Advances regarding the mechanism of endoplasmic reticulum stress in diabetic kidney disease and pharmacological interventions (Review)

PAI ZHANG[1], YABIN CUI[2], CHUNYAN LIU[2], CHENGJI CUI[2], SHOULIN ZHANG[2], YUE ZHANG[1] and FAN LI[1]

[1]College of Traditional Chinese Medicine, Changchun University of Traditional Chinese Medicine, Changchun, Jilin 130117, P.R. China; [2]Department of Nephrology, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun, Jilin 130012, P.R. China

Received July 1, 2025; Accepted November 19, 2025

DOI: 10.3892/mmr.2025.13778

Abstract. As an important clinical microvascular complication in diabetic patients, diabetic kidney disease (DKD) exhibits cardinal symptoms such as edema, proteinuria and unceasing reduction of renal function, and endoplasmic reticulum (ER) stress (ERS) profoundly affects its pathological course. ERS is triggered by an imbalance of ER homeostasis, which activates the three classical pathways of the unfolded protein response, including the PKR-like ER kinase, inositol-requiring enzyme 1α and activating transcription factor 6 pathways, to restore homeostasis. However, sustained ERS leads to apoptosis and inflammatory responses that accelerate kidney injury. Podocyte injury, renal tubular dysfunction and extracellular matrix deposition induced by ERS collectively drive the progression of DKD. The present review offer novel perspectives on potential clinical interventions for patients with DKD.

Contents

1. Introduction
2. ER and ERS
3. Mechanisms of ERS in DKD
4. Pharmacological interventions for ERS to ameliorate DKD
5. Summary and outlook

Correspondence to: Dr Chengji Cui, Department of Nephrology, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, 1478 Workers' and Peasants' Avenue, Changchun, Jilin 130012, P.R. China
E-mail: chengjicui@126.com

Mr. Pai Zhang, College of Traditional Chinese Medicine, Changchun University of Traditional Chinese Medicine, 1035 Boshuo Road, Nanguan, Changchun, Jilin 130117, P.R. China
E-mail: 1446884429@qq.com

Key words: endoplasmic reticulum stress, diabetic kidney disease, autophagy pathway, apoptosis pathway, traditional Chinese medicine

1. Introduction

Diabetic kidney disease (DKD), recognized as a severe chronic microvascular complication of diabetes, has emerged as the leading cause of chronic kidney disease, surpassing chronic glomerulonephritis in incidence (1). Clinically, DKD is characterized by progressive proteinuria, edema and hypertension. Pathologically, it affects multiple renal structures, including glomeruli, tubules and microvessels, ultimately culminating in end-stage renal disease (2). DKD diagnosis is performed through biopsy; however, the filtration rate and albumin excretion rate enable initial identification (3). Notably, accumulating evidence has underscored pre-biopsy biomarker screening as important for curbing disease progression (4-6). Therefore, the identification of important therapeutic targets and molecular biomarkers in early-stage DKD holds notable clinical implications. Shifting away from established DKD research models, the present review identified endoplasmic reticulum (ER) stress (ERS) as a prospective therapeutic focus, including a systematic dissection of its role in disease progression and a thorough re-evaluation of herbal treatment approaches.

2. ER and ERS

The ER, a notable cellular organelle, orchestrates polypeptide folding and protein processing, functions that underpin its roles in calcium storage and regulation, lipid metabolism, and glucose homeostasis (7). ERS can be initiated by two distinct mechanisms: i) Endogenous factors such as cancer and neurodegenerative diseases, which disrupt cellular processes (8); and ii) exogenous stressors such as microenvironmental alterations and chemical insults that induce ERS responses (9). Microenvironmental perturbations and diverse stressors, including metabolic dysregulation, cancer-associated stress, drug toxicity and radiation, elicit the unfolded protein response (UPR) in the ER, a hallmark of ERS (10). ERS serves as one of the fundamental mechanisms underlying metabolic dysfunction across renal organs and tissues. As a trophic signaling hub in

metabolic disorders such as obesity and type 2 diabetes, the ER integrates inflammation, autophagy and apoptosis pathways, while modulating cytokine release (11). ERS induces dynamic changes in the expression of inositol-requiring enzyme 1α (IRE1α), PKR-like ER kinase (PERK), activating transcription factor (ATF)6 and glucose-regulated protein (GRP)78/binding immunoglobulin protein (BiP). Following energy metabolism fluctuations, these metabolism sensors (IRE1α, PERK and ATF6) dissociate from GRP78/BiP, triggering increased metabolic activity and protective responses such as autophagy (10). Failure to restore homeostasis via translational arrest and chaperone upregulation leads to the initiation of CHOP-dependent apoptosis, a determinant of stressed cell fate (2,12).

ERS-related protective responses activate three stress protein pathways. First, starting with the IRE1α-spliced X-box binding protein 1 (XBP1s) pathway, phosphorylated (p-)IRE1α dimerization catalyzes XBP1 mRNA splicing, generating nuclear-translocated XBP1 that activates ER-associated degradation (ERAD) or promotes mRNA decay during adaptive UPR. Concurrently, tumor necrosis factor receptor-associated factor 2 (TRAF2)-mediated JNK activation contributes to dual-function UPR signaling, balancing adaptive and apoptotic responses. Second, p-PERK dimerization in the PERK/eukaryotic initiation factor 2 (eIF2) pathway drives eIF2 phosphorylation, which enhances ATF4 translation to elicit adaptive UPR. During severe ERS, ATF4 induces CHOP expression, activating the apoptotic arm of the UPR. Third, in the ATF6 axis, chaperone dissociation of GRP78/BiP promotes Golgi trafficking, where proteolytic processing generates ATF6 p50. This nuclear effector drives the adaptive UPR via chaperone and foldase transcription or the apoptotic UPR via ERAD activation (13).

Collectively, the IRE1α/XBP1s, PERK/eIF2 and ATF6 pathways balance ERS-induced survival and apoptosis through UPR modulation: Moderate UPR restores homeostasis, while persistent ERS activates apoptotic signals such as caspase-12, leading to cell death (Fig. 1) (8-14).

3. Mechanisms of ERS in DKD

Effect of ERS on renal pathological organization in DKD. Preclinical and clinical investigations have consistently revealed ERS marker upregulation in renal tissues of patients with DKD and relevant animal models (15-17). Pathological changes in DKD tend to start early with thickening of the basement membrane, gradually spreading to glomeruli, microvessels and tubules. By contrast, changes in glomerular hyaluronan appear in the late stages of DKD (18,19). Persistent urinary protein abnormalities stem predominantly from four sources: i) Renal filtration barrier defects, including those affecting the basement membrane, podocytes and associated cells (20); ii) damage across renal tubular segments (21); iii) renal interstitial functional impairment (22); and iv) immune cell population dysregulation (23). In conclusion, renal histopathology reveals that ERS impacts DKD in three notable manners: Glomerular filtration membrane injury, renal tubular reabsorptive dysfunction and renal interstitial remodeling with immune cell dysregulation (24).

Effects on glomerular filtration membranes. Studies in DKD model mice have revealed that ERS contributes to glomerular injury, as demonstrated by increased GRP78/caspase-12 expression and reduced Bcl-2 levels (25-27) Notably, genetic deletion of ER protein 44 in db/db mice upregulated ATF6, XBP1 and CHOP, further indicating ERS involvement in glomerular filtration membrane injury (28). Composed of endothelial cells, basement membrane and podocytes, the glomerular filtration membrane is important for blood filtration. Damage to these components drives early DKD progression and proteinuria (27). Surface-bound GRP78 drives extracellular matrix (ECM) accumulation through PI3K/Akt activation, while the AMP-activated protein kinase (AMPK)/mTOR pathway promotes late-stage PERK/CHOP upregulation to enhance autophagy, and the IRE1/NF-κB pathway mediates ERS-induced inflammation in podocytes (29-31). Compared with individuals without DKD,renal biopsy analyses of patients with DKD have revealed increased GRP78 and caspase-12 expression in human glomerular podocytes (28,32). The elevation of ATF6 and PERK in human podocytes triggers lipid metabolism disorders and inflammation, which are suppressed by JNK-mediated insulin activity (33). Mechanistically, the high glucose-induced elevation of PERK, ATF6 and IRE1α in rat podocytes is linked to protein arginine methyltransferase 1 (PRMT1) (34). Concurrently, the activation of XBP1s in glomerular mesangial cells triggers histone-lysine N-methyltransferase SETD7-mediated histone methylation, leading to the upregulation of DKD-associated monocyte chemoattractant protein 1 (35,36). These findings indicate that ERS influences the expression of UPR-induced transcription factors, which in turn contribute to fibrotic and inflammatory pathological changes, thereby regulating the balance between adaptive and apoptotic states in podocytes.

The depletion of terminally differentiated podocytes, which form the glomerular filtration barrier, is characteristic of chronic kidney diseases, including DKD. Numerous studies have revealed an association between ERS and podocyte injury in DKD, as ERS markers are upregulated in human and murine podocytes exposed to high glucose; this process is induced by the dysregulation of hyperglycemia, lipid metabolism and insulin signaling (37,38). In mouse podocytes, the accumulation of advanced glycation end-products (AGEs) and high-glucose exposure activate GRP78, CHOP and caspase-12 through distinct pathways, ultimately driving podocyte apoptotic processes (39). PERK-eIF2α activation induces CHOP-mediated podocyte apoptosis, and PERK phosphorylation triggers a CHOP-reticulon 1A (RTN1A) positive feedback loop for synergistic apoptotic enhancement (40). Dysfunction in the insulin PI3K/Akt pathway may underlie GRP78/CHOP-mediated ERS and podocyte apoptosis. Reduced activity of PTEN, a downstream inhibitory regulator, exacerbates ERS, while MEK/ERK signaling counteracts this pathological effect (41). The GRP78-mediated modulation of the MEK kinase 1 (MEKK1)/JNK signaling cascade induces podocyte apoptosis through MEKK1-dependent Ser280 phosphorylation (42).

The ERAD pathway is a specialized mechanism within the ER that employs the ubiquitin-proteasome system to degrade misfolded or aberrantly modified proteins, serving an important role in eliminating these faulty proteins from cells (43). Derlin-2 expression is elevated in podocytes from patients with DKD biopsies, triggering ERAD to sustain the cellular

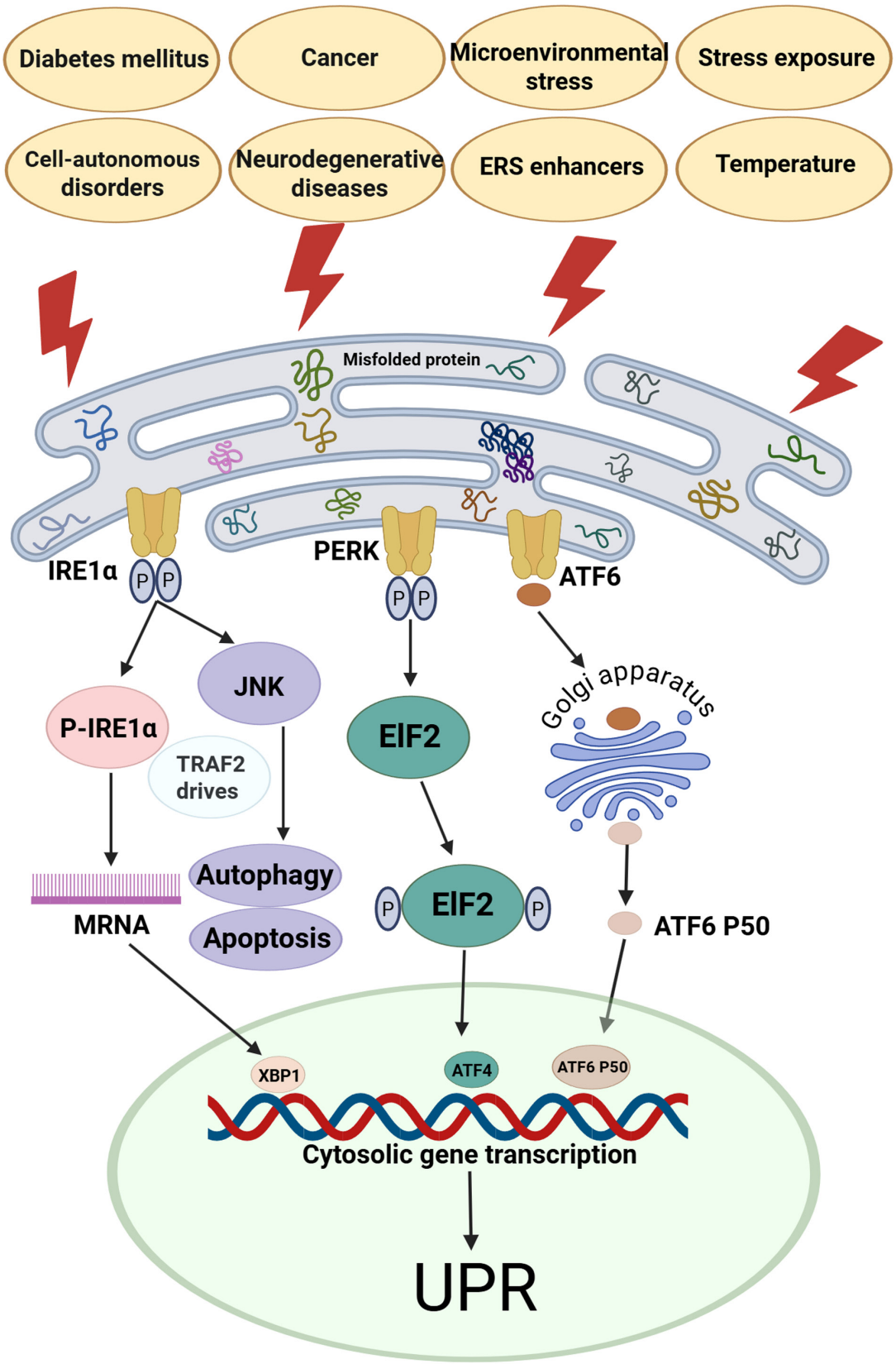

Figure 1. ERS mechanisms. Stressors or disease-causing factors trigger the accumulation of misfolded proteins within the ER. This activates transcription of nuclear genes via IRE1α, PERK, and ATF6-initiating the UPR to counteract ERS. ATF, activating transcription factor; eIF2, eukaryotic initiation factor 2; ERS, endoplasmic reticulum stress; IRE1α, inositol-requiring enzyme 1α; P-, phosphorylated; PERK, PKR-like ER kinase; TRAF2, tumor necrosis factor receptor-associated factor 2; UPR, unfolded protein response; XBP1, X-box binding protein 1.

balance (44,45). Similarly, ERS serves an important role in balancing podocyte survival and apoptosis through autophagy, given that compared with DKD, podocytes inherently exhibit a higher basal autophagic activity (46) High glucose levels

increase eIF2α, CHOP, caspase-3/12, GRP78, ATF6 and PERK levels in podocytes through the inhibition of autophagy, whereas sarcoendoplasmic reticulum calcium-ATPase (SERCA)2b-mediated ERS attenuation is associated with AMPKα-induced autophagy (46,47). The intercellular transmission of ERS signals, coupled with podocyte-intraglomerular cell interactions, suppresses ERAD through derlin-2 downregulation, inducing podocyte apoptosis in DKD (48). Additional evidence has shown that GRP78/CHOP activation in endothelial cells drives epithelial-mesenchymal transition (EMT) (49), implying a potential role for glomerular endothelial cells in DKD pathogenesis, although the underlying mechanisms remain ambiguous.

UPR-activated transcription factors drive fibrosis and inflammation in glomerular podocytes at the early stage of diabetic kidney injury. Three ERS pathways collectively influence disease progression, including: i) Regulation of podocyte apoptosis through the PI3K/Akt, PTEN and MEK/ERK signaling pathways; ii) maintenance of cellular homeostasis through the activation of ERAD; and iii) modulation of podocyte autophagy via AMPK (50,51). In addition, key ERS factors also contribute to the DKD process by affecting intraglomerular mesangial cells and podocytes (52).

Effects on renal tubules and reabsorption. Composed of Henle's loop, proximal and distal tubules and collecting ducts, renal tubules reabsorb small molecules and lipids, with their epithelium serving as a key DKD-targeted cell type susceptible to injury (53,54). Extensive research has established that ERS contributes to DKD-related renal tubular injury, as evidenced by the upregulation of differential ERS markers in human biopsies, animal tissues and *in vitro* models (15,55-57). This process is driven by the AGE/receptor for AGEs (RAGE) axis, PRMT1 and histone H4 deacetylation (15,58,59), while it is alleviated by calbindin-D28k, transmembrane BAX inhibitor motif-containing protein 6, sestrin 2 and dapagliflozin (60,61). Renal tubular ERS markers (notably including GRP78) can modulate the autophagic processes and drive inflammatory responses by regulating mitochondrial function and reactive oxygen species (ROS) generation (62,63). Saturated fatty acid-associated factors, such as carbohydrate-responsive element-binding protein, cholesterol and palmitic acid (PA), promote ERS marker upregulation in renal tubular cells, causing lipid accumulation and apoptotic cell death (64,65). Therefore, the comprehensive role of ERS in renal tubules is closely intertwined with autophagy, inflammation and lipid peroxidation.

In the renal tubular system, the proximal tubule reabsorbs glucose, amino acids, HCO_3^-, Cl^- and Na^+, while secreting H^+. By contrast, the distal tubule and collecting ducts mainly mediate Na^+ and water reabsorption alongside K^+ secretion. The proximal and distal tubule of the kidney functional distinction partially explain the structural variations in ERS signaling, with GRP78-governed ATF4/p16/p21 axes promoting AGE/RAGE-driven premature cellular senescence in mouse proximal tubular cells (66). GRP78 and protein disulfide isomerase exhibit distinct regulatory dynamics between proximal and distal tubules, varying across early and late stages of diabetes-induced ERS. Early-stage diabetes triggers PERK activation, while late-stage disease promotes ATF6 activation in renal tubules, resulting in stage-dependent differential ERS responses between proximal and distal segments in DKD (67).

Mechanism of the effect of ERS on DKD-related pathways. ERS notably regulates renal cell function by suppressing inflammation, inhibiting abnormal proliferation and fibrosis, and combating oxidative damage through the precise modulation of DKD pathways, including the PERK/CHOP and caspase-12 pathways (53,68,69). The mechanistic exploration of ERS in DKD pathway regulation sheds light on DKD pathogenesis and facilitates the identification of novel therapeutic targets (Fig. 2).

PERK/CHOP signaling pathway. The PERK/CHOP pathway regulates ERS and contributes to DKD. The core aspects of the PERK/CHOP pathway comprise the following mechanisms: Initially, ERS is triggered when high glucose levels, oxidative stress and inflammation lead to misfolded protein accumulation in the ER, prompting GRP78/BiP dissociation from PERK and subsequent kinase activation (70). Subsequently, the PERK/eIF2α/ATF4 axis is activated; PERK phosphorylates eIF2α, globally inhibiting translation to reduce ERS burden. Simultaneously, p-eIF2α selectively promotes ATF4 translation, leading to CHOP expression (71) Finally, CHOP-mediated apoptotic signaling occurs (72) CHOP, a transcription factor, upregulates pro-apoptotic genes, such as Bcl-2-interacting mediator of cell death (Bim), p53 upregulated modulator of apoptosis and Bax, and downregulates Bcl-2, ultimately inducing apoptosis (73).

The PERK/CHOP pathway mediates DKD podocyte injury through high glucose-activated PERK/eIF2α/ATF4/CHOP signaling, inducing apoptosis, foot process effacement, proteinuria and glomerulosclerosis, which are exacerbated by pathway hyperactivation (74). The PERK/CHOP pathway drives mesangial cell proliferation, fibrosis and ECM deposition, mediated via pathways such as the TGF-β1/connective tissue growth factor pathway, in DKD, additionally serving as a central mediator of proteinuria and glomerulosclerosis (75). In DKD, the CHOP pathway mediates renal tubular injury. High glucose-induced ERS promotes tubular apoptosis through the PERK/CHOP axis and activates pro-inflammatory cytokines such as IL-6 and TNF-α to exacerbate renal interstitial inflammation (68). Renal tubulointerstitial fibrosis is an important step in the progression of DKD to end-stage renal disease. Sustained PERK activation enhances ATF4 transcription to upregulate CHOP, which downregulates Bcl-2 and promotes apoptosis through ROS production and ATP depletion (76). Concurrently, CHOP triggers growth arrest and DNA-damage-inducible 34 activation to facilitate eIF2α dephosphorylation, a negative feedback mechanism that restores transiently-arrested protein synthesis in the PERK pathway (77).

The PERK/CHOP regulatory axis balances adaptive and apoptotic responses to ERS through integrated positive and negative feedback mechanisms (78). PERK and its downstream effector CHOP exhibit segment-specific regulation across different regions of the renal tubule. Renal tubular cells secrete CHOP-induced fibronectin, driving mesenchymal fibrosis in DKD, a process implying that PERK/CHOP signaling controls the synthesis and release of ECM proteins in these cells (79). The RTN1A/PERK/CHOP positive feedback loop exacerbates ERS-induced podocyte apoptosis, highlighting the dual role of the PERK/CHOP

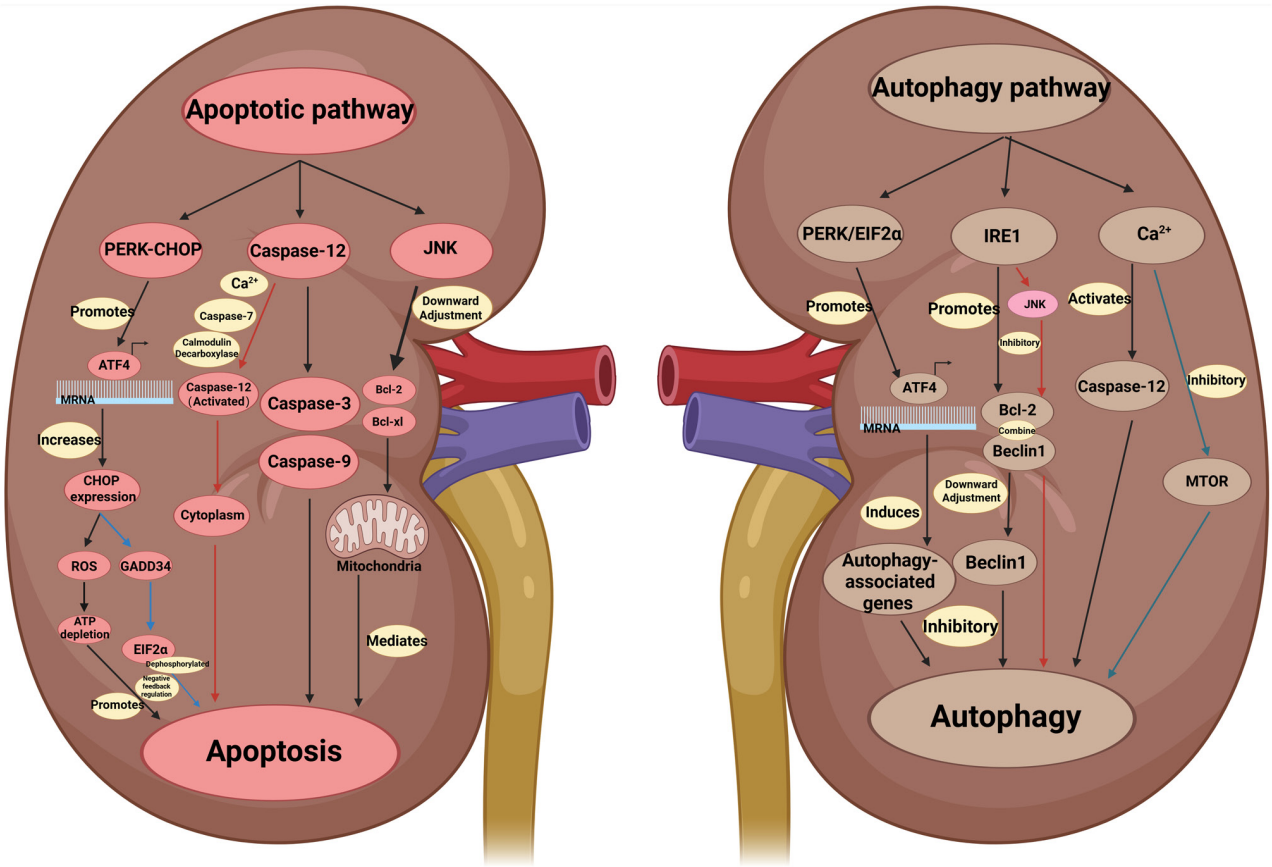

Figure 2. Renal endoplasmic reticulum stress pathway in diabetic kidney disease. ATF, activating transcription factor; eIF2α, eukaryotic initiation factor 2α; GADD34, growth arrest and DNA-damage-inducible 34; IRE1, inositol-requiring enzyme 1; PERK, PKR-like ER kinase; ROS, reactive oxygen species. The apoptosis pathway induces cell death via the Perk-CHOP, Caspase-12, and JNK branches; on the right is the autophagy pathway, which regulates cellular autophagy via the Perk/eIF2α, IRE1, and Ca^{2+} branches. Different line colours carry no distinct meaning; they are solely intended to enable readers to discern the status of the passageway more clearly.

pathway in maintaining ERS balance and promoting pathological cell death (80).

Caspase-12 signaling pathway. Caspase-12 acts as a key executor of apoptotic signaling, with its activation closely linked to ERS-induced cell death (81). Upon ER misfolded protein accumulation, for example, due to high blood glucose levels, oxidative stress or calcium dyshomeostasis, GRP78/BiP dissociates from ER membrane sensors such as PERK, IRE1 and ATF6 to bind misfolded proteins, triggering the activation of caspase-12 as a downstream responder to ERS signals (82,83). In non-stressed cells, GRP78 associates with pro-caspase-12 to suppress its activity. During ERS, GRP78 dissociation exposes the active site for proteolytic processing by upstream enzymes, including IRE1α and calpain, generating active caspase-12 (p35/p12 subunits) that cleaves caspase-3 to initiate apoptosis (84,85).

In patients with DKD, high glucose induces ERS, which activates caspase-12 and promotes the apoptosis of podocytes and tubular epithelial cells, accelerating proteinuria and renal interstitial fibrosis (86). In the DKD mouse model, CHOP overexpression upregulates caspase-12 to promote apoptosis, whereas caspase-12 inhibition attenuates high glucose-induced renal cell injury (87). ERS also induces calcium dyshomeostasis and mitochondrial calcium overload, indirectly activating the mitochondrial apoptotic pathway via the ER-mitochondrial axis (88). ER-released Ca^{2+} activates peripheral calpains, prompting their translocation to the cytoplasm. Calpain activation results in translocation to the ER outer membrane, triggering caspase-7 translocation and activation (87,89). Both factors process pro-caspase-12 into an active form that translocates to the cytoplasm, activates caspase-9 and -3 through the cytochrome *c* (CytC)-independent pathway and induces apoptosis (90). In addition, the IRE1α-TRAF2 complex activates caspase-12 through calmodulin decarboxylase, thereby initiating the caspase-mediated apoptotic pathway (91). Caspase-12-dependent signaling contributes to severe podocyte and tubular cell injury in DKD. Therapeutic targeting of this pathway mitigates ERS-mediated apoptosis, slowing DKD progression (92,93). Therefore, caspase-12 signaling is important for ERS-induced apoptosis. Despite genetic polymorphisms limiting its activity in humans, caspase-12 retains diagnostic and therapeutic value for ERS (94). Targeting the caspase-12 pathway may provide novel targets for the treatment of DKD.

JNK signaling pathway. JNK, originally identified in its capacity to phosphorylate the amino terminus of the transcription factor c-Jun (95), is also referred to as stress-activated protein kinase. Extracellular stimuli, such as stress signals, cytokines and growth factors, activate JNK, with the activation relying on the cellular microenvironment. JNK inhibition

reduces podocyte apoptosis and matrix deposition, and combination with PERK/CHOP inhibitors may enhance therapeutic efficacy (96,97). As an important branch of the MAPK cascade, the JNK pathway orchestrates multiple physiological processes (98). During ERS, activated IRE1α engages TRAF2 to trigger apoptosis signal-regulating kinase 1 (ASK1) activation, generating a trimeric complex that sequentially activates JNK, CHOP and pro-apoptotic factors such as BH3-interacting domain death agonist and Bim, a process that suppresses anti-apoptotic genes, including Bcl-2 and Bcl-xL, and initiates mitochondrial apoptotic pathways (99-102). In addition, phosphorylation at the MEKK1 Ser280 residue activates the JNK signaling pathway, thereby promoting ERS-induced podocyte apoptosis (38,103). High glucose triggers JNK activation in renal cells, inducing apoptosis and fibrosis. These processes are alleviated by JNK inhibitors, which reduce CHOP/caspase-3-dependent apoptosis in ERS-impaired podocytes to mitigate DKD-related renal injury (33). Acting as a central stress response hub, the JNK pathway integrates external stimuli with intracellular signaling to govern inflammation and disease progression, with functional complexity emerging from stimulus subtype specificity, stimulus intensity and cellular context (104,105). Despite the challenges of drug development targeting JNK (such as poor specificity and high concentrations required to inhibit c-Jun phosphorylation), its potential applications in areas such as DKD and neurodegenerative diseases make it a promising therapeutic target (106-109).

PERK/eIF2α signaling pathway. The PERK/eIF2α signaling axis, a key branch of ERS signaling, maintains intracellular proteostasis by regulating protein synthesis and gene expression (110). Following the accumulation of misfolded or unfolded proteins in the ER, this pathway is activated to promote either stress adaptation or apoptosis through global translation inhibition and induction of stress-responsive genes (111). The key component of this pathway, PERK, is an ER transmembrane protein with a kinase domain on the cytoplasmic side, while only its stress-sensing domain is present within the lumen of the ER) (112). In unstressed cells, PERK stays inactive by associating with the ER chaperone BiP that has dissociated from GRP78 (113). By contrast, eIF2α is a key factor in the initiation of protein translation, and phosphorylation at its Ser51 site is a central event in the activation of the PERK/eIF2α pathway. This pathway coordinates cellular homeostasis through multifaceted mechanisms, such as translation repression for energy conservation, amino acid transporter induction for survival and proteostasis regulation through reduced synthesis, enhanced folding through mechanisms such as BiP upregulation, or misfolded protein degradation, for example, via ERAD (72).

The PERK/eIF2α branch of the UPR signaling pathway induces autophagy-associated gene expression through the transcriptional regulation of ATF4, thereby promoting the transcription of autophagy-associated genes (114). Downstream genetic effectors include beclin-1, which mediates autophagosome biogenesis and maturation, the ubiquitin-like system and transport receptor genes such as p62 and next to BRCA1 gene 1 protein (115). These transport receptor genes undergo selective degradation via ubiquitinated cargoes. Vaspin, a serine protease inhibitor, suppresses p62 aggregation by forming complexes with GRP78 and heat shock 70 kDa protein 1L (116,117). This mechanism protects organelles from metabolic stress-induced damage through endocytosis-driven autophagy facilitation, maintaining cellular homeostasis under stress (118). The PERK/eIF2α pathway is a 'regulatory hub' for ERS through precise regulation at the translational level and reprogramming of gene expression to maintain a balance between cell adaptation and death (119).

IRE1 signaling pathway. The IRE1 signaling cascade acts as a core ERS effector, governing adaptive or apoptotic cell fates predominantly by modulating mRNA splicing and gene transcription (120,121). The pathway is highly evolutionarily conserved from yeast to mammals and is a key mechanism for maintaining ER protein homeostasis. The IRE1/XBP1 axis preserves cellular homeostasis during acute stress by boosting protein folding, degradation and transport, while governing the activity of secretory cells, such as plasma and pancreatic β-cells, for efficient antibody and insulin production (122,123). Conversely, chronic ERS in pancreatic β-cells engages the IRE1/JNK pathway, causing β-cell death and diminishing insulin release (124,125).

The IRE1 pathway engages in crosstalk with the other two UPR arms: The PERK/eIF2α and ATF6 pathways. The PERK branch suppresses global translation through eIF2α phosphorylation to reduce protein synthesis load, while ATF6 activates BiP, ERAD and other chaperone genes through nuclear translocation (126,127). The IRE1 pathway promotes protein folding and degradation through XBP1 splicing, concurrently regulating cell fate through JNK activation and the regulated IRE1-dependent decay (RIDD) pathway (111,128). Collectively, these three pathways dictate cellular outcomes during stress, promoting survival under acute stress conditions and triggering apoptosis under prolonged or severe stress (129). In the ERS state, IRE1/XBP1 signaling directly promotes the expression of Bcl-2, increases the binding of Bcl-2 to beclin-1 and downregulates the activity of beclin-1, thus inhibiting autophagy (2). During early ERS, IRE1α assembles with TRAF2 and ASK1 to activate the downstream JNK signaling cascade, which phosphorylates Bcl-2 to promote its dissociation from beclin-1 and encourages subsequent autophagy initiation (92,93). In addition, XBP1, a downstream effector of IRE1α, promotes autophagy through beclin-1 activation (43). Blocking the kinase and RNase activities of IRE1α has been shown to intensify PA-induced cytotoxicity in renal tubular cells, indicating that IRE1α protects against PA-mediated kidney injury in DKD (130). The IRE1 signaling pathway is a 'multifunctional hub' of the ERS response, responsible for shutting down and splicing of the mRNA that encodes secretory proteins in a process called regulated RIDD to decrease ER protein load and spliced mRNA of XBP1 that activated the transcription of ER hemostatic factors as chaperone and endoplasmic reticulum-associated degradation components that degraded unfolded and misfolded proteins in an attempt to resolve endoplasmic reticulum stress; if this stress was unresolved, XBP1 upregulated the expression of JNK that activated podocytes, tubular apoptosis, and inflammation (131), and its aberrant activation is closely associated with a variety of diseases(such as Sepsis, DKD, breast cancer et.) (131-133).

Calcium channels. Calcium channels are the core molecular machinery regulating the intracellular flow of

Ca^{2+} across the membrane (129). DKD marked by glomerular mesangial matrix dilation, basement membrane thickening, tubulointerstitial fibrosis and renal unit loss involves Ca^{2+} as a key signaling molecule; calcium homeostatic imbalance markedly drives disease pathogenesis (134,135). The ER functions as a primary intracellular Ca^{2+} store, regulating calcium homeostasis (136). During stress, Ca^{2+} influx sustains cellular homeostasis by activating the MAPK pathway, thereby promoting intracellular protein folding (137,138). Excessive release of Ca^{2+} into the cytoplasm initiates ERS, thereby activating caspase-12-dependent autophagy (139). The transient ER surface calcium concentration is a key signal that determines the activation of ER autophagy (140). In addition, ATP and other Ca^{2+} mobilizers antagonize mTOR-mediated autophagy inhibition via Ca^{2+}-dependent pathways, thereby promoting beclin-1- or autophagy-related gene 7-dependent autophagosome biogenesis (141,142). In addition, Ca^{2+} can activate both protein kinase C (PKC) and death-associated protein kinase (DAPK). PKC induces autophagy through an mTOR-independent pathway, whereas DAPK promotes beclin-1 phosphorylation and disrupts the beclin-1/Bcl-2 complex, thereby activating autophagy (143,144). The ERS-associated inhibition of PERK and IRE1 protects against kidney injury, mitochondrial dysfunction and renal cell apoptosis by maintaining Ca^{2+} homeostasis, which blocks cytosolic release of CytC and apoptosis-inducing factor, inhibits caspase-9 activation and restores mitochondrial membrane integrity, thereby suppressing pathological cell death pathways (145). Calcium channels are 'signaling hubs' for cellular functions, and their diversity and sophisticated regulatory mechanisms serve key roles in physiological and pathological processes (129,134).

4. Pharmacological interventions for ERS to ameliorate DKD

ERS-based modulation of DKD by traditional Chinese medicine (TCM)

Astragaloside (AS). As the major bioactive tetracyclic triterpenoid saponin of *Astragalus membranaceus*, AS exhibits extensive pharmacological activity, including immune enhancement. AS-II promotes the concanavalin A-induced proliferation of murine splenocytes, as well as mixed lymphocyte reactions and primary splenocyte proliferation induced by alloantigen or anti-CD3. AS-II increases the secretion of IL-2 and IFN-γ, upregulates IFN-γ and T-bet mRNA expression in splenocytes, and promotes CD25/CD69 expression in T-cell receptor-stimulated primary $CD4^+$ T cells (146,147) In addition, it facilitates CD45-mediated lymphocyte-specific protein tyrosine kinase dephosphorylation of Tyr505 in primary T cells, enhancing their activation by modulating CD45 protein tyrosine phosphatase activity (147). AS-IV can further enhance both cellular and humoral immune responses (148). *In vivo* studies (146-148) using male mice to examine the effects of ASs on immune-response cytokines have revealed that AS-VII promotes the secretion of T helper (Th)1 cytokines, including IL-2 and IFN-γ, while inhibiting the production of Th2 cytokines such as IL-4. Immunohistochemical analyses of spleen and lymph node tissues from experimental mice revealed induced expression of CD25 and CD69 surface receptors, confirming Th1 cytokine activation (149).

Research on AS modulation of DKD through ERS intervention has primarily focused on DKD rodent models and meta-analyses (26,47,150-152). In DKD rat models (47,150) induced by a high-fat diet combined with streptozotocin (STZ), intragastric administration of AS-IV effectively mitigated apoptosis in renal tubular epithelial cells. This protective effect involved two primary mechanisms: i) Downregulation of ERS-associated proteins, including p-PERK, ATF4 and CHOP; and ii) restoration of the homeostatic balance between the pro-apoptotic protein Bax and anti-apoptotic protein Bcl-2 (47,150). In STZ-induced DKD rats (26,151,152), AS-IV alleviated ERS-driven podocyte apoptosis through three coordinated pathways: i) Suppression of the PERK/ATF4/CHOP signaling cascade; ii) inhibition of oxysterol-binding protein-related protein 150 (ORP150) and GRP78 expression; and iii) reduction of phosphorylation levels of PERK, eIF2α and JNK (26,151). Similarly, in db/db mice and podocytes exposed to high glucose or PA, two important pathological stimuli in DKD, AS-IV mitigated ERS and reduced podocyte apoptosis by restoring SERCA2 expression and activity (152). Collectively, AS-IV exerted anti-ERS effects through a multi-targeted strategy: Blocking three important ERS signaling pathways, including the PERK/ATF4/CHOP, PERK/eIF2α and IRE1/JNK pathways, increasing SERCA2 expression and decreasing ORP150 and GRP78 expression (Table I) (26,151,152).

Regarding clinical efficacy, numerous studies (153-158) have supported the therapeutic value of Radix Astragali (RA) in DKD: A meta-analysis encompassing 21 randomized controlled trials and four controlled trials involving 1,804 subjects demonstrated that intravenous RA injection has a superior efficacy compared with that of angiotensin-converting enzyme inhibitor/angiotensin II type 1 receptor blocker (ACEI/ARB) treatment alone, notably reducing blood urea nitrogen, serum creatinine (Scr), creatinine clearance and urinary protein levels, while elevating serum albumin (ALB) levels (153-155). Second, broad population studies: A previous meta-analysis including 66 randomized controlled trials and 4,785 patients without renal function stage restrictions indicated that combination of various RA preparations, including tablets, granules, decoctions, extracts and injections, with standard ACEI/ARB therapy reduced proteinuria and Scr levels (156). Third, long-term prognosis study: A 5-year retrospective cohort study involving 6,648 pre-dialysis patients with DKD revealed a reduction in all-cause mortality among RA users compared with other Chinese herbal medicine users (157). At present, there is no consensus on an optimal regimen regarding RA formulation and dosage. Among intravenous formulations, RA injections (20-50 ml; once daily) are most commonly administered. Oral preparations, including RA tablets (2.2 g; twice daily), granules (4-15 g; once or twice daily) and *Astragalus* injections (250 mg; once daily) are also frequently employed (158). Further research is warranted to evaluate the comparative efficacy of different administration routes.

Huangkui. Huangkui is a TCM approved by the Chinese National FDA for nephritis treatment. Its therapeutic effect on DKD is primarily mediated by active ingredients, particularly flavonoid derivatives such as quercetin glycosides and kaempferol glycosides. These components intervene in the core pathological mechanisms of DKD, including ERS, oxidative

Table I. Mechanism of action of Chinese medicine in modulating ERS in DKD.

First author/s, year	Chinese medicine	Model system	Modeling method	Pharmacological effect	Targets	(Refs.)
Guo *et al*, 2017	AS-IV	C57BL/6J mouse	STZ	Protected podocytes and renal function, while ameliorating glomerular hypertrophy, mesangial hyperplasia, glomerulosclerosis and proteinuria.	Regulated AMPK/PI3K/Akt/mTOR signaling, inhibited ERS and promoted autophagy.	(47)
		Mouse podocytes	HG	Protected podocytes.		
Ju *et al*, 2019	AS-IV	Male SD rat	STZ	Protected TECs from apoptosis and preserved renal function, while alleviating epithelial cell edema, GBM thickening, ECM deposition and proteinuria.	Modulated caspase and Bcl-2 protein families and inhibited ERS.	(150)
Guo *et al*, 2016	AS-IV	db/db mice	/	Protected podocytes and renal function, ameliorated glomerular hypertrophy and mesangial hyperplasia, reduced proteinuria, and normalized glucose tolerance and insulin sensitivity while alleviating hypertension.	Modulated caspase and Bcl-2 protein families and inhibited ERS.	(26)
		Mouse podocytes	Palmitic acid	Protected podocytes.		
Chen *et al*, 2014	AS-IV	Male SD rats	STZ	Ameliorated mesangial hyperplasia, protected podocytes and lessened proteinuria.	Modulated Bcl-2 protein family, downregulated the PERK/ATF4/CHOP pathway and inhibited ERS.	(151)
Wang *et al*, 2015	AS-IV	Male SD rats	STZ	Ameliorated mesangial hyperplasia and reduced ECM deposition.	Modulated caspase protein family and inhibited ERS.	(152)
		Mouse podocytes	Tunicamycin	Protected podocytes.		
Ge *et al*, 2016	Huangkui capsule	Male SD rats	STZ	Enhanced PPARα/γ transcriptional activity, reduced serum triglycerides, cholesterol, renal fat and renal inflammatory gene expression, alleviated ERS, inhibited JNK activation in DKD rat livers and kidneys, and improved renal injury.	Improved lipid metabolic disorders by activating PPARα/γ and attenuating ERS.	(33)
Lee *et al*, 2016	Oleanolic acid	Male OLETF rats	/	Administration reduced the ALB-creatinine ratio in DKD mice. The increase in ERS markers, such as p-PERK, p-inositol-requiring enzyme 2α, ATF6, binding immunoglobulin protein and CHOP, was markedly diminished following oleanolic acid treatment, which also reduced reactive oxygen species and nuclear factor erythroid 2-related factor 2 levels in glomerular mesangial cells. TGF-β/Smad2/3 signaling and α-smooth muscle actin were reduced.	Repaired renal damage, reduced albuminuria, suppressed diabetes-induced renal fibrosis, suppressed ERS and apoptosis, ameliorated oxidative stress, and reduced ERS-induced TGF-β/Smad2/3 signaling.	(178)

Table I. Continued.

First author/s, year	Chinese medicine	Model system	Modeling method	Pharmacological effect	Targets	(Refs.)
Liu *et al*, 2022	Oleanolic acid	Male SD rats	STZ	Elevated expression levels of renal proteins, p-AMPK/AMPK and PGC-1α; reduced expression of CD68, collagen- IV, TLR4, NF-κB and TGF-β1.	AMPK/PGC-1α and TLR4/NF-κB signaling pathways improved lipid metabolism and inflammation.	(177)
Suganya *et al*, 2018	Quercetin	Male albino Wistar rats	STZ	Reduced blood glucose levels while promoting the restoration of normal islet morphology, cell density and size. Decreased immunoreactivity of CHOP, an ERS marker, reduced ET-1-positive cells, accelerated recovery of pancreatic endothelial β-cells, reduced lipid peroxidation reactions and enhanced pro-antioxidant enzyme activity, including superoxide dismutase, catalase and glutamic-pyruvic transaminase activity.	Lowered blood sugar and repaired islets, reduced cellular stress and damage, and improved oxidative status.	(189)
Zhang *et al*, 2019	Arctigenin	db/db mice	/	Reduced UACR and 24-h UAER, and improved glycemic control and body weight. Suppressed increased caspase-12 expression, with concurrent inhibition of HG-induced upregulation of GRP78, CHOP and caspase-12 in HK2 cells.	Downregulated expression levels of GRP78 and CHOP in the renal cortex, inhibiting diabetes-mediated ERS activation. Improved baseline indicators and reduced apoptosis.	(56)

SD, Sprague-Dawley; AS-IV, astragaloside-IV; STZ, streptozotocin; HG, high glucose; ECM, extracellular matrix; ERS, endoplasmic reticulum stress; PERK, PKR-like ER kinase; ATF, activating transcription factor; PPAR, peroxisome proliferator-activated receptor; DKD, diabetic kidney disease; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; TLR4, Toll-like receptor 4; GRP78, glucose-regulated protein 78; p-, phosphorylated; TEC, tubular Epithelial Cells. GBM: Glomerular Basement Membrane. The GBM constitutes a vital component of the glomerular filtration barrier, situated between endothelial cells and podocytes, and functions as a molecular sieve. In diabetic nephropathy, thickening of the GBM frequently occurs, representing a characteristic early pathological change in the disease. OLETF: Otsuka Long-Evans Tokushima Fatty rats. A spontaneous type 2 diabetes animal model, frequently employed in studies investigating the pathological mechanisms and pharmacological interventions for diabetic nephropathy due to its naturally occurring obesity, hyperglycemia, and renal damage. ET-1: Endothelin-1. It is a peptide with potent vasoconstrictive effects, also involved in inflammatory responses and apoptosis regulation; elevated ET-1 expression in diabetic nephropathy exacerbates renal microvascular damage. UACR: Urinary Albumin-Creatinine Ratio. It serves as a key indicator for assessing urinary albumin excretion, calculated by simultaneously measuring albumin and creatinine concentrations in urine. This ratio is employed for the early screening and disease monitoring of diabetic nephropathy. UAER: Urinary Albumin Excretion Rate This represents the rate of albumin excretion in urine per unit time, commonly measured over a 24-h period (24-h UAER). It serves as one of the core indicators reflecting impairment of glomerular filtration function. ALB: Albumin. This plasma protein, primarily synthesised by the liver, functions to maintain plasma osmotic pressure and transport nutrients. In diabetic nephropathy, damage to the glomerular filtration barrier may result in urinary loss of ALB (proteinuria) or reduced serum ALB levels. AMPK: AMP-activated Protein Kinase. It is a key kinase regulating cellular energy metabolism, involved in autophagy and lipid metabolism regulation.

stress, the inflammatory response, apoptosis and renal interstitial fibrosis, thereby forming a multi-dimensional protective network (159-164). Huangkui (158,159) can restore ER protein homeostasis: The upregulation of molecular chaperone proteins GRP78 and GRP94 promotes correct protein folding, enhances ERAD of misfolded proteins, and attenuates ER loading (165).

For DKD, Wu *et al* (166) reported that Huangkui capsules could attenuate early glomerular pathological alterations by inhibiting the Akt/mTOR/70 kDa ribosomal protein S6 kinase signaling pathway. Regarding renal tubular protection, Han *et al* (167) confirmed that Huangkui capsules alleviated renal tubular EMT by inhibiting the activation of the NOD-, LRR- and pyrin domain-containing protein 3 inflammasome and the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway. In addition, Zhu *et al* (168) indicated that Huangkui capsules attenuated DKD by inducing mitophagy

through the stimulator of IFN genes 1/PTEN-induced kinase 1 signaling pathway in renal tubular cells. From a microecological perspective, Shi *et al* (169) demonstrated that *Abelmoschus manihot* improves levels of circulating DKD-related metabolites by modulating gut microbiota in non-obese diabetic mice. In terms of clinical research, Zhang *et al* (170) conducted a prospective, multicenter, randomized controlled trial that confirmed the efficacy and safety of Huangkui capsules in treating primary glomerular disease.

In summary, Huangkui capsules exert protective effects against both glomerular and tubular injuries by regulating multiple mechanisms, including signal transduction pathways, nuclear receptor activities, inflammatory responses, mitochondrial function and gut microbiota, thus providing novel drugs and approaches for the treatment of kidney disease. Ge *et al* (33) demonstrated that Huangkui ameliorated renal damage by attenuating ERS in DKD model rats. Through its multi-targeted mechanism, encompassing ERS inhibition, and antioxidant, anti-inflammatory, antifibrotic and podocyte-protective effects, Huangkui mediates multi-level regulatory effects in DKD progression, with notable promise in proteinuria control and delaying renal interstitial fibrosis (33,171,172). The natural medicinal properties of Huangkui provide a novel strategy for early intervention in DKD, and the combination of Chinese and Western medicine, which is particularly suitable for the long-term management of patients with mild to moderate proteinuria (170)

Oleic acid (OA) and oleanolic acid (OlaA). OA, as a monounsaturated fatty acid, serves an important role in the development of DKD, and its involvement in kidney injury through the regulation of ERS has attracted increasing attention. OA is naturally found in fruits and vegetables. Podocytes, early DKD targets, exhibit dose-dependent OA responses: Low-dose OA mitigates injury, while high-dose OA triggers ERS-PERK-mediated apoptosis, impairing podocyte protein synthesis and filtration barrier integrity. Mechanistically, CHOP upregulation inhibits Bcl-2, activating mitochondrial apoptotic cascades, such as the caspase-3-mediated cascade (173,174). OA also exerts context-dependent effects on tubular fibrosis: Low ERS inhibits fibrosis, while OA-induced ERS activates ATF6/CHOP to upregulate TGF-β1/α-smooth muscle actin (α-SMA), driving EMT (175). Excessive OA drives mesangial cell proliferation and ECM accumulation through ERS-hyperactivated mTOR signaling, contributing to glomerulosclerosis (176). This underscores OA concentration modulation as a promising DKD therapeutic strategy.

In preclinical models, OlA exhibits antioxidant, antiglycation, anti-inflammatory and bactericidal activity, notably ameliorating DKD by reducing ERS. In diabetic rats, OlA treatment enhances the renal protein expression of p-AMPK/AMPK and peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α), while concurrently decreasing the expression of CD68, collagen-IV, TLR4, NF-κB and TGF-β1 (177). By regulating lipid metabolism and inflammation through the AMPK/PGC-1α and TLR4/NF-κB pathways, OlA mitigates renal injury in diabetic rats. In DKD model mice, OlA administration notably reduces the ALB-creatinine ratio (ACR). The marked DKD-induced elevation in ERS markers, such as p-PERK, p-eIF2α, ATF-6, BiP and CHOP, was notably decreased following OlA treatment, accompanied by marked reductions in ROS and nuclear factor erythroid 2-related factor 2 levels in glomerular mesangial cells (177,178). Furthermore, OlA administration reduces TGF-β/Smad2/3 signaling and α-SMA expression, repairs renal damage, alleviates albuminuria and suppresses diabetes-induced renal fibrosis by inhibiting ERS and apoptosis (179). In combination with N-acetylcysteine, OlA further attenuates oxidative stress and reduces the ERS-induced activation of TGF-β/Smad2/3 signaling (180).

Quercetin. Quercetin, a widely distributed natural polyphenol, exhibits potent antioxidant, anti-inflammatory and multi-target regulatory effects, making it a focal point of interdisciplinary research in disease prevention (181,182). Quercetin exhibits efficacy in treating metabolic diseases, including diabetes and its complications. Quercetin enhances cell-mediated immunity by upregulating IFN-γ secretion from Th1 lymphocytes and reduces inflammation by downregulating IL-4 secretion from Th2 lymphocytes (183). The protective effects of quercetin are mediated through multiple mechanisms, including inhibition of ROS production and mitochondrial permeability transition-pore opening, suppression of lipid peroxidation, elevation of glutathione and superoxide dismutase levels (184), inhibition of NF-κB, TNF-α and IL-6 signaling (185), reduction of inflammatory mediator release, suppression of angiotensin-converting enzyme and NF-κB activity, and enhancement of endothelial-dependent vasodilation (184,185). These actions collectively regulate blood pressure and reduce urinary protein excretion.

Quercetin may improve glucose homeostasis by modulating the expression of the microRNA-29 family, thereby increasing glucose transporters and insulin-like growth factor 1 gene expression, ultimately mitigating diabetic complications (186). In STZ-induced diabetic male Wistar rats, quercetin exhibited hypoglycemic effects, restored pancreatic morphology and β-cell function, reduced ERS markers such as CHOP and endothelin-1, inhibited lipid peroxidation, and enhanced antioxidant enzyme activities (183,187). Consequently, it lowered blood glucose levels, protected pancreatic tissues, alleviated ERS and improved oxidative status. Quercetin also inhibits platelet aggregation, hypertension and lipid peroxidation (188). In metabolic disorders, quercetin ameliorates diabetic endothelial dysfunction by targeting ERS, highlighting its role in metabolic-endothelial crosstalk (189).

Arctigenin (ATG). ATG, a lignan extracted from *Arctium lappa* L. seeds and derived from burdock sapogenins, has a fat-soluble aromatic structure, which is important for its biological activities (190). In db/db mice, ATG reduced the urine ACR and 24-h urinary albumin excretion rate, improved blood glucose levels and body weight and inhibited caspase-12 expression (191). In HK2 cells exposed to high glucose, ATG suppressed the upregulation of ERS markers GRP78 and CHOP, and similarly downregulated GRP78 and CHOP expression in the renal cortex (56,192). These effects collectively improved clinical biomarkers, reduced apoptosis and alleviated ERS. The biological activities of ATG include antioxidant, anti-inflammatory, antifibrotic and ERS modulation properties, all of which contribute to its nephroprotective potential in various disease models, particularly in DKD, by targeting the ERS pathway (56).

ERS-based modulation of DKD by Western drugs

Aliskiren and valsartan. As metabolic disease therapy, the renin-angiotensin system (RAS) inhibitors aliskiren (193,194) and valsartan (195,196) reduce DKD proteinuria by lowering glomerular pressure, with evidence showing that ERS pathway regulation contributes to their renoprotective effects in RAS-driven DKD.

ACEIs and ARBs such as aliskiren and valsartan inhibit renal ERS in DKD, and dual therapy yields cumulative renoprotective effects via synergistic RAS blockade and ERS control (193). Valsartan is recommended by several guidelines, including the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (197), as the preferred ARB for DKD with hypertension, and its nephroprotective effect is partly attributed to ERS modulation. The clinical use of aliskiren is currently limited due to early clinical trials, such as the ALTITUDE study (72,198), showing an increased risk of hyperkalemia and renal injury when used in combination with an ARB, but its single-agent modulation of ERS remains worth studying (199-201). Aliskiren and valsartan exert anti-apoptotic, anti-inflammatory and anti-fibrotic effects in DKD by inhibiting RAS overactivation and modulating upstream or downstream ERS. Valsartan, as a classical ARB, has been clinically validated as an ERS regulator, particularly in the context of DKD treatment. However, the ERS-targeting effect of aliskiren (a direct renin inhibitor) remains to be further evaluated and balanced in terms of its efficacy and safety (193). Basic research has confirmed that angiotensin II exacerbates ERS in renal tubular epithelial cells by activating the PERK/eIF2α/CHOP pathway, while ACEIs and ARBs downregulate stress markers such as GRP78 and CHOP in renal tissue (196,202). However, clinical studies have yet to incorporate assessments of ERS-related biomarkers, thus direct clinical evidence of ACEI and ARB exerting effects via inhibition of ERS is lacking (193,196). The 2024 KDIGO guidelines recommend RAS inhibitors for patients with DKD with proteinuria, emphasizing blood pressure and proteinuria management but omitting the discussion of ERS-related mechanisms (202).

Cannabinoid receptor 1 (CB1R) antagonists. CB1R, a notable cannabinoid receptor, is widely distributed in renal vascular endothelial, mesangial, tubular and immune cells (203,204). In DKD, hyperglycemia, oxidative stress and inflammation activate CB1R, inducing renal inflammation, fibrosis and metabolic dysfunction, including insulin resistance (205-207). CB1R antagonists, such as rimonabant and AM251, have been shown to improve glucose-lipid metabolism in metabolic disorders through the blockade of CB1R signaling, and their protective mechanism against DKD has been demonstrated to be closely associated with modulation of the ERS pathway (208,209). The protective effect of CB1R inhibition in DKD is linked to ERS pathway modulation, with CB1R, abundantly expressed in diabetic rats kidneys, mediating ERS and apoptosis in rat mesangial Cells) under high glucose. CB1R regulates palmitic acid-induced apoptosis in human renal proximal tubular cells through the ERS pathway (210,211). CB1R antagonists are not recommended in DKD guidelines; rimonabant has been withdrawn globally due to severe psychiatric side effects such as depression and anxiety (212). Subsequent candidate CB1R antagonists, such as AM6545, remain in preclinical research for DKD and have not yet been incorporated into guidelines (213,214).

Endogenous cannabinoids activating CB1R may serve a notable role in the pathogenesis of diabetic cardiomyopathy by promoting MAPK activation, type-1 angiotensin II receptor expression and signaling, AGE accumulation, oxidative and nitrosative stress, inflammation, and fibrosis (215,216). Conversely, CB1R antagonists exert anti-diabetic effects by increasing pancreatic β-cell glucokinase and glucose transporter (GLUT)-2 expression, improving β-cell insulin signaling and proliferation (for example, mitigating β-cell loss in male Zucker diabetic obese rats, independent of weight loss) (216,217). CB1R antagonists also upregulate skeletal muscle GLUT-4 to ameliorate intermittent hypoxia-induced insulin resistance, whereas CB1R agonists interfere with insulin signaling pathways (218,219). CB1R antagonists modulate the ERS pathway by blocking high-glucose- or inflammation-induced CB1R signaling on several levels: i) Inhibiting oxidative stress and calcium disruption (211); and ii) attenuating inflammation and fibrosis, thereby improving renal cell survival and renal function (220). The use of CB1R antagonists is subject to notable limitations. Currently, to the best of our knowledge, no human studies using CB1R antagonists have been conducted, and the risk of psychiatric side effects remains to be assessed (221,222). Consequently, clinical advancement cannot proceed at this stage (223). However, it holds potential and may provide a basis for DKD treatment following future animal studies and clinical trials.

Chemical chaperones. Chemical chaperones, such as TUDCA and 4-PBA, are small molecules responsible for stabilizing protein conformation, enhancing ER folding and promoting mutant protein transport. TUDCA, a secondary bile acid, exhibits beneficial effects in various disorders, including diabetes, obesity and neurodegenerative disease (224). The cytoprotective mechanisms of chemical chaperones primarily involve the alleviation of ERS. 4-PBA, a small-molecule chaperone employed in urea-cycle disorders, mitigates ERS to normalize hyperglycemia and insulin resistance (225-227). Preclinical study has demonstrated the efficacy of 4-PBA in preventing podocyte apoptosis in type 2 diabetes (228). In addition, three widely used ERS inducers, clindamycin, dithiothreitol and carbobenzoxy-Leu-Leu-leucinal, have been applied to assess ERS in animal models and cell lines. 4-PBA was shown to alleviate drug-induced ERS (229), while drugs targeting PERK, IRE1α, eIF2α and ATF4, such as GSK2606414, MKC-3946, salubrinal and trazodone, offer promise for ERS-related disorder management (230,231). In rats fed a high-salt diet, damage to the glomeruli and proximal tubules was exacerbated, accompanied by increased urinary protein excretion. Following treatment with TUDCA, the levels of proximal tubular giant cells increased and urinary protein levels were markedly decreased (232). TUDCA and 4-PBA are not formally included in clinical guidelines for DKD. However, the Chinese Guidelines for the Prevention and Treatment of Diabetic Kidney Disease (2021 Edition) mention in the section on 'Novel Therapeutic Targets for DKD' that 'chemical companions may improve renal injury by alleviating ERS', listing TUDCA as a potential candidate drug (233).

Repurposed drugs show promise in DKD ERS inhibition in preclinical studies. *In vitro* and *in vivo* studies have

shown that recombinant human rhodopsin kinase, epidermal growth factor receptor inhibitor (EGFRi) and dapagliflozin mitigate ERS and improve renal function (234,235). Shih *et al* (236) further found that dapagliflozin reduced myocardial ERS in patients with DKD. To the best of our knowledge, recombinant human retinal pigment kinase is not mentioned in any DKD-related clinical guidelines for the treatment of DKD or ERS suppression, as its primary research domain is hereditary retinal diseases, which bear no direct relationship with DKD. A previous study has suggested that recombinant human retinal pigment kinase may indirectly influence the ERS pathway by regulating protein folding (237), although this has not been validated in DKD renal cells or animal models. Nevertheless, based on the discussion of the impact of ERS on DKD, recombinant human retinal pigment kinase holds notable potential for DKD treatment. EGFRi was found to alleviate renal inflammation, oxidative stress and fibrosis in a mouse model of obesity-related kidney disease, with TLR4 primarily regulating EGFR pathway activation through phosphorylation of the c-Src/EGFR complex (238). No authoritative DKD clinical guidelines currently formally recommend EGFRi as a DKD therapeutic agent or ERS inhibitory target drug. However, excessive EGFR activation may exacerbate renal ERS injury through the PERK/ATF4/CHOP pathway. EGFRi may potentially alleviate DKD progression by inhibiting this pathway (239-243); however, further animal studies and clinical evidence are required to substantiate this.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, currently represent first-line therapies for DKD. Their regulation of ERS involves indirect multi-pathway interventions, and the direct association between their renal protective effects and ERS inhibition requires validation through mechanistic clinical trials (244,245). The 2024 KDIGO guidelines classify SGLT2 inhibitors as a first-line therapy with Class 1A recommendation for patients with DKD with an estimated glomerular filtration rate (eGFR) ≥20 ml/min/1.73 m^2, emphasizing their role in delaying renal progression (246,247). However, ERS-related mechanisms are not addressed. Existing large-scale clinical trials have primarily focused on definitive renal endpoints, such as eGFR decline and end-stage kidney disease, without systematic assessment of ERS biomarkers (202,248-251). Thus, attention to ERS treatment is warranted for kidney disease.

The aforementioned drugs exhibit pleiotropic effects, indicating their lack of specificity for ERS inhibition; thus, development of ERS-targeted therapeutics is warranted. Notably, ERS exhibits dual effects: Moderate ERS restores intracellular homeostasis, while sustained ERS drives renal damage in DKD, meaning that human-targeted ERS research is warranted (252-254). A deeper understanding of the mechanisms underlying this process will help improve the treatment of DKD.

5. Summary and outlook

As a major microvascular complication of diabetes mellitus, DKD is closely associated with aberrant activation of ERS. Factors such as hyperglycemia and oxidative stress trigger an imbalance of protein folding in renal podocytes, tubular epithelial and renal capsule cells, which activates the three core pathways of the UPR, namely the IRE1α/XBP1, PERK/eIF2α/ATF4 and ATF6 pathways (50,255). Short-term ERS maintains cellular homeostasis by promoting protein folding and degradation, whereas sustained overactivation induces pro-apoptotic factor expression, such as CHOP expression, exacerbating inflammatory responses through NF-κB pathway activation and mesangial fibrosis via TGF-β1/Smad3 pathway dysregulation, which ultimately leads to glomerulosclerosis and renal failure. Several stimuli disrupting cellular homeostatic function induce ERS (58,256) (Fig. 1). The present review discusses ERS-related experimental agents, preclinical models and clinical data, alongside an analysis of the three UPR pathways in DKD renal histopathology.

Phase I and II clinical trials are underway for ERS-modulating compounds such as alginate and TUDCA (257). Pharmacological interventions against ERS have focused on blocking the excessive stress response. However, although the aforementioned RAS inhibitors, SGLT2 inhibitors, 4-PBA and CB1R antagonists may regulate ERS through indirect pathways, existing guidelines do not provide specific recommendations based on this mechanism (258-260). Clinical trials lack ERS-related endpoint data, and the causal relationship between medications for the treatment of DKD,ERS) requires further validation through targeted research. Western drugs, such as PERK inhibitors, IRE1α endonuclease inhibitors and CHOP antagonists, have demonstrated potential in attenuating apoptosis and fibrosis in animal models (203,261-263); however, challenges associated with target specificity and long-term safety remain.

ERS inhibitors commonly used in laboratory studies, such as the chemical chaperone 4-PBA or the pathway-specific PERK inhibitor GSK2606414, generally exhibit good tolerability in rodent DKD models (264,265), but their clinical safety assessments present significant challenges. Primarily, ERS is a fundamental physiological mechanism enabling cellular responses to abnormal protein folding, which is important in metabolically active tissues such as pancreatic β-cells and hepatocytes. While 4-PBA alleviates ERS in renal tissues of rat models (266-268), its prolonged clinical application may cause hyperammonemia and gastrointestinal mucosal irritation. Furthermore, suppressing ERS responses in pancreatic β-cells can impair insulin synthesis, potentially exacerbating glycemic dysregulation (225). Secondly, the risk of kidney-specific toxicity may be underestimated. Animal models commonly involve young, healthy rats, whereas clinical patients with DKD typically present with comorbidities such as hypertension, cardiovascular disease and renal insufficiency, markedly reducing drug metabolism capacity. In addition, drug interactions remain unclear: Patients with DKD frequently require concomitant hypoglycemic, antihypertensive and lipid-lowering medications (269,270). Furthermore, ERS inhibitors may compete with SGLT2 inhibitors for renal tubular excretion pathways or affect the renal metabolism of ACEIs, increasing the risk of adverse reactions such as hyperkalemia (271). Such interactions are challenging to detect in controlled, single-factor laboratory settings. Additionally, the complex multi-pathway regulatory nature of ERS, coordinated by PERK, IRE1α and ATF6, combined with individual

heterogeneity among patients with DKD makes 'precision targeting' a translational challenge. Laboratory studies often target single pathways, whereas clinical ERS activation patterns vary notably among patients with DKD: Some cases of DKD primarily involve activation of the PERK/eIF2α pathway, accompanied by extensive tubular epithelial apoptosis, while others predominantly involve activation of the ATF6 pathway, accompanied by inflammatory mediator release (for example, elevated IL-6 and TNF-α levels) (71). Furthermore, ERS in DKD involves glomerular mesangial cells, podocytes and tubular epithelial cells; however, existing drugs exhibit systemic distribution, complicating precise delivery to specific renal cell subpopulations (18,19).

Addressing these bottlenecks requires further research. Safety evaluations should incorporate multiple animal models with renal insufficiency to more accurately replicate drug metabolism characteristics observed in clinical populations. For target optimization, kidney-specific drug formulations could be developed to enhance renal tissue accumulation. Only through these approaches can ERS inhibition strategies transition from being mechanistically effective in laboratory settings to being safe and beneficial in clinical practice.

The active constituents of TCM, such as AS and Huangkui total flavonoids, exert multi-target modulatory effects on ERS, including the downregulation of CHOP and inhibition of IRE1α phosphorylation (47,166). These compounds also exert antioxidant, anti-inflammatory and podocyte-protective effects, supporting clinical evidence of reduced proteinuria and delayed renal function decline in DKD. Such findings underscore the potential of TCM-Western medicine integration as a promising research avenue for DKD management. The development and translation of ER-specific reagents targeting protein folding, UPR signaling and ER calcium homeostasis hold promise for novel therapeutic strategies (7).

In future research, it is important to investigate ERS biomarkers for early DKD diagnosis by elucidating the underlying ERS mechanisms. BiP/GRP78, as a sentinel protein for ERS activation, exhibits increased expression levels that signal early ERS and are directly associated with the severity of renal pathological damage in DKD, thereby providing a foundational reference for assessing disease progression (112). Concurrently, p-PERK, p-eIF2α and ATF4 from the PERK pathway, p-IRE1α and XBP1s from the IRE1α pathway and ATF6f (a type II transmembrane protein that under ER stress is translocated to the Golgi apparatus where it is proteolytically processed, releasing the cytoplasmic fragment of ATF6) (77). from the ATF6 pathway indicate the activation status of the three principal UPR branches, accurately reflecting the ERS-mediated pathological transition from adaptive protection to apoptosis initiation. The comprehensive assessment of these markers not only clarifies the molecular mechanisms of ERS in DKD but also provides molecular evidence for staging disease progression (16). These biomarkers thus hold potential for translation into early diagnostic tools and therapeutic efficacy-monitoring indicators for DKD, enabling precise clinical interventions. Simultaneously, the development of inhibitors targeting specific pathways, such as IRE1α-specific inhibitors, is important, offering novel therapeutic strategies for DKD management. Given the growing potential of ERS-targeted therapies, focused clinical studies are required to deepen the current understanding of DKD pathogenesis and refine targeted interventions. Collectively, these efforts will advance DKD treatment and provide insights that are relevant to broader ERS-associated disorders.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Jilin Province Science and Technology Development Program (grant no. 20210101201JC).

Availability of data and materials

Not applicable.

Authors' contributions

PZ contributed to writing the manuscript and prepared the figures. YZ made substantial contributions to the conception and design of the study, conducting a comprehensive and systematic literature review to identify key studies and ensuring the research was grounded in relevant and current findings in the field of DKD. YZ also played a crucial role in the analysis and interpretation of data, particularly in understanding the mechanisms of ERS in DKD. Additionally, YZ contributed to drafting significant portions of the manuscript and critically revised it for important intellectual content. YZ approved the final version of the manuscript and takes full responsibility for the integrity and accuracy of the work, ensuring all aspects of the research were thoroughly addressed. CC, YC, FL, SZ and CL revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhang L, Long J, Jiang W, Shi Y, He X, Zhou Z, Li Y, Yeung RO, Wang J, Matsushita K, *et al*: Trends in chronic kidney disease in China. N Engl J Med 375: 905-906, 2016.
2. Cybulsky AV: Endoplasmic reticulum stress, the unfolded protein response and autophagy in kidney diseases. Nat Rev Nephrol 13: 681-696, 2017.
3. American Diabetes Association: 11 Microvascular complications and foot care: Standards of medical care in diabetes-2020. Diabetes Care 43 (Suppl 1): S135-S151, 2020.

4. Pena MJ, Mischak H and Heerspink HJ: Proteomics for prediction of disease progression and response to therapy in diabetic kidney disease. Diabetologia 59: 1819-1831, 2016.
5. Bustamante P, Tsering T, Coblentz J, Mastromonaco C, Abdouh M, Fonseca C, Proença RP, Blanchard N, Dugé CL, Andujar RAS, *et al*: Circulating tumor DNA tracking through driver mutations as a liquid biopsy-based biomarker for uveal melanoma. J Exp Clin Cancer Res 40: 196, 2021.
6. Tang M, Sun J and Cai Z: PCK2 inhibits lung adenocarcinoma tumor cell immune escape through oxidative stress-induced senescence as a potential therapeutic target. J Thorac Dis 15: 2601-2615, 2023.
7. Almanza A, Carlesso A, Chintha C, Creedican S, Doultsinos D, Leuzzi B, Luís A, McCarthy N, Montibeller L, More S, *et al*: Endoplasmic reticulum stress signalling - from basic mechanisms to clinical applications. FEBS J 286: 241-278, 2019.
8. Tilija Pun N, Lee N, Song SH and Jeong CH: pitavastatin induces cancer cell apoptosis by blocking autophagy flux. Front Pharmacol 13: 854506, 2022.
9. Çiftçi YC, Yurtsever Y and Akgül B: Long non-coding RNA-mediated modulation of endoplasmic reticulum stress under pathological conditions. J Cell Mol Med 28: e18561, 2024.
10. Kober L, Zehe C and Bode J: Development of a novel ER stress based selection system for the isolation of highly productive clones. Biotechnol Bioeng 109: 2599-2611, 2012.
11. Hotamisligil GS: Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell 140: 900-917, 2010.
12. Shahzad K, Ghosh S, Mathew A and Isermann B: Methods to detect endoplasmic reticulum stress and apoptosis in diabetic nephropathy. Methods Mol Biol 2067: 153-173, 2020.
13. Hetz C and Papa FR: The unfolded protein response and cell fate control. Mol Cell 69: 169-181, 2018.
14. Guzmán Mendoza NA, Homma K, Osada H, Toda E, Ban N, Nagai N, Negishi K, Tsubota K and Ozawa Y: Neuroprotective effect of 4-phenylbutyric acid against photo-stress in the Retina. Antioxidants (Basel) 10: 1147, 2021.
15. Chen YY, Peng XF, Liu GY, Liu JS, Sun L, Liu H, Xiao L and He LY: Protein arginine methyltranferase-1 induces ER stress and epithe-lial-mesenchymal transition in renal tubular epithelial cells and contributes to diabetic nephropathy. Biochim Biophys Acta Mol Basis Dis 1865: 2563-2575, 2019.
16. Liu H and Sun HL: LncRNA TCF7 triggered endoplasmic reticulum stress through a sponge action with miR-200c in patients with diabetic nephropathy. Eur Rev Med Pharmacol Sci 23: 5912-5922, 2019.
17. Chen N, Song S, Yang Z, Wu M, Mu L, Zhou T and Shi Y: ChREBP deficiency alleviates apoptosis by inhibiting TXNIP/oxidative stress in diabetic nephropathy. J Diabetes Complications 35: 108050, 2021.
18. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, Ferrario F, Fogo AB, Haas M, de Heer E, *et al*: Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 21: 556-563, 2010.
19. Oshima M, Shimizu M, Yamanouchi M, Toyama T, Hara A, Furuichi K and Wada T: Trajectories of kidney function in diabetes: A clinicopathological update. Nat Rev Nephrol 17: 740-750, 2021.
20. Garg P: A review of podocyte biology. Am J Nephrol 47 (Suppl 1): S3-S13, 2018.
21. O'Toole JF: Renal manifestations of genetic mitochondrial disease. Int J Nephrol Renovasc Dis 7: 57-67, 2014.
22. Nath KA: Tubulointerstitial changes as a major determinant in the progression of renal damage. Am J Kidney Dis 20: 1-17, 1992.
23. Tang J, Yao D, Yan H, Chen X, Wang L and Zhan H: The role of MicroRNAs in the pathogenesis of diabetic nephropathy. Int J Endocrinol 2019: 8719060, 2019.
24. Bazzi C, Bakoush O and Gesualdo L: Proteinuria: From molecular to clinical applications in glomerulonephritis. Int J Nephrol 2012: 424968, 2012.
25. Edirs S, Jiang L, Xin X and Aisa HA: Kursi Wufarikun Ziyabit improves the physiological changes by regulating endoplasmic reticulum stress in the type 2 diabetes db/db mice. Evid Based Complement Alternat Med 2021: 2100128, 2021.
26. Guo H, Cao A, Chu S, Wang Y, Zang Y, Mao X, Wang H, Wang Y, Liu C, Zhang X and Peng W: Astragaloside IV attenuates podocyte apoptosis mediated by endoplasmic reticulum stress through upregulating sarco/endoplasmic reticulum Ca2+-ATPase 2 expression in diabetic nephropathy. Front Pharmacol 7: 500, 2016.
27. Wang D, Wang YS, Zhao HM, Lu P, Li M, Li W, Cui HT, Zhang ZY and Lv SQ: Plantamajoside improves type 2 diabetes mellitus pancreatic β-cell damage by inhibiting endoplasmic reticulum stress through Dnajc1 up-regulation. World J Diabetes 16: 99053, 2025.
28. Zhang HX, Yuan J and Li RS: Thalidomide mitigates apoptosis via endoplasmic reticulum stress in diabetic nephropathy. Endocr Metab Immune Disord Drug Targets 22: 787-794, 2022.
29. Van Krieken R, Mehta N, Wang T, Zheng M, Li R, Gao B, Ayaub E, Ask K, Paton JC, Paton AW, *et al*: Cell surface expression of 78-kDa glucose-regulated protein (GRP78) mediates diabetic nephropathy. J Biol Chem 294: 7755-7768, 2019.
30. Zhang MZ, Wang Y, Paueksakon P and Harris RC: 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: 2063-2072, 2014.
31. Chen J, Hou XF, Wang G, Zhong QX, Liu Y, Qiu HH, Yang N, Gu JF, Wang CF, Zhang L, *et al*: Terpene glycoside component from Moutan Cortex ameliorates diabetic nephropathy by regulating endoplasmic reticulum stress related inflammatory responses. J Ethnopharmacol 193: 433-444, 2016.
32. Yao F, Li Z, Ehara T, Yang L, Wang D, Feng L, Zhang Y, Wang K, Shi Y, Duan H and Zhang L: Fatty acid-binding protein 4 mediates apoptosis via endoplasmic reticulum stress in mesangial cells of diabetic nephropathy. Mol Cell Endocrinol 411: 232-242, 2015.
33. Ge J, Miao JJ, Sun XY and Yu JY: Huangkui capsule, an extract from Abelmoschus manihot (L.) medic, improves diabetic nephropathy via activating peroxisome proliferator-activated receptor (PPAR)-α/γ and attenuating endoplasmic reticulum stress in rats. J Ethnopharmacol 189: 238-249, 2016.
34. Park MJ, Han HJ and Kim DI: Lipotoxicity-Induced PRMT1 exacerbates mesangial cell apoptosis via endoplasmic reticulum stress. Int J Mol Sci 18: 1421, 2017.
35. Khoi CS, Xiao CQ, Hung KY, Lin TY and Chiang CK: Oxidative stress-induced growth inhibitor (OSGIN1), a Target of X-Box-Binding Protein 1, protects palmitic acid-induced vascular lipotoxicity through maintaining autophagy. Biomedicines 10: 992, 2022.
36. Jeon HY, Moon CH, Kim EB, Sayyed ND, Lee AJ and Ha KS: Simultaneous attenuation of hyperglycemic memory-induced retinal, pulmonary, and glomerular dysfunctions by proinsulin C-peptide in diabetes. BMC Med 21: 49, 2023.
37. Jiao Y, Liu X, Shi J, An J, Yu T, Zou G, Li W and Zhuo L: Unraveling the interplay of ferroptosis and immune dysregulation in diabetic kidney disease: A comprehensive molecular analysis. Diabetol Metab Syndr 16: 86, 2024.
38. Liu F, Yang Z, Li J, Wu T, Li X, Zhao L, Wang W, Yu W, Zhang G and Xu Y: Targeting programmed cell death in diabetic kidney disease: from molecular mechanisms to pharmacotherapy. Mol Med 30: 265, 2024.
39. Cao Y, Hao Y, Li H, Liu Q, Gao F, Liu W and Duan H: Role of endoplasmic reticulum stress in apoptosis of differentiated mouse podocytes induced by high glucose. Int J Mol Med 33: 809-816, 2014.
40. Tian N, Gao Y, Wang X, Wu X, Zou D, Zhu Z, Han Z, Wang T and Shi Y: Emodin mitigates podocytes apoptosis induced by endoplasmic reticulum stress through the inhibition of the PERK pathway in diabetic nephropathy. Drug Des Devel Ther 12: 2195-2211, 2018.
41. Garner KL, Betin VMS, Pinto V, Graham M, Abgueguen E, Barnes M, Bedford DC, McArdle CA and Coward RJM: Enhanced insulin receptor, but not PI3K,signalling protects podocytes from ER stress. Sci Rep 8: 3902, 2018.
42. Zhang Y, Gao X, Chen S, Zhao M, Chen J, Liu R, Cheng S, Qi M, Wang S and Liu W: Cyclin-dependent kinase 5 contributes to endoplasmic reticulum stress induced podocyte apoptosis via promoting MEKK1 phosphorylation at Ser280 in diabetic nephropathy. Cell Signal 31: 31-40, 2017.
43. Cybulsky AV: The intersecting roles of endoplasmic reticulum stress, ubiquitin-proteasome system, and autophagy in the pathogenesis of proteinuric kidney disease. Kidney Int 84: 25-33, 2013.
44. Dong Z, Liu N and Sun M: The distinct biological role of JAML positions it as a promising target for treating human cancers and a range of other diseases. Front Immunol 16: 1558488, 2025.
45. Feng Z, Tang L, Wu L, Cui S, Hong Q, Cai G, Wu D, Fu B, Wei R and Chen X: Na+/H+ exchanger-1 reduces podocyte injury caused by endoplasmic reticulum stress via autophagy activation. Lab Invest 94: 439-454, 2014.

46. Fang L, Li X, Luo Y, He W, Dai C and Yang J: Autophagy inhibition induces podocyte apoptosis by activating the proapoptotic pathway of endoplasmic reticulum stress. Exp Cell Res 322: 290-301, 2014.
47. Guo H, Wang Y, Zhang X, Zang Y, Zhang Y, Wang L, Wang H, Wang Y, Cao A and Peng W: Astragaloside IV protects against podocyte injury via SERCA2-dependent ER stress reduction and AMPKα-regulated autophagy induction in streptozotocin-induced diabetic nephropathy. Sci Rep 7: 6852, 2017.
48. Kato M: Intercellular transmission of endoplasmic reticulum stress through gap junction targeted by microRNAs as a keystep of diabetic kidney diseases? Ann Transl Med 9: 827, 2021.
49. Liang X, Duan N, Wang Y, Shu S, Xiang X, Guo T, Yang L, Zhang S, Tang X and Zhang J: Advanced oxidation protein products induce endothelial-to-mesenchymal transition in human renal glomerular endothelial cellsthrough induction of endoplasmic reticulum stress. J Diabetes Complications 30: 573-579, 2016.
50. Ma X, Ma J, Leng T, Yuan Z, Hu T, Liu Q and Shen T: Advances in oxidative stress in pathogenesis of diabetic kidney disease and efficacy of TCM intervention. Ren Fail 45: 2146512, 2023.
51. Cao Y, Chen Z, Hu J, Feng J, Zhu Z, Fan Y, Lin Q and Ding G: Mfn2 regulates high glucose-induced MAMs dysfunction and apoptosis in podocytes via PERK pathway. Front Cell Dev Biol 9: 769213, 2021.
52. Mega C, Teixeira-de-Lemos E, Fernandes R and Reis F: Renoprotective effects of the dipeptidyl peptidase-4 inhibitor sitagliptin: A review in type 2 diabetes. J Diabetes Res 2017: 5164292, 2017.
53. Feng A, Yin R, Xu R, Zhang B and Yang L: An update on renal tubular injury as related to glycolipid metabolism in diabetic kidney disease. Front Pharmacol 16: 1559026, 2025.
54. Bondue T, van den Heuvel L, Levtchenko E and Brock R: The potential of RNA-based therapy for kidney diseases. Pediatr Nephrol 38: 327-344, 2023.
55. Zhang J, Dong XJ, Ding MR, You CY, Lin X, Wang Y, Wu MJ, Xu GF and Wang GD: Resveratrol decreases high glucose-induced apoptosis in renal tubular cells via suppressing endoplasmic reticulum stress. Mol Med Rep 22: 4367-4375, 2020.
56. Zhang J, Cao P, Gui J, Wang X, Han J, Wang Y and Wang G: Arc-tigenin ameliorates renal impairment and inhibits endoplasmic reticulum stress in diabetic db/db mice. Life Sci 223: 194-201, 2019.
57. Han J, Pang X, Shi X, Zhang Y, Peng Z and Xing Y: Ginkgo biloba extract EGB761 ameliorates the extracellular matrix accumulation and mesenchymal transformation of renal tubules in diabetic kidney disease by inhibiting endoplasmic reticulum stress. Biomed Res Int 2021: 6657206, 2021.
58. Huang KH, Guan SS, Lin WH, Wu CT, Sheu ML, Chiang CK and Liu SH: Role of calbindin-D28k in diabetes-associated advanced glycation end-products-induced renal proximal tubule cell injury. Cells 8: 660, 2019.
59. Sun X, Sun Y, Lin S, Xu Y and Zhao D: Histone deacetylase inhibitor valproic acid attenuates high glucoseinduced endoplas-mic reticulum stress and apoptosis in NRK52E cells. Mol Med Rep 22: 4041-4047, 2020.
60. Shibusawa R, Yamada E, Okada S, Nakajima Y, Bastie CC, Maeshima A. Kaira K and Yamada M: Dapagliflozin rescues endoplasmic reticulum stress-mediated cell death. Sci Rep 9: 9887, 2019.
61. Wu L, Wang Q, Guo F, Ma X, Wang J, Zhao Y, Yan Y and Qin G: Involvement of miR-27a-3p in diabetic nephropathy via affect-ing renal fibrosis, mitochondrial dysfunction, and endoplasmic reticulum stress. J Cell Physiol 236: 1454-1468, 2021.
62. Fang L, Xie D, Wu X, Cao H, Su W and Yang J: Involvement of endoplasmic reticulum stress in albuminuria induced inflam-masome activation in renal proximal tubular cells. PLoS One 8: e72344, 2013.
63. Kang JM, Lee HS, Kim J, Yang DH, Jeong HY, Lee YH, Kim DJ, Park SH, Sung M, Kim J, *et al*: Beneficial effect of Chloroquine and Amodiaquine on type 1 Diabetic Tubulopathy by attenuating mitochondrial Nox4 and endoplasmic reticulum stress. J Korean Med Sci 35: e305, 2020
64. Sun H, Yuan Y and Sun Z: Update on mechanisms of renal tubule injury caused by advanced glycation end products. Biomed Res Int 2016: 5475120, 2019.
65. Iwai T, Kume S, Chin-Kanasaki M, Kuwagata S, Araki H, Takeda N, Sugaya T, Uzu T, Maegawa H and Araki SI: Stearoyl-CoA Desaturase-1 protects cells against lipotoxicity-mediated apoptosis in proximal tubular cells. Int J Mol Sci 17: 1868, 2016.
66. Liu J, Yang JR, Chen XM, Cai GY, Lin LR and He YN: Impact of ER stress-regulated ATF4/p16 signaling on the premature senescence of renal tubular epithelial cells in diabetic nephropathy. Am J Physiol Cell Physiol 308: C621-C630, 2015.
67. Barati MT, Powell DW, Kechavarzi BD, Isaacs SM, Zheng S, Epstein PN, Cai L, Coventry S, Rane MJ and Klein JB: Differential expression of endoplasmic reticulum stress-response proteins in different renal tubule subtypes of OVE26 diabetic mice. Cell Stress Chaperones 21: 155-166, 2016.
68. Liu Y, Chen DQ, Han JX, Zhao TT and Li SJ: A review of traditional Chinese medicine in treating renal interstitial fibrosis via endoplasmic reticulum stress-mediated apoptosis. Biomed Res Int 2021: 6667791, 2021.
69. Wang J, Lu L, Chen S, Xie J, Lu S, Zhou Y and Jiang H: PERK overexpression-mediated Nrf2/HO-1 pathway alleviates hypoxia/reoxygenation-induced injury in neonatal murine cardiomyocytes via improving endoplasmic reticulum stress. Biomed Res Int 2020: 6458060, 2020.
70. Chen Z, Feng H, Peng C, Zhang Z, Yuan Q, Gao H, Tang S and Xie C: Renoprotective effects of tanshinone IIA: A literature review. Molecules 28: 1990, 2023.
71. Nakka VP, Prakash-Babu P and Vemuganti R: Crosstalk between endoplasmic reticulum stress, oxidative stress, and autophagy: Potential therapeutic targets for acute CNS injuries. Mol Neurobiol 53: 532-544, 2016.
72. Qiu M, Li S, Jin L, Feng P, Kong Y, Zhao X, Lin Y, Xu Y, Li C and Wang W: Combination of chymostatin and aliskiren attenuates ER stress induced by lipid overload in kidney tubular cells. Lipids Health Dis 17: 183, 2018.
73. Chai H, Yao S, Gao Y, Hu Q and Su W: Developments in the connection between epithelial-mesenchymal transition and endoplasmic reticulum stress (Review). Int J Mol Med 56: 102, 2025.
74. Wang WW, Liu YL, Wang MZ, Li H, Liu BH, Tu Y, Yuan CC, Fang QJ, Chen JX, Wang J, *et al*: Inhibition of renal tubular epithelial mesenchymal transition and endoplasmic reticulum stress-induced apoptosis with shenkang injection attenuates diabetic tubulopathy. Front Pharmacol 12: 662706, 2021.
75. Wang W, Ke B, Wang C, Xiong X, Feng X and Yan H: Targeting ion channel networks in diabetic kidney disease: from molecular crosstalk to precision therapeutics and clinical innovation. Front Med (Lausanne) 12: 1607701, 2025.
76. Jo HJ, Yang JW, Park JH, Choi ES, Lim CS, Lee S and Han CY: Endoplasmic reticulum stress increases DUSP5 expression via PERK-CHOP pathway, leading to hepatocyte death. Int J Mol Sci 20: 4369, 2019.
77. Hu H, Tian M, Ding C and Yu S: The C/EBP homologous protein (CHOP) transcription factor functions in endoplasmic reticulum Stress-Induced apoptosis and microbial infection. Front Immunol 9: 3083, 2019.
78. Jin R, Zhao A, Han S, Zhang D, Sun H, Li M, Su D and Liang X: The interaction of S100A16 and GRP78 actives endoplasmic reticulum stress-mediated through the IRE1α/XBP1 pathway in renal tubulointerstitial fibrosis. Cell Death Dis 12: 942, 2021.
79. Fan Y, Zhang J, Xiao W, Lee K, Li Z, Wen J, He L, Gui D, Xue R, Jian G, *et al*: Rtn1a-Mediated endoplasmic reticulum stress in podocyte injury and diabetic nephropathy. Sci Rep 7: 323, 2017.
80. Zhang GQ, Tao YK, Bai YP, Yan ST and Zhao SP: Inhibitory effects of simvastatin on oxidized low-density lipoprotein-induced endoplasmic reticulum stress and apoptosis in vascular endothelial cells. Chin Med J (Engl) 131: 950-955, 2018.
81. Ni L, Yang L and Lin Y: Recent progress of endoplasmic reticulum stress in the mechanism of atherosclerosis. Front Cardiovasc Med 11: 1413441, 2024.
82. Li HY, Huang LF, Huang XR, Wu D, Chen XC, Tang JX, An N, Liu HF and Yang C: Endoplasmic reticulum stress in systemic lupus erythematosus and lupus nephritis: Potential therapeutic target. J Immunol Res 2023: 7625817, 2023.
83. Shu S, Wang H, Zhu J, Liu Z, Yang D, Wu W, Cai J, Chen A, Tang C and Dong Z: Reciprocal regulation between ER stress and autophagy in renal tubular fibrosis and apoptosis. Cell Death Dis 12: 1016, 2021.
84. Li D, Zhang J, Su X, Yang Y, Lai J, Wei X, Chen H, Liu Y, Wang H and Sun L: Calpain1 inhibition enhances autophagy-lysosomal pathway and ameliorates tubulointerstitial fibrosis in Nephronophthisis. Mol Med 31: 166, 2025.
85. Laorodphun P, Cherngwelling R, Panya A and Arjinajarn P: Curcumin protects rats against gentamicin-induced nephrotoxicity by amelioration of oxidative stress, endoplasmic reticulum stress and apoptosis. Pharm Biol 60: 491-500, 2022.

86. Ma N, Xu N, Yin D, Zheng P, Liu W, Wang G, Hui Y, Han G, Yang C and Cheng X: Levels of circulating GRP78 and CHOP in endoplasmic reticulum stress pathways in Chinese type 2 diabetic kidney disease patients. Medicine (Baltimore) 100: e26879, 2021.
87. Zhao DM, Zhong R, Wang XT and Yan ZH: Mitochondrial dysfunction in diabetic nephropathy: Insights and therapeutic avenues from traditional Chinese medicine. Front Endocrinol (Lausanne) 15: 1429420, 2024.
88. Yan DY and Xu B: The role of autophagy in manganese-induced neurotoxicity. Front Neurosci 14: 574750, 2020.
89. Abo-Zaid OA, Moawed FS, Taha EF, Ahmed ESA and Kawara RS: Melissa officinalis extract suppresses endoplasmic reticulum stress-induced apoptosis in the brain of hypothyroidism-induced rats exposed to γ-radiation. Cell Stress Chaperones 28: 709-720, 2023.
90. Kong FJ, Ma LL, Guo JJ, Xu LH, Li Y and Qu S: Endoplasmic reticulum stress/autophagy pathway is involved in diabetes induced neuronal apoptosis and cognitive decline in mice. Clin Sci (Lond) 132: 111-125, 2018.
91. Tomicic MT, Meise R, Aasland D, Berte N, Kitzinger R, Krämer OH, Kaina B and Christmann M: Apoptosis induced by temozolomide and nimustine in glioblastoma cells is supported by JNK/c-Jun-mediated induction of the BH3-only protein BIM. Oncotarget 6: 33755-33768, 2015.
92. Gao Z, Liu G, Hu Z, Shi W, Chen B, Zou P and Li X: Grape seed proanthocyanidins protect against streptozotocin-induced diabetic nephropathy by attenuating endoplasmic reticulum stress-induced apoptosis. Mol Med Rep 18: 1447-1454, 2018.
93. Sun XY, Qin HJ, Zhang Z, Xu Y, Yang XC, Zhao DM, Li XN and Sun LK: Valproate attenuates diabetic nephropathy through inhibition of endoplasmic reticulum stress-induced apoptosis. Mol Med Rep 13: 661-668, 2016.
94. Suzuki Y, Inoue T, Murai M, Suzuki-Karasaki M, Ochiai T and Ra C: Depolarization potentiates TRAIL-induced apoptosis in human melanoma cells: role for ATP-sensitive K+ channels and endoplasmic reticulum stress. Int J Oncol 41: 465-475, 2012.
95. Hibi M, Lin A, Smeal T, Minden A and Karin M: Identification of an oncoprotein- and UV-responsive protein kinase that binds and potentiates the c-Jun activation domain. Genes Dev 7: 2135-2148, 1993.
96. Shang H, Cao Z, Zhao J, Guan J, Liu J, Peng J, Chen Y, Joseph Sferra T, Sankararaman S and Lin J: Babao Dan induces gastric cancer cell apoptosis via regulating MAPK and NF-κB signaling pathways. J Int Med Res 47: 5106-5119, 2019.
97. Liu Y, Long Y, Xing Z and Zhang D: C-Jun recruits the NSL complex to regulate its target gene expression by modulating H4K16 acetylation and promoting the release of the repressive NuRD complex. Oncotarget 6: 14497-14506, 2015.
98. Vilas-Boas EA, Almeida DC, Roma LP, Ortis F and Carpinelli AR: Lipotoxicity and β-Cell failure in type 2 diabetes: Oxidative stress linked to NADPH oxidase and ER stress. Cells 10: 3328, 2021.
99. Chhabra R, Dubey R and Saini N: Gene expression profiling indicate role of ER stress in miR-23a ~ 27a ~ 24 - 2 cluster induced apoptosis in HEK293T cells. RNA Biol 8: 648-664, 2011.
100. Rodríguez-Hernández MA, González R, de la Rosa ÁJ, Gallego P, Ordóñez R, Navarro-Villarán E, Contreras L, Rodríguez-Arribas M, González-Gallego J, Álamo-Martínez JM, *et al*: Molecular characterisation of autophagic and apoptotic signalling induced by sorafenib in liver cancer cells. J Cell Physiol 234: 692-708, 2018.
101. Zeng T, Peng L, Chao H, Xi H, Fu B, Wang Y, Zhu Z and Wang G: IRE1α-TRAF2-ASK1 complex-mediated endoplasmic reticulum stress and mitochondrial dysfunction contribute to CXC195-induced apoptosis in human bladder carcinoma T24 cells. Biochem Biophys Res Commun 460: 530-536, 2015.
102. Zhang J, Liang Y, Lin Y, Liu Y, YouYou and Yin W: IRE1α-TRAF2-ASK1 pathway is involved in CSTMP-induced apoptosis and ER stress in human non-small cell lung cancer A549 cells. Biomed Pharmacother 82: 281-289, 2016.
103. Ha J, Kang E, Seo J and Cho S: Phosphorylation dynamics of JNK signaling: Effects of dual-specificity phosphatases (DUSPs) on the JNK pathway. Int J Mol Sci 20: 6157, 2019.
104. Li L, Chen J, Lin L, Pan G, Zhang S, Chen H, Zhang M, Xuan Y, Wang Y and You Z: Quzhou Fructus Aurantii Extract suppresses inflammation via regulation of MAPK, NF-κB, and AMPK signaling pathway. Sci Rep 10: 1593, 2020.
105. Muraleva NA, Tikhonov DI, Zhdankina AA, Plotnikov MB, Khlebnikov AI, Logvinov SV and Kolosova NG: Alterations of JNK signaling pathway activity in the rat retina: Effects of age, age-related macular degeneration-like pathology, and a JNK inhibitor (IQ-1S). Cells 14: 896, 2025.
106. Bain J, Later L, Elliot M, Shpiro N, Hastie CJ, Mclauchlan H, Klevernic I, Arthur JS, Alessi DR and Cohen P: The selectivity of protein kinase inhibitors: A further update. Biochem J 408: 297-315, 2007.
107. Bennett BL, Sasaki DT, Murray BW, O'Leary EC, Sakata ST, Xu W, Leisten JC, Motiwala A, Pierce S, Satoh Y, *et al*: SP600125, an anthrapyrazolone inhibitor of Jun N-Terminal kinase. Proc Natl Acad Sci USA 98: 13681, 2021.
108. Inesta-Vaquera FA, Campbell DG, Arthur JS and Cuenda A: ERK5 pathway regulates the phosphorylation of tumour suppressor hDlg during mitosis. Biochem Biophy Res Commun 399: 84-90, 2010.
109. Zhang T, Inesta-Vaquera F, Niepel M, Zhang J, Ficarro SB, Machleidt T, Xie T, Marto JA, Kim N, Sim T, *et al*: Discovery of potent and selective covalent inhibitors of JNK. Chem Biol 19: 140-154, 2012.
110. Lupachyk S, Watcho P, Stavniichuk R, Shevalye H and Obrosova IG: Endoplasmic reticulum stress plays a key role in the pathogenesis of diabetic peripheral neuropathy. Diabetes 62: 944-952, 2013.
111. Mei Y, Thompson MD, Cohen RA and Tong X: Endoplasmic reticulum stress and related pathological processes. J Pharmacol Biomed Anal 1: 1000107, 2013.
112. Zhang SX, Sanders E, Fliesler SJ and Wang JJ: Endoplasmic reticulum stress and the unfolded protein responses in retinal degeneration. Exp Eye Res 125: 30-40, 2014.
113. Faria JA, Reis PA, Reis MT, Rosado GL, Pinheiro GL, Mendes GC and Fontes EP: The NAC domain-containing protein, GmNAC6, is a downstream component of the ER stress- and osmotic stress-induced NRP-mediated cell-death signaling pathway. BMC Plant Biol 11: 129, 2011.
114. Tsai TC, Lai KH, Su JH, Wu YJ and Sheu JH: 7-Acetylsinumaximol B induces apoptosis and autophagy in human gastric carcinoma cells through Mitochondria Dysfunction and activation of the PERK/eIF2α/ATF4/CHOP signalling pathway. Mar Drugs 16: 104, 2018.
115. Narasimhan M and Rajasekaran NS: Reductive potential-a savior turns stressor in protein aggregation cardiomyopathy. Biochim Biophys Acta 1852: 53-60, 2015.
116. Wu K, Li B, Zhang X, Fang Y, Zeng S, Hu W, Liu X, Liu X, Lu Z, Li X, *et al*: Correction for Wu *et al*., 'CSFV restricts necroptosis to sustain infection by inducing autophagy/mitophagy-targeted degradation of RIPK3'. Microbiol Spectr 13: e0318824, 2025.
117. Koniari I, Velissaris D, Kounis NG, Koufou E, Artopoulou E, de Gregorio C, Mplani V, Paraskevas T, Tsigkas G, Hung MY, *et al*: Anti-diabetic therapy, heart failure and oxidative stress: An update. J Clin Med 11: 4660,2022.
118. Gonen N, Sabath N, Burge CB and Shalgi R: Widespread PERK-dependent repression of ER targets in response to ER stress. Sci Rep 9: 4330, 2019.
119. Nita M and Grzybowski A: Antioxidative role of heterophagy, autophagy, and mitophagy in the retina and their association with the age-related macular degeneration (AMD) etiopathogenesis. Antioxidants (Basel) 12: 1368, 2023.
120. Bae D, Jones RE, Piscopo KM, Tyagi M, Shepherd JD and Hollien J: Regulation of Blos1 by IRE1 prevents the accumulation of Huntingtin protein aggregates. Mol Biol Cell 33: ar125, 2022.
121. Jin B, Ishikawa T, Taniguchi M, Ninagawa S, Okada T, Kagaya S and Mori K: Development of a rapid in vivo assay to evaluate the efficacy of IRE1-specific inhibitors of the unfolded protein response using medaka fish. Cell Struct Funct 45: 23-31, 2020.
122. Niu F, Liu W, Ren Y, Tian Y, Shi W, Li M, Li Y, Xiong Y and Qian L: β-cell neogenesis: A rising star to rescue diabetes mellitus. J Adv Res 62: 71-89, 2024.
123. Flintoaca Alexandru PR, Chiritoiu GN, Lixandru D, Zurac S, Ionescu-Targoviste C and Petrescu SM: EDEM1 regulates the insulin mRNA level by inhibiting the endoplasmic reticulum stress-induced IRE1/JNK/c-Jun pathway. iScience 26: 107956, 2023.
124. Flores-Santibáñez F, Medel B, Bernales JI and Osorio F: Understanding the role of the unfolded protein response sensor IRE1 in the biology of antigen presenting cells. Cells 8: 1563, 2019.

125. Arunagiri A, Haataja L, Cunningham CN, Shrestha N, Tsai B, Qi L, Liu M and Arvan P: Misfolded proinsulin in the endoplasmic reticulum during development of beta cell failure in diabetes. Ann NY Acad Sci 1418: 5-19, 2018.
126. Figueroa-Juárez E, Noriega LG, Pérez-Monter C, Alemán G, Hernández-Pando R, Correa-Rotter R, Ramírez V, Tovar AR, Torre-Villalvazo I and Tovar-Palacio C: The role of the unfolded protein response on renal lipogenesis in C57BL/6 mice. Biomolecules 11: 73, 2021.
127. Wu L, He S, Ye W, Shen J, Zhao K, Zhang Y, Zhang R, Wei J, Cao S, Chen K, *et al*: Surf4 facilitates reprogramming by activating the cellular response to endoplasmic reticulum stress. Cell Prolif 54: e13133, 2021.
128. Fu YL, Han DY, Wang YJ, Di XJ, Yu HB and Mu TW: Remodeling the endoplasmic reticulum proteostasis network restores proteostasis of pathogenic GABAA receptors. PLoS One 13: e0207948, 2018.
129. Wang D, Qu S, Zhang Z, Tan L, Chen X, Zhong HJ and Chong CM: Strategies targeting endoplasmic reticulum stress to improve Parkinson's disease. Front Pharmacol 14: 1288894, 2023.
130. Pérez-Martí A, Ramakrishnan S, Li J, Dugourd A, Molenaar MR, De La Motte LR, Grand K, Mansouri A, Parisot M, Lienkamp SS, *et al*: Reducing lipid bilayer stress by monounsaturated fatty acids protects renal proximal tubules in diabetes. Elife 11: e74391, 2022.
131. Hollien J and Weissman JS: Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. Science 313: 104-107, 2006.
132. Huang M, Cai S and Su J: The pathogenesis of sepsis and potential therapeutic targets. Int J Mol Sci 20: 5376, 2019.
133. Wise R, Duhachek-Muggy S, Qi Y, Zolkiewski M and Zolkiewska A: Protein disulfide isomerases in the endoplasmic reticulum promote anchorage-independent growth of breast cancer cells. Breast Cancer Res Treat 157: 241-252, 2016.
134. Schäffer DE, Iyer LM, Burroughs AM and Aravind L: Functional innovation in the evolution of the calcium-dependent system of the eukaryotic endoplasmic reticulum. Front Genet 11: 34, 2020.
135. AlBashtawi J, Al-Jaber H, Ahmed S and Al-Mansoori L: Impact of obesity-related endoplasmic reticulum stress on cancer and associated molecular targets. Biomedicines 12: 793, 2024.
136. Park SJ, Li C and Chen YM: Endoplasmic reticulum calcium homeostasis in kidney disease: Pathogenesis and therapeutic targets. Am J Pathol 191: 256-265, 2021.
137. Krebs J, Agellon LB and Michalak M: Ca(2+) homeostasis and endoplasmic reticulum (ER) stress: an integrated view of calcium signaling. Biochem. Biophys Res Commun 460: 114-121, 2015.
138. Lim W, Yang C, Jeong M, Bazer FW and Song G: Coumestrol induces mitochondrial dysfunction by stimulating ROS production and calcium ion influx into mitochondria in human placental choriocarcinoma cells. Mol Hum Reprod 23: 786-802, 2017.
139. Bahar E, Kim H and Yoon H: ER stress-mediated signaling: Action potential and ca(2+) as key players. Int J Mol Sci 17: 1558, 2016.
140. Zheng Q, Chen Y, Chen D, Zhao H, Feng Y, Meng Q, Zhao Y and Zhang H: Calcium transients on the ER surface trigger liquid-liquid phase separation of FIP200 to specify autophagosome initiation sites. Cell 185: 4082-4098.e22, 2022.
141. Høyer-Hansen M, Bastholm L, Szyniarowski P, Campanella M, Szabadkai G, Farkas T, Bianchi K, Fehrenbacher N, Elling F, Rizzuto R, *et al*: Control of macroautophagy by calcium, calmodulin-dependent kinase kinase-beta, and Bcl-2. Mol Cell 25: 193-205, 2007.
142. La Rovere RM, Roest G, Bultynck G and Parys JB: Intracellular ca(2+) signalling and ca(2+) microdomains in the control of cell survival, apoptosis and autophagy. Cell Calcium 60: 74-87, 2016.
143. Sakaki K, Wu J and Kaufman RJ: Protein kinase Ctheta is required for autophagy in response to stress in the endoplasmic reticulum. J Biol Chem 283: 15370-15380, 2008.
144. Levin-Salomon V, Bialik S and Kimchi A: DAP-kinase and autophagy. Apoptosis 19: 346-356, 2014.
145. Zhong Y, Jin C, Han J, Zhu J, Liu Q, Sun D, Xia X, Zhang Y and Peng X: Diosgenin protects against kidney Injury and mitochondrial apoptosis Induced by 3-MCPD through the regulation of ER stress, Ca(2+) homeostasis, and Bcl2 expression. Mol Nutr Food Res 65: e2001202, 2021.
146. Pu Q, Yu L, Wang X, Yan H, Xie Y, Jiang Y and Yang Z: Immunomodulatory effect of traditional Chinese medicine combined with systemic therapy on patients with liver cancer: A systemic review and network meta-analysis. J Cancer 13: 3280-3296, 2022.
147. Wan CP, Gao LX, Hou LF, Yang XQ, He PL, Yang YF, Tang W, Yue JM, Li J and Zuo JP: Astragaloside II triggers T cell activation through regulation of CD45 protein tyrosine phosphatase activity. Acta Pharmacol Sin 34: 522-530, 2013.
148. Shen L, Luo H, Fan L, Tian X, Tang A, Wu X, Dong K and Su Z: Potential immunoregulatory mechanism of plant saponins: A review. Molecules 29: 113, 2023.
149. Nalbantsoy A, Nesil T, Yılmaz-Dilsiz O, Aksu G, Khan S and Bedir E: Evaluation of the immunomodulatory properties in mice and in vitro anti-inflammatory activity of cycloartane type saponins from Astragalus species. J Ethnopharmacol 139: 574-581, 2012.
150. Ju Y, Su Y, Chen Q, Ma K, Ji T, Wang Z, Li W and Li W: Protective effects of astragaloside IV on endoplasmic reticulum stress-induced renal tubular epithelial cells apoptosis in type 2 diabetic nephropathy rats. Biomed Pharmacother 109: 84-92, 2019.
151. Chen Y, Gui D, Chen J, He D, Luo Y and Wang N: Down-regulation of PERK-ATF4-CHOP pathway by astragaloside IV is associated with the inhibition of endoplasmic reticulum stress-induced podocyte apoptosis in diabetic rats. Cell Physiol Biochem 33: 1975-1987, 2014.
152. Wang ZS, Xiong F, Xie XH, Chen D, Pan JH and Cheng L: Astragaloside IV attenuates proteinuria in streptozotocin-induced diabetic nephropathy via the inhibition of endoplasmic reticulum stress. BMC Nephrol 16: 44, 2015.
153. Li M, Wang W, Xue J, Gu Y and Lin S: Meta-analysis of the clinical value of Astragalus membranaceus in diabetic nephropathy. J Ethnopharmacol 133: 412-419, 2011.
154. Xue HZ, Chen Y, Wang SD, Yang YM, Cai LQ, Zhao JX, Huang WJ and Xiao YH: Radix astragali and its representative extracts for diabetic nephropathy: Efficacy and molecular mechanism. J Diabetes Res 2024: 5216113, 2024.
155. Li Y and Wang J: Possible mechanism for the protective effect of active ingredients of astragalus membranaceus on diabetes nephropathy. J Asian Nat Prod Res 26: 1276-1284, 2024.
156. Zhang L, Shergis JL, Yang L, Zhang AL, Guo X, Zhang L, Zhou S, Zeng L, Mao W and Xue CC: Astragalus membranaceus (Huang Qi) as adjunctive therapy for diabetic kidney disease: an updated systematic review and meta-analysis. J Ethnopharmacol 239: 111921, 2019.
157. Guo JC, Pan HC, Yeh BY, Lu YC, Chen JL, Yang CW, Chen YC, Lin YH and Chen HY: Associations between using Chinese herbal medicine and long-term outcome among pre-dialysis diabetic nephropathy patients: A retrospective population-based cohort study. Front Pharmacol 12: 616522, 2021.
158. Cao JL, Liang LY, Liu YH, Xu ZM, Wang X, Wei WX, Wan HJ, Lyu XH, Li WX, Zhang YX, *et al*: Medication rules of Astragali Radix in ancient Chinese medical books based on 'disease-medicine-dose' pattern. Zhongguo Zhong Yao Za Zhi 50: 798-811, 2025 (In Chinese).
159. Hassanpour Fard M, Naseh G, Lotfi N, Hosseini SM and Hosseini M: Effects of aqueous extract of turnip leaf (Brassica rapa) in alloxan-induced diabetic rats. Avicenna J Phytomed 5: 148-156, 2015.
160. Santos M, Fortunato RH and Spotorno VG: Analysis of flavonoid glycosides with potential medicinal properties on Bauhinia uruguayensis and Bauhinia forficate subspecies pruinosa. Nat Prod Res 33: 2574-2578, 2019.
161. Chhatre S, Nesari T, Somani G, Kanchan D and Sathaye S: Phytopharmacological overview of Tribulus terrestris. Pharmacogn Rev 8: 45-51, 2014.
162. Abdou HM and Abd Elkader HAE: The potential therapeutic effects of Trifolium alexandrinum extract, hesperetin and quercetin against diabetic nephropathy via attenuation of oxidative stress, inflammation, GSK-3β and apoptosis in male rats. Chem Biol Interact 352: 109781, 2022.
163. Alshehri AS: Kaempferol attenuates diabetic nephropathy in streptozotocin-induced diabetic rats by a hypoglycaemic effect and concomitant activation of the Nrf-2/Ho-1/antioxidants axis. Arch Physiol Biochem 129: 984-997, 2023.
164. Luo W, Chen X, Ye L, Chen X, Jia W, Zhao Y, Samorodov AV, Zhang Y, Hu X, Zhuang F, *et al*: Kaempferol attenuates streptozotocin-induced diabetic nephropathy by downregulating TRAF6 expression: The role of TRAF6 in diabetic nephropathy. J Ethnopharmacol 268: 113553, 2021.
165. Li K, Wang YJ, Chen C, Wang XJ and Li W: Targeting pyroptosis: A novel strategy of ginseng for the treatment of diabetes and its chronic complications. Phytomedicine 138: 156430, 2025.

166. Wu W, Hu W, Han WB, Liu YL, Tu Y, Yang HM, Fang QJ, Zhou MY, Wan ZY, Tang RM, *et al*: Inhibition of Akt/mTOR/p70S6K signaling activity with Huangkui capsule alleviates the early glomerular pathological changes in diabetic nephropathy. Front Pharmacol 9: 443, 2018.
167. Han W, Ma Q, Liu Y, Wu W, Tu Y, Huang L, Long Y, Wang W, Yee H, Wan Z, *et al*: Huangkui capsule alleviates renal tubular epithelial-mesenchymal transition in diabetic nephropathy via inhibiting NLRP3 inflammasome activation and TLR4/NF-κB signaling. Phytomedicine 57: 203-214, 2019.
168. Zhu Z, Luan G, Peng S, Fang Y, Fang Q, Shen S, Wu K, Qian S, Jia W, Ye J and Wei L: Huangkui capsule attenuates diabetic kidney disease through the induction of mitophagy mediated by STING1/ PINK1 signaling in tubular cells. Phytomedicine 119: 154975, 2023.
169. Shi R, Tao Y, Tang H, Wu C, Fei J, Ge H, Gu HF and Wu J: Abelmoschus Manihot ameliorates the levels of circulating metabolites in diabetic nephropathy by modulating gut microbiota in non-obese diabetes mice. Microb Biotechnol 16: 813-826, 2023.
170. Zhang L, Li P, Xing CY, Zhao JY, He YN, Wang JQ, Wu XF, Liu ZS, Zhang AP, Lin HL, *et al*: Efficacy and safety of Abelmoschus manihot for primary glomerular disease: A prospective, multicenter randomized controlled clinical trial. Am J Kidney Dis 64: 57-65, 2014.
171. Chen X, Yu Y, Xiao C, Li S, Wu T, Wu H, Li X, Lin C, Chen X, Guo X and Liu S: Huangkui capsules for diabetic nephropathy: Comprehensive review of efficacy and molecular mechanisms. Phytomedicine 147: 157207, 2025.
172. Liu X, Zhang C, Fu Y, Dai J, Lu J, Liu G and Yang X: Huangkui capsule combined with finerenone attenuates diabetic nephropathy by regulating the JAK2/STAT3 signaling pathway based on network pharmacology, molecular docking, and experimental verification. Front Pharmacol 16: 1625286, 2025.
173. Wang Y, He X, Xue M, Yu H, He Q and Jin J: Integrated 16S rRNA sequencing and metabolomic analysis reveals the potential protective mechanism of Germacrone on diabetic nephropathy in mice. Acta Biochim Biophys Sin (Shanghai) 56: 414-426, 2024.
174. Lee HS, Suh JY, Kang BC and Lee E: Lipotoxicity dysregulates the immunoproteasome in podocytes and kidneys in type 2 diabetes. Am J Physiol Renal Physiol 320: F548-F558, 2021.
175. Nemecz M, Constantin A, Dumitrescu M, Alexandru N, Filippi A, Tanko G and Georgescu A: The distinct effects of palmitic and oleic acid on pancreatic beta cell function: The elucidation of associated mechanisms and effector molecules. Front Pharmacol 9: 1554, 2021.
176. Liu Y, Jia Z, Liu S, Downton M, Liu G, Du Y and Yang T: Combined losartan and nitro-oleic acid remarkably improves diabetic nephropathy in mice. Am J Physiol Renal Physiol 305: F1555-F1562, 2013.
177. Liu Y, Hu Z, Xing H, Kang L, Chen X, Liu B and Niu K: Renoprotective effects of oleanolic acid and its possible mechanisms in rats with diabetic kidney disease. Biochem Biophys Res Commun 636 (Pt 1): 1-9, 2022.
178. Lee ES, Kim HM, Kang JS, Lee EY, Yadav D, Kwon MH, Kim YM, Kim HS and Chung CH: Oleanolic acid and N-acetylcysteine ameliorate diabetic nephropathy through reduction of oxidative stress and endoplasmic reticulum stress in a type 2 diabetic rat model. Nephrol Dial Transplant 31: 391-400, 2016.
179. Gao D, Li Q, Li Y, Liu Z, Liu Z, Fan Y, Han Z, Li J and Li K: Antidiabetic potential of oleanolic acid from Ligustrum lucidum Ait. Can J Physiol Pharmacol 85: 1076-1083, 2007.
180. Sultana N and Ata A: Oleanolic acid and related derivatives as medicinally important compounds. J Enzyme Inhib Med Chem 23: 739-756, 2008.
181. Abudoureyimu A, Chen C, Hu Y, Nuermaimaiti D and Liu T: Quercetin alleviates diabetic nephropathy by inhibiting M1 macrophage polarization via targeting NLRC5/NLRP3 pathway. Cell Immunol 414: 104997, 2025.
182. Yan X, Li P, Liu C, Yin F, Han J, Sun H, Zheng Y, Chen X, Guan S and Wang X: Exploring the molecular mechanisms for renoprotective effects of Huangkui capsule on diabetic nephropathy mice by comprehensive serum metabolomics analysis. J Ethnopharmacol 340: 119223, 2025.
183. Brito JCM, Lima WG, Cordeiro LPB and da Cruz Nizer WS: Effectiveness of supplementation with quercetin-type flavonols for treatment of viral lower respiratory tract infections: Systematic review and meta-analysis of preclinical studies. Phytother Res 35: 4930-4942, 2021.
184. Hu Q, Qu C, Xiao X, Zhang W, Jiang Y, Wu Z, Song D, Peng X, Ma X and Zhao Y: Flavonoids on diabetic nephropathy: Advances and therapeutic opportunities. Chin Med 16: 74, 2021.
185. Hu T, Yue J, Tang Q, Cheng KW, Chen F, Peng M, Zhou Q and Wang M: The effect of quercetin on diabetic nephropathy (DN): A systematic review and meta-analysis of animal studies. Food Funct 13: 4789-4803, 2022.
186. Lai WF and Wong WT: Design and optimization of quercetin-based functional foods. Crit Rev Food Sci Nutr 62: 7319-7335, 2022.
187. Albadrani GM, Binmowyna MN, Bin-Jumah MN, El-Akabawy G, Aldera H and Al-Farga AM: Quercetin protects against experimentally-induced myocardial infarction in rats by an antioxidant potential and concomitant activation of signal transducer and activator of transcription 3. J Physiol Pharmacol: Apri 22, 2020 (Epub ahead of print).
188. Dini S, Zakeri M, Ebrahimpour S, Dehghanian F and Esmaeili A: Quercetin-conjugated superparamagnetic iron oxide nanoparticles modulate glucose metabolism-related genes and miR-29 family in the hippocampus of diabetic rats. Sci Rep 11: 8618, 2021.
189. Suganya N, Dornadula S, Chatterjee S and Mohanram RK: Quercetin improves endothelial function in diabetic rats through inhibition of endoplasmic reticulum stress-mediated oxidative stress. Eur J Pharmacol 819: 80-88, 2018.
190. Zhong Y, Lee K, Deng Y, Ma Y, Chen Y, Li X, Wei C, Yang S, Wang T, Wong J, *et al*: Arctigenin attenuates diabetic kidney disease through the activation of PP2A in podocytes. Nat Commun 10: 4523, 2019.
191. Li X, Wang J, Yan J, He JC, Li Y and Zhong Y: Additive renal protective effects between arctigenin and puerarin in diabetic kidney disease. Biomed Pharmacother 171: 116107, 2024.
192. Medras ZJH, Mostafa YM, Ahmed AAM and El-Sayed NM: Arctigenin improves neuropathy via ameliorating apoptosis and modulating autophagy in streptozotocin-induced diabetic mice. CNS Neurosci Ther 29: 3068-3080, 2023.
193. Wang W, Qiu L, Howard A, Solis N, Li C, Wang X, Kopp JB and Levi M:. Protective effects of aliskiren and valsartan in mice with diabetic nephropathy. J Renin Angiotensin Aldosterone Syst 15: 384-395, 2014.
194. López V, Martin M, Cobelo C, Aranda P, Cabello M, Sola E, Gutierrez C, Burgos D, Martínez D and Hernandez D: Renin-angiotensin system dual blockade using angiotensin receptor plus aliskiren decreases severe proteinuria in kidney transplant recipients. Transplant Proc 42: 2883-2885, 2010.
195. Sun Y, Peng PA, Ma Y, Liu XL, Yu Y, Jia S, Xu XH, Wu SJ and Zhou YJ: Valsartan protects against contrast-induced acute kidney injury in rats by inhibiting endoplasmic reticulum stress-induced apoptosis. Curr Vasc Pharmacol 15: 174-183, 2017.
196. Li C, Lin Y, Luo R, Chen S, Wang F, Zheng P, Levi M, Yang T and Wang W: Intrarenal renin-angiotensin system mediates fatty acid-induced ER stress in the kidney. Am J Physiol Renal Physiol 310: F351-F363, 2016.
197. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group: KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 98 (4S): S1-S115, 2020.
198. Chang TT, Wu TC, Huang PH, Lin CP, Chen JS, Lin LY, Lin SJ and Chen JW: Direct renin inhibition with aliskiren improves ischemia-induced neovasculogenesis in diabetic animals via the SDF-1 related mechanism. PLoS One 10: e0136627, 2015.
199. Wang Z, Yuan A, Liu C, Liu Y, Qiao L, Xu Z, Bi S, Tian J, Yu B, Lin Z, *et al*: Identification of key antifibrotic targets FPR1, TAS2R5, and LRP2BP of valsartan in diabetic nephropathy: A transcriptomics-driven study integrating machine learning, molecular docking, and dynamics simulations. Int J Biol Macromol 297: 139842, 2025.
200. Zhang H, Liu G, Zhou W, Zhang W, Wang K and Zhang J: Neprilysin inhibitor-angiotensin II receptor blocker combination therapy (Sacubitril/valsartan) suppresses atherosclerotic plaque formation and inhibits inflammation in apolipoprotein E-deficient mice. Sci Rep 9: 6509, 2019.
201. Ma Y, Xie D, Liu J, Han X, Xu H and Chen Y: Angiopoietin-like protein 3 deficiency combined with valsartan administration protects better against podocyte damage in streptozotocin-induced diabetic nephropathy mice. Int Immunopharmacol 115: 109715, 2023.

202. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 105: S117-S314, 2024.
203. Mori K, Togo A, Ohta K, Asahi T, Nozaki C and Kataoka K: CB1 receptor agonist ACEA Resists ER stress-mediated apoptosis via CB1R-independent mechanism. Biol Pharm Bull 48: 769-781, 2025.
204. Vasincu A, Rusu RN, Ababei DC, Neamțu M, Arcan OD, Macadan I, Beșchea Chiriac S, Bild W and Bild V: Exploring the therapeutic potential of cannabinoid receptor antagonists in inflammation, diabetes mellitus, and obesity. Biomedicines 11: 1667, 2023.
205. Aguirre CA, Castillo VA and Llanos MN: Excess of the endocannabinoid anandamide during lactation induces overweight, fat accumulation and insulin resistance in adult mice. Diabetol Metab Syndr 4: 35, 2012.
206. Kumawat VS and Kaur G: Cannabinoid receptor 2 (CB2) agonists and L-arginine ameliorate diabetic nephropathy in rats by suppressing inflammation and fibrosis through NF-κβ pathway. Naunyn Schmiedebergs Arch Pharmacol 397: 381-393, 2024.
207. Jourdan T, Park JK, Varga ZV, Pálóczi J, Coffey NJ, Rosenberg AZ, Godlewski G, Cinar R, Mackie K, Pacher P and Kunos G: Cannabinoid-1 receptor deletion in podocytes mitigates both glomerular and tubular dysfunction in a mouse model of diabetic nephropathy. Diabetes Obes Metab 20: 698-708, 2018.
208. Barutta F, Piscitelli F, Pinach S, Bruno G, Gambino R, Rastaldi MP, Salvidio G, Di Marzo V, Cavallo Perin P and Gruden G: Protective role of cannabinoid receptor type 2 in a mouse model of diabetic nephropathy. Diabetes 60: 2386-2396, 2011.
209. Yang HM, Kim J, Kim BK, Seo HJ, Kim JY, Lee JE, Lee J, You J, Jin S, Kwon YW, *et al*: Resistin regulates inflammation and insulin resistance in humans via the endocannabinoid system. Research (Wash D C) 7: 0326, 2024.
210. Lim JC, Lim SK, Park MJ, Kim GY, Han HJ and Park SH: Cannabinoid receptor 1 mediates high glucose induced apoptosis via endoplasmic reticulum stress in primary cultured rat mesangial cells. Am J Physiol Renal Physiol 301: F179-F188, 2011.
211. Lim JC, Lim SK, Han HJ, and Park SH: Cannabinoid receptor 1 mediates palmitic acid-induced apoptosis via endoplasmic reticulum stress in human renal proximal tubular cells. J Cell Physiol 225: 654-663, 2010.
212. Panlilio LV, Goldberg SR and Justinova Z: Cannabinoid abuse and addiction: Clinical and preclinical findings. Clin Pharmacol Ther 97: 616-627, 2015.
213. Cinar R, Iyer MR and Kunos G: The therapeutic potential of second and third generation CB_1R antagonists. Pharmacol Ther 208: 107477, 2020.
214. Mińczuk K, Baranowska-Kuczko M, Krzyżewska A, Schlicker E and Malinowska B: Cross-Talk between the (Endo) cannabinoid and renin-angiotensin systems: Basic evidence and potential therapeutic significance. Int J Mol Sci 23: 6350, 2022.
215. Jourdan T, Szanda G, Cinar R, Godlewski G, Holovac DJ, Park JK, Nicoloro S, Shen Y, Liu J, Rosenberg AZ, *et al*: Developmental role of macrophage cannabinoid-1 receptor signaling in type 2 diabetes. Diabetes 66: 994-1007, 2017.
216. Jourdan T, Szanda G, Rosenberg AZ, Tam J, Earley BJ, Godlewski G, Cinar R, Liu Z, Liu J, Ju C, *et al*: Overactive cannabinoid 1 receptor in podocytes drives type 2 diabetic nephropathy. Proc Natl Acad Sci USA 111: E5420-E5428, 2014.
217. Ghosh A, Peyot ML, Leung YH, Ravenelle F, Madiraju SRM and Prentki M: A peripherally restricted cannabinoid-1 receptor inverse agonist promotes insulin secretion and protects from cytokine toxicity in human pancreatic islets. Eur J Pharmacol 944: 175589, 2023.
218. Rajesh M, Bátkai S, Kechrid M, Mukhopadhyay P, Lee WS, Horváth B, Holovac E, Cinar R, Liaudet L, Mackie K, *et al*: Cannabinoid 1 receptor promotes cardiac dysfunction, oxidative stress, inflammation, and fibrosis in diabetic cardiomyopathy. Diabetes 61: 716-727, 2012.
219. Haspula D and Clark MA: Cannabinoid receptors: An update on cell signaling, pathophysiological roles and therapeutic opportunities in neurological, cardiovascular, and inflammatory diseases. Int J Mol Sci 21: 7693, 2020.
220. Pointeau O, Ba AI, Geissler A, Barbosa R, Basu A, Muhammad A, Nivot M, Loriot M, Leemput J, Passilly-Degrace P, *et al*: Blockade of cannabinoid CB receptors potentiates the anti-fibrotic effects mediated by SGLT2 inhibition in a mouse model of diabetic nephropathy. Br J Pharmacol 182: 5355-5377, 2025.
221. Dagon Y, Avraham Y, Link G, Zolotarev O, Mechoulam R and Berry EM: The synthetic cannabinoid HU-210 attenuates neural damage in diabetic mice and hyperglycemic pheochromocytoma PC12 cells. Neurobiol Dis 27: 174-181, 2007.
222. Navas-Madroñal M, Almendra-Pegueros R, Puertas-Umbert L, Jiménez-Altayó F, Julve J, Pérez B, Consegal-Pérez M, Kassan M, Martínez-González J, Rodriguez C and Galán M: Targeting mitochondrial stress with szeto-schiller 31 prevents experimental abdominal aortic aneurysm: Crosstalk with endoplasmic reticulum stress. Br J Pharmacol 180: 2230-2249, 2023.
223. Hinden L, Udi S, Drori A, Gammal A, Nemirovski A, Hadar R, Baraghithy S, Permyakova A, Geron M, Cohen M, *et al*: Modulation of renal GLUT2 by the cannabinoid-1 receptor: Implications for the treatment of diabetic nephropathy. J Am Soc Nephrol 29: 434-448, 2018.
224. Kusaczuk M: Tauroursodeoxycholate-bile acid with chaperoning activity: Molecular and cellular effects and therapeutic perspectives. Cell 8: 1471, 2019.
225. Zheng P, Lin Y, Wang F, Luo R, Zhang T, Hu S, Feng P, Liang X, Li C and Wang W: 4-PBA improves lithiuminduced nephrogenic diabetes insipidus by attenuating ER stress. Am J Physiol Renal Physiol 311: F763-F776, 2016.
226. Guo Q, Xu L, Li H, Sun H, Wu S and Zhou B: 4-PBA reverses autophagic dysfunction and improves insulin sensitivity in adipose tissue of obese mice via Akt/mTOR signaling. Biochem Biophys Res Commun 484: 529-535, 2017.
227. Ji X, Yao L, Wang M, Liu X, Peng S, Li K, Xu M, Shen N, Luo L and Sun C: Cystatin C attenuates insulin signaling transduction by promoting endoplasmic reticulum stress in hepatocytes. FEBS Lett 589 (24 Part B): 3938-3944, 2015.
228. Cao AL, Wang L, Chen X, Wang YM, Guo HJ, Chu S, Liu C, Zhang XM and Peng W: Ursodeoxycholic acid and 4-phenylbutyrate prevent endoplasmic reticulum stressinduced podocyte apoptosis in diabetic nephropathy. Lab Invest 96: 610-622, 2016.
229. Qin L, Wang Z, Tao L and Wang Y: ER stress negatively regulates AKT/TSC/mTOR pathway to enhance autophagy. Autophagy 6: 239-247, 2010.
230. Ni L, Yuan C and Wu X: Endoplasmic reticulum stress in diabetic nephrology: Regulation, pathological role, and therapeutic potential. Oxid Med Cell Longev 2021: 7277966, 2021.
231. Chang YC, Hee SW, Hsieh ML, Jeng YM and Chuang LM: The role of organelle stresses in diabetes mellitus and obesity: Implication for treatment. Anal Cell Pathol (Amst) 2015: 972891, 2015.
232. De Miguel C, Sedaka R, Kasztan M, Lever JM, Sonnenberger M, Abad A, Jin C, Carmines PK, Pollock DM and Pollock JS: Tauroursodeoxycholic acid (TUDCA) abolishes chronic high salt-induced renal injury and inflammation. Acta Physiol (Oxf) 226: e13227, 2019.
233. Microvascular Complications Group of Chinese Diabetes Society: Clinical guideline for the prevention and treatment of diabetic kidney disease in China (2021 edition). Chin J Diabetes Mellitus 13: 762-784, 2021 (In Chinese).
234. Li Z, Li Y, Overstreet JM, Chung S, Niu A, Fan X, Wang S, Wang Y, Zhang MZ and Harris RC: Inhibition of epidermal growth factor receptor activation is associated with improved diabetic nephropathy and insulin resistance in type 2 diabetes. Diabetes 67: 1847-1857, 2018.
235. Rao VRA/LBV, Tan SH, Candasamy M and Bhattamisra SK: Diabetic nephropathy: An update on pathogenesis and drug development. Diabetes Metab Syndr 13: 754-762, 2019.
236. Shih JY, Lin YW, Fisch S, Cheng JT, Kang NW, Hong CS, Chen ZC and Chang WT: Dapagliflozin suppresses ER stress and improves subclinical myocardial function in diabetes. From bedside to bench. Diabetes 70: 262-267, 2021.
237. Yu Y, Xia X, Li H, Zhang Y, Zhou X and Jiang H: A new rhodopsin R135W mutation induces endoplasmic reticulum stress and apoptosis in retinal pigment epithelial cells. J Cell Physiol 234: 14100-14108, 2019.
238. Fang Q, Zou C, Zhong P, Lin F, Li W, Wang L, Zhang Y, Zheng C, Wang Y, Li X and Liang G: EGFR mediates hyperlipidemia-induced renal injury via regulating inflammation and oxidative stress: The detrimental role and mechanism of EGFR activation. Oncotarget 7: 24361-24373, 2016.
239. Martín-Pérez R, Palacios C, Yerbes R, Cano-González A, Iglesias-Serret D, Gil J, Reginato MJ and López-Rivas A: Activated ERBB2/HER2 licenses sensitivity to apoptosis upon endoplasmic reticulum stress through a PERK-dependent pathway. Cancer Res 74: 1766-1777, 2014.

240. Zhou K, Zi X, Song J, Zhao Q, Liu J, Bao H and Li L: Molecular mechanistic pathways targeted by natural compounds in the prevention and treatment of diabetic kidney disease. Molecules 27: 6221, 2022.
241. Zhang L, Li C, Fu L, Yu Z, Xu G, Zhou J, Shen M, Feng Z, Zhu H, Xie T, *et al*: Protection of catalpol against triptolide-induced hepatotoxicity by inhibiting excessive autophagy via the PERK-ATF4-CHOP pathway. PeerJ 10: e12759, 2022.
242. Itoh T, Hatano R, Horimoto Y, Yamada T, Song D, Otsuka H, Shirakawa Y, Mastuoka S, Iwao N, Aune TM, *et al*: IL-26 mediates epidermal growth factor receptor-tyrosine kinase inhibitor resistance through endoplasmic reticulum stress signaling pathway in triple-negative breast cancer cells. Cell Death Dis 12: 520, 2021.
243. Wang L, Ding S, Hu Y, Su J, Zhu G, Hong H, Hou B, Dong Z, Xue Z, Wang J, *et al*: Targeting programmed cell death pathways: Emerging therapeutic strategies for diabetic kidney disease. Front Endocrinol (Lausanne) 16: 1513895, 2025.
244. Mima A: A narrative review of diabetic kidney disease: Previous and current evidence-based therapeutic approaches. Adv Ther 39: 3488-3500, 2022.
245. Kume S and Maegawa H: Lipotoxicity, nutrient-sensing signals, and autophagy in diabetic nephropathy. JMA J 3: 87-94, 2020.
246. Beal B, Buizen L, Yeung EK, Heath L, Houston L, Cherney DZI, Jardine M, Pollock C, Arnott C, Kotwal SS, *et al*: Effects of SGLT2 inhibition on insulin use in CKD and type 2 diabetes: Insights from the CREDENCE trial. Nephrol Dial Transplant 40: 1727-1735, 2025.
247. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group: KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 102 (5S): S1-S127, 2022.
248. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC and Zinman B; EMPA-REG OUTCOME Investigators: Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375: 323-334, 2016.
249. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M and Matthews DR; CANVAS Program Collaborative Group: Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377: 644-657, 2017.
250. Wiviott SD, Raz l, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, *et al*: Dapagliflozinand cardiovascular outcomes in type 2 diabetes. N Engl J Med 380: 347-357, 2019.
251. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, *et al*: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380: 2295-2306, 2019.
252. Barreiro E, Salazar-Degracia A, Sancho-Muñoz A and Gea J: Endoplasmic reticulum stress and unfolded protein response profile in quadriceps of sarcopenic patients with respiratory diseases. J Cell Physiol 234: 11315-11329, 2019.
253. Bohnert KR, McMillan JD and Kumar A: Emerging roles of ER stress and unfolded protein response pathways in skeletal muscle health and disease. J Cell Physiol 233: 67-78, 2018.
254. Liu CY, Hsu CC, Huang TT, Lee CH, Chen JL, Yang SH, Jiang JK, Chen WS, Lee KD and Teng HW: ER stress-related ATF6 upregulates CIP2A and contributes to poor prognosis of colon cancer. Mol Oncol 12: 1706-1717, 2018.
255. Ryu D, Seo WY, Yoon YS, Kim YN, Kim SS, Kim HJ, Park TS, Choi CS and Koo SH: Endoplasmic reticulum stress promotes LIPIN2-dependent hepatic insulin resistance. Diabetes 60: 1072-1081, 2011.
256. Toma L, Stancu CS and Sima AV: Endothelial dysfunction in diabetes is aggravated by glycated lipoproteins; Novel molecular therapies. Biomedicines 9: 18, 2020.
257. Marciniak SJ, Chambers JE and Ron D: Pharmacological targeting of endoplasmic reticulum stress in disease. Nat Rev Drug Discov 21: 115-140, 2022.
258. Anumas S and Inagi R: Mitigating lipotoxicity: A potential mechanism to delay chronic kidney disease progression using current pharmacological therapies. Nephrology (Carlton) 30: e70098, 2025.
259. Zheng T, Luo L, Wang X, Deng X and Xue M: Canagliflozin ameliorates diabetic podocyte damage via enriching mitochondria-associated endoplasmic reticulum membranes. Cell Signal 135: 112038, 2025.
260. Wang Y, Liu S, Zhu F, Wang X, Wang H, Long L, Xiao J and Guo C: Improved bioavailability and anti-nephrotoxicity efficacy of polydatin on cisplatin-induced AKI via a dual-targeting fucoidan delivery system. Int J Pharm X 10: 100422, 2025.
261. Fang Z, Liu R, Xie J and He JC: Molecular mechanism of renal lipid accumulation in diabetic kidney disease. J Cell Mol Med 28: e18364, 2024.
262. Ye S, Cheng Z, Zhuo D and Liu S: Different types of cell death in diabetic neuropathy: A focus on mechanisms and therapeutic strategies. Int J Mol Sci 25: 8126, 2024.
263. Ghemrawi R, Battaglia-Hsu SF and Arnold C: Endoplasmic reticulum stress in metabolic disorders. Cells 7: 63, 2018.
264. Chattopadhyay A, Kwartler CS, Kaw K, Li Y, Kaw A, Chen J, LeMaire SA, Shen YH and Milewicz DM: Cholesterol-induced phenotypic modulation of smooth muscle cells to macrophage/fibroblast-like cells is driven by an unfolded protein response. Arterioscler Thromb Vasc Biol 41: 302-316, 2021.
265. Dong L, Xu M, Li Y, Xu W, Wu C, Zheng H, Xiao Z, Sun G, Ding L, Li X, *et al*: SMURF1 attenuates endoplasmic reticulum stress by promoting the degradation of KEAP1 to activate NRF2 antioxidant pathway. Cell Death Dis 14: 361, 2023.
266. Rabhi N, Denechaud PD, Gromada X, Hannou SA, Zhang H, Rashid T, Salas E, Durand E, Sand O, Bonnefond A, *et al*: KAT2B is required for pancreatic beta cell adaptation to metabolic stress by controlling the unfolded protein response. Cell Rep 15: 1051-1061, 2016.
267. Wang Y, Zhou X, Zhao D, Wang X, Gurley EC, Liu R, Li X, Hylemon PB, Chen W and Zhou H: Berberine inhibits free fatty acid and LPS-induced inflammation via modulating ER stress response in macrophages and hepatocytes. PLoS One 15: e0232630, 2020.
268. Yang M, Liu C, Jiang N, Liu Y, Luo S, Li C, Zhao H, Han Y, Chen W, Li L, *et al*: Endoplasmic reticulum homeostasis: A potential target for diabetic nephropathy. Front Endocrinol (Lausanne) 14: 1182848, 2023.
269. Pennell JP: Optimizing medical management of patients with pre-end-stage renal disease. Am J Med 111: 559-568, 2001.
270. Kim SH, Yoo JH, Lee WJ and Park CY: Gemigliptin: An update of its clinical use in the management of type 2 diabetes mellitus. Diabetes Metab J 40: 339-353, 2016.
271. Frăţilă VG, Lupuşoru G, Sorohan BM, Obrişcă B, Mocanu V, Lupuşoru M and İsmail G: Nephrotic Syndrome: From pathophysiology to novel therapeutic approaches. Biomedicines 12: 569, 2024.