients showed potential therapeutic effects on molecular level studies. Evidence is growing to support the notion that the PI3k/Akt pathway regulates the remodeling of the actin cytoskeleton and cell viability, which could be crucial to podocyte injury (Cantley, 2002; Franke et al., 2003).

Furthermore, natural substances such as berberine (Li et al., 2020), astragaloside IV (Guo et al., 2017), cyclocarya paliurus (Zhang et al., 2019), and emodin (Liu et al., 2021) were reported to affect upregulating and activating AMPK to initiate autophagy. The involvement of sirtuin in the mechanism of various diseases is vast and complicated, so far, studies could elucidate its association with mTOR and AMPK, which are both equally crucial for understanding the pathogenesis of podocyte injury, but more studies towards the current medication being used on CKD patients should be conducted. The beneficial usage of glucocorticoids in patients with glomerulonephritis is not fully understood by far, the connection between glucocorticoids receptor in podocyte with sirtuin, AMPK and mTOR pathways may bring profound understanding of its working mechanism and provide clearer pathogenesis of glomerular diseases such as minimal change disease, focal segmental glomerulosclerosis, and diabetic nephropathy.

VEGF secreted by podocyte was observed to be synthesized from TASCC that provides an environment where mTORC1 and autophagy could be mutually regulated to work as an essential compartmentalized plant for secretory protein synthesis (Huber et al., 2012). mTOR was negatively regulated VEGF expression (Miaomiao et al., 2016; Xu et al., 2020), while increasing sirt1 expression would increase VEGF expression (Morris, 2021). FOXO1 could promote the expression of sirt1 and potentially increase the level of VEGF(Morris, 2021). The overexpression of VEGF was associated with DN podocyte injury, and this suggested that the beneficial role of mTOR in podocyte autophagy ameliorate podocyte injury in DN. Under many circumstances, sirtuin could be a potent therapeutic approach to induce autophagy, while mTOR to suppress the autophagy activation but with the increased VEGF level that might pose a risk to podocyte injury needs mTOR to safeguard the expression of VEGF. This hints that supporting the independent role of mTOR needs a delicate balance to maintain podocyte health. Future studies need to elucidate the independent role of mTOR in podocyte autophagy and its connection with FOXO1 and sirtuin1. The use of rapamycin that could ameliorate podocyte injury indicated a connection with the mTOR signaling pathway, but details of the mechanism of its involvement are still unclear.

Limited studies reported that mTOR inhibitors such as everolimus and sirolimus were not helpful for MCD and FSGS patients (Teh et al., 2021). The reason could be that the targeted patients did not fit into this mTOR inhibitor-needing category nor being investigated from an autophagy perspective because, in the previous studies, the renal biopsy was not performed to determine the condition of the disease; hence the need for mTOR inhibitor was not determined which poised a confusing result of the role and usage of rapamycin in kidney disease (Fervenza et al., 2004). In a separate study, sirolimus caused proteinuria in an individual who had no significant proteinuria before (Letavernier et al., 2007); this may be the reason of sirolimus broke the balance of the mTOR signaling pathway, thus disrupting the autophagy activities, but this speculation was not mentioned in the studies nor being verified in any studies, which make it an exciting point to be investigated further. Another study about the role of everolimus was performed on low nephron numbers in the animal study, making the role of everolimus in podocyte autophagy inconclusive (Vogelbacher et al., 2007). Nevertheless, the inhibitor's dosage should be carefully experimenting with in-vitro/vivo to determine the optimum dosage to effectively reduce podocyte injury in the mTOR signaling pathway perspective that negatively regulated podocyte autophagy. Sirolimus was reported to inhibit mTOR activities through FK506-binding protein, thus negatively regulating autophagy by interfering in the autophagosome phase (Ma et al., 2018). Table 4 shows different signaling pathways in podocyte autophagy studies conducted between diabetic and non-diabetic kidney diseases.

There was an adverse effect that both sirolimus and everolimus shared: the possibility of worsening the kidney's health and causing proteinuria (Tang et al., 2020; Teh et al., 2021). This adverse effect of sirolimus and everolimus (Fervenza et al., 2004; Vogelbacher et al., 2007) could be the dosage issue that caused the delicate balance was not achieved between autophagy inhibition and activation. There seems to be a time-sensitive threshold that autophagy could protect podocytes from hyperglycemia in vitro (Tang et al., 2020). This hint enables the speculation that prolonged starvation with mTOR inhibition and autophagy activation enables mTOR again, contributing to DN's progression (Qi et al., 2018). This speculation could suggest that the reason to induce podocyte injury might be necessary for mTOR. Perhaps an mTOR range of injury could be ameliorated by fixing through autophagy, and future research is needed to elucidate the details of this aspect. Minimal clinical studies were available to know about the role of sirolimus and everolimus in kidney diseases, podocytes, and autophagy. Future studies of mTOR inhibitors dosage towards podocyte injury in different kidney diseases are vital because it was evident that the parietal epithelial cells of the kidney are very responsive to mTOR level changes in other cells within the kidney (McNicholas et al., 2016). It is also worthy of exploring the patient profile type suitable for mTOR inhibitors in their treatments. Besides, the critical role of Sirtuin-1 in the mTOR signaling pathway, autophagy activation, AMPK regulation, and its involvement in various vital target's activities in Table 1 in regulating podocyte health is urgently suggesting for in-depth future investigation for its mechanism and pathogenesis in podocyte injury. Glomerular diseases should be viewed as and potentially treated as symptoms of aging (Morigi et al., 2018; Y.-N. Wang et al., 2019; Y. Wang et al., 2019; W.

Table 4
Current signaling pathway in podocyte autophagy studies between diabetic and non-diabetic kidney diseases.

Signaling Pathway	Diabetes (Title)	Non-diabetes (Disease & Title)
1. mTOR	mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice (Inoki et al., 2011)	**Fabry's Disease**: Dysregulated Autophagy Contributes to Podocyte Damage in Fabry's Disease (Liebau et al., 2013)
	Rapamycin promotes podocyte autophagy and ameliorates renal injury in diabetic mice (Xiao et al., 2014)	**Minimal Change Nephrotic Syndrome**: Trehalose, an mTOR Independent Autophagy Inducer, Alleviates Human Podocyte Injury after Puromycin Aminonucleoside Treatment (Kang et al., 2014)
	Emerging role of podocyte autophagy in the progression of diabetic nephropathy (Yasuda-Yamahara et al., 2015)	**Not specified**: Autophagy is activated to protect against podocyte injury in adriamycin-induced nephropathy (Yi et al., 2017)
	Impaired Podocyte Autophagy Exacerbates Proteinuria in Diabetic Nephropathy (Tagawa et al., 2016)	**Not specified**: Amino acid starvation promotes podocyte autophagy through mammalian target of rapamycin inhibition and transcription factor EB activation (Chen et al., 2018)
2. mTOR/ AMPK/ STIR1	None	**Not specified**: Liver X receptor activation induces podocyte injury via inhibiting autophagic activity (P. Zhang et al., 2020; Z. Zhang et al., 2020)
3. mTOR-ULK1	None	**Not Specified**: Rapamycin Upregulates Autophagy by Inhibiting the mTOR-ULK1 Pathway, Resulting in Reduced Podocyte Injury (Wu et al., 2013)
4. mTOR/ P70S6K/ 4EBP1	Berberine mitigates high glucose-induced podocyte apoptosis by modulating autophagy via the mTOR/ P70S6K/4EBP1 pathway (Li et al., 2020)	**Idiopathic membranous nephropathy**: Rapamycin Reduces Podocyte Apoptosis and is Involved in Autophagy and mTOR/ P70S6K/4EBP1 Signaling (Jin et al., 2018)
5. PI3K/ Akt/mTOR	Notoginsenoside R1 attenuates glucose-induced podocyte injury via the inhibition of apoptosis and the activation of autophagy through the PI3K/ Akt/mTOR signaling pathway (Huang et al., 2017)	None
	Curcumin alleviates diabetic nephropathy via inhibiting podocyte mesenchymal transdifferentiation and inducing autophagy in rats and MPC5 cells (Tu et al., 2019)	None
	Paecilomyces cicadae-fermented Radix astragali activates podocyte autophagy by attenuating PI3K/AKT/ mTOR pathways to protect against diabetic nephropathy in mice (Yang et al., 2020)	None
6. PI3K/Akt	None	**Not Specified**: Na^+/H^+ exchanger-1 reduces podocyte injury caused by endoplasmic reticulum stress via autophagy activation (Feng et al., 2014)
7. PI3K	None	**Not Specified**: Tripterygium glycoside protects against puromycin amino nucleoside-induced podocyte injury by upregulating autophagy (Gong et al., 2018)
8. Notch-PTEN-PI3K/ Akt/mTOR	p66Shc regulates podocyte autophagy in high glucose environment through the Notch-PTEN-PI3K/Akt/mTOR pathway (Zheng et al., 2020).	None
9. Notch	None	**Not Specified**: Autophagy is involved in mouse kidney development and podocyte differentiation regulated by Notch signalling (Zhang et al., 2017)
10. PTEN	Repression of miR-217 protects against high glucose-induced podocyte injury and insulin resistance by restoring PTEN-mediated autophagy pathway (Sun et al., 2017)	None
11. AMPK	Astragaloside IV protects against podocyte injury via SERCA2-dependent ER stress reduction AMPK alpha-regulated autophagy induction in streptozotocin-induced diabetic nephropathy (Guo et al., 2017)	**Not Specified**: Ginsenoside Rg1 inhibits angiotensin II-induced podocyte autophagy via AMPK/mTOR/PI3K pathway (Mao et al., 2016)
12. AMPK-mTOR-ULK1	Mangiferin prevents diabetic nephropathy progression and protects podocyte function via autophagy in diabetic rat glomeruli (M. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; X. Wang et al., 2018)	None
13. Wnt/ ß-catenin	Alleviation by Mahuang Fuzi and Shenzhuo Decoction in High Glucose-Induced Podocyte Injury by Inhibiting the Activation of Wnt/ β-Catenin Signaling Pathway, Resulting in Activation of Podocyte Autophagy (Dai et al., 2020)	**Tubulo-interstitial fibrosis**: Novel inhibitors of the cellular renin-angiotensin system components, poricoic acids, target Smad3 phosphorylation and Wnt/β-catenin pathway against renal fibrosis (X. Wang et al., 2018; X.-Q. Wang et al., 2018; P. Wang et al., 2018; M. Wang et al., 2018)
14. HDAC4-STAT 1	HDAC4 blocks autophagy to trigger podocyte injury: non-epigenetic action in diabetic nephropathy (Wei and Dong, 2014)	None
15. NF-κB/ iNOS signaling pathway	Valproate attenuates the proteinuria, podocyte and renal injury by facilitating autophagy and inactivation of NF-κB/iNOS signaling in the diabetic rat (Khan et al., 2015)	None
16. Pim1-p21-mTOR	Hispidulin alleviates high-glucose-induced podocyte injury by regulating protective autophagy (Wu et al., 2018)	None
17. PGRN-CAMKK-AMPK	Progranulin alleviates podocyte injury via regulating CAMKK/AMPK-mediated autophagy under diabetic conditions (Zhou et al., 2019)	None

Wang et al., 2019; Gui and Dai, 2020). Regardless, the mTOR signaling pathways' over-activation or under-activation is not helping podocyte autophagy to improve the injuries as the autophagy activities level was reasonably believed to be at a moderate level to achieve optimum podocyte health. However, the moderate environment is yet to be determined.

10. Conclusion

Podocyte autophagy is an exciting and attractive therapeutic strategy for podocyte injury. The role of autophagy should be investigated in other podocyte-related diseases such as minimal change disease and focal segmental glomerulosclerosis because most podocyte autophagy studies were diabetic nephropathy oriented. Evidence shows the mTOR signaling pathway as crucial in regulating podocyte autophagy. Sirtuin-1 has a vital key role in regulating mTOR signaling, AMPK, autophagy activation, and various critical podocyte health-related pathways and metabolism; it has substantial investigation value to provide clearer podocyte injury pathogenesis. The critical association of podocyte injury in autophagy with Sirtuin-1 strongly suggests that podocyte injury could signify aging. The optimum dosage of the medication that targets the mTOR signaling pathway shall be further investigated. Besides, glucose level plays a vital role in determining podocyte health; calories restriction diet, which was believed to be elevated Sirtuin-1 level hence autophagy inducing, shall be investigated in podocyte autophagy to understand the practice further and potentially become the therapeutic approach. Multiple therapeutic strategies focus on podocyte, and podocyte autophagy could help understand the unclear pathogenesis of podocyte injury.

Ethical approval

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Authors' contributions

Yoong Mond Teh contributed to drafting the article, revising it critically for important content, **Siti Aisyah Mualif** reviewed the draft thoroughly, and **Soon Kun Lim** provided insightful comments, editing and approved the final version to be submitted. The authors contributed equally to all aspects of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors have no competing interests in this review.

Availability of data and materials

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