REVIEW

Resveratrol: Evidence for Its Nephroprotective Effect in Diabetic Nephropathy

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ABSTRACT

Diabetic nephropathy (DN) is a severe complication of diabetes mellitus (DM). Dietary habits play a major role in determining the onset and progression of DM-related disorders and a proper diet (rich in fruits and vegetables) can delay or prevent the process of DM pathogenesis. Thus, increasing attention has been paid to polyphenols and polyphenol-rich foods since their increased intake has been associated with a reduced incidence of DM and its associated complications. Resveratrol is a polyphenolic phytoalexin that is mainly found in grapevines and berries. It is available in various pharmaceutical dosages and is widely recommended as a dietary supplement due to its beneficial effects. Remarkably, resveratrol's capability to effectively lower blood glucose levels without any side effects has been amply demonstrated in many in vitro and in vivo studies. Herein, we comprehensively review and discuss the nephroprotective effect of resveratrol during DN and its associated mechanisms. Resveratrol exerts its nephroprotective effects via various mechanisms including reducing oxidative stress and advanced glycation end-product (AGE) production, stimulating autophagy, inhibiting endoplasmic reticulum (ER) stress and inflammation, ameliorating lipotoxicity, activating the AMP kinase (AMPK) pathway, and modulating angiogenesis. Moreover, the use of resveratrol as an adjuvant to conventional antidiabetic therapies could be an effective approach to manage DN in humans. However, evidence is scarce to support whether resveratrol has beneficial effects in humans during DN. Therefore, clinical studies are warranted to elucidate resveratrol's role against DN. *Adv Nutr* 2020;11:1555–1568.

Keywords: polyphenols, diabetes mellitus, diabetic nephropathy, oxidative stress, AMPK, autophagy

Introduction

Diabetes mellitus (DM) is a noncommunicable chronic metabolic disease, which is predisposed by sustained hyperglycemia due to defects in either insulin secretion or insulin action (1). The complication associated with DM in the kidneys is often referred to as diabetic nephropathy (DN), which accounts for ~44.5% of end-stage renal disease (ESRD) in the United States alone (2). DN is one of the major and serious long-term complications of DM (3). Pathologically, DN is characterized by glomerular and basal membrane thickening, accumulation of extracellular matrix (ECM) components, and associated progressive mesangial expansion, glomerulosclerosis, and extensive reduction in glomerular filtration surface (4). These complex procedures in the kidneys eventually result in ESRD, and in such conditions dialysis or transplantation is required for treatment. Numerous factors have been identified behind these pathological changes, such as hyperglycemia, accumulation of advanced glycation end-products (AGEs), oxidative stress, mechanical stress, upregulation of the polyol pathway, and enhanced expression of growth factors including transforming growth factor β (TGF-β) and angiotensin II (5, 6).

The progression of DN can be divided into 5 clinical stages depending on the disease duration and conditions. The first stage of DN starts soon after the onset of DM in which renal vasodilation and hyperfiltration occur (7). Stage 2 of DN is characterized by morphologic lesions and an augmented glomerular filtration rate (GFR) (8). The third stage of DN, also referred to as "incipient DN," is characterized by small amounts of urine albumin, and this may progress to microalbuminuria (30–299 mg/d) accompanied by increased blood pressure and reduced GFR [<60 mL/(min · 1.73 m^2)] (9). Stage 4 of DN is referred to as "overt DN," which is characterized by macroalbuminuria (>300 mg/d) or persistent proteinuria (>500 mg/d), hypertension, and declined renal function [GFR, <30 mL/(min · 1.73 m^2)] (10). The last stage of DN is typically referred to as

ESRD, which is characterized by uremia and a severe decline in GFR [<15 mL/(min · 1.73 m^2)] (11).

Dietary habits play a major role in determining the onset and progression of DM-related disorders, and a proper diet (rich in fruits and vegetables) can delay or prevent the process of DM pathogenesis (12). Thus, increasing attention has been paid to polyphenols and polyphenol-rich foods since their increased intake has been associated with a reduced incidence of DM and its associated complications (13). Resveratrol is a phytoalexin phenolic metabolite produced in response to environmental stress in >70 plant species, especially grapevine (14). In addition, resveratrol is also available in various pharmaceutical dosages and is widely recommended as a dietary supplement (15). Several animal studies revealed the beneficial effects of resveratrol against DM and its associated complications (16–18). Resveratrol was also found to prevent DM-induced renal inflammation and mesangial cell proliferation and ameliorate glomerular matrix expansion and mesangial cell glucolipotoxicity, indicating its beneficial effect on kidney function during DM (19, 20). Although there are many clinical trials on the effect of resveratrol treatment in individuals with DM, very limited studies are available on its effect on kidney function during DM. In a randomized, double-blind study by Brasnyó et al. (21), oral administration of resveratrol (10 mg/d) in individuals with type 2 diabetes (T2D) significantly improved their kidney function as evidenced by decreased serum creatinine concentrations and maintained GFR (21). In another study, administration of resveratrol (250 mg/d) for 4 mo in T2D patients resulted in reduced serum creatinine and urea nitrogen concentrations and total protein excretion (22). Furthermore, a recent randomized, double-blind, placebo-controlled clinical trial showed that resveratrol (500 mg/d) significantly reduced the albumin to creatinine ratio in T2D patients, indicating that resveratrol is a promising adjuvant to angiotensin receptor blockers (ARBs) for reducing urinary albumin excretion in patients with DN (23). Altogether, a plethora of studies including in vitro and preclinical studies have contributed to a better understanding of the efficacy of resveratrol for the management of DN. In this review, we summarize and discuss the major mechanisms and associated signaling pathways underlying resveratrol's protective effects against DN to shed some light on the potential of this remarkable phytochemical for the control of DN.

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Abbreviations used: AGE, advanced glycation end-product; AdipoR, adiponectin receptor; Akt, protein kinase B; AMPK, AMP-activated protein kinase; ARB, angiotensin receptor blocker; ATF, activating transcription factor; Atg, autophagy gene; ATM, protein kinase ataxia-telangiectasia; (Bnip3), BCL2/adenovirus E1B 19kDa interacting protein 3; CHOP, C/EBP homologous protein; DM, diabetes mellitus; DN, diabetic nephropathy; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ESRD, end-stage renal disease; Flk-1, fetal liver kinase; FOXO, forkhead box O; GFR, glomerular filtration rate; GRP78, glucose-regulated protein 78; Keap1, Kelch-like ECH-associated protein 1; LC3, microtubule-associated protein 1A/1B-light chain 3; miRNA, microRNA; MnSOD, manganese superoxide dismutase; mTOR, mammalian target of rapamycin; NOX, NAD(P)H oxidase; NRF2, nuclear factor erythroid 2–related factor 2; p-, phosphorylated; PAI-1, plasminogen activator inhibitor 1; PCNA, proliferating cell nuclear antigen; PERK, protein kinase R-like ER kinase; PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α; PPARα, peroxisome proliferator-activated receptor α; PRR, Pro renin receptor; RAAS, renin-angiotensin aldosterone system; RAGE, advanced glycation end-product receptor; ROS, reactive oxygen species; SIRT1, sirtuin 1; SREBP1, sterol regulatory element-binding transcription factor 1; TGF-β1, transforming growth factor β1; T2D, type 2 diabetes mellitus; UPR, unfolded protein response; VEGF, vascular endothelial growth factor.

Current Status of Knowledge

Pathogenesis of DN

Subjects without DM do not develop the same kind of nephropathy as is developed in subjects with hyperglycemia; it is thought that hyperglycemia contributes largely to DN via initiating renal structural injury (24). Clusters of lesions including thickening of glomerular and tubular basement membrane, mesangial cell expansion, glomerular hyperfiltration, increased glomerular hydrostatic pressure, glomerulosclerosis, Kimmelstiel-Wilson nodules, and arteriolar hyalinosis represent the unique features of DN. These key features appear to be eventually involved in the escalation of albuminuria, reduced rate of glomerular filtration, arterial blood pressure elevation, and fluid retention (25–27). All of these pathological events contribute to the progression of the disease.

A number of studies have been conducted to delineate the molecular mechanisms involved in the pathological process of DN. Thus far, the literature data suggest that various pathways are altered in the course of DN. Activation of the small-GTPase binding protein Rho (Rho-kinase) signaling pathway can elicit endothelial dysfunction, ECM overproduction in mesangial cells, abnormal podocytes, and tubulointerstitial fibrosis (28). The hemodynamic pathway also has an important role in DN pathogenesis by upregulating the renin-angiotensin aldosterone system (RAAS) (29, 30). Binding of renin to its receptor [(Pro) renin receptor (PRR)] leads to elevation in inflammatory cytokines including TNF-α and IL-1β (31). Renin/PRR also modulates the expression of fibrotic factors such as transforming growth factor β1 (TGF-β1) and plasminogen activator inhibitor 1 (PAI-1), causing increased renal production of fibronectin and collagen type I and IV (32), and upregulates vascular endothelial growth factor (VEGF) (33). Intrarenal angiotensin II was considered to be the most biologically active product of the RAAS and its hyperactivation results in compromised renal function including reduced sodium excretion, which eventually leads to the renal injury observed in DN (34). Similar to renin, angiotensin II was also reported to increase the production of fibrotic elements such as TGF-β and PAI-1, thus instigating the accumulation of ECM components such as fibronectin, collagens, and laminin, which eventually perturb renal function (35, 36).

Mechanisms underlying the nephroprotective effects of resveratrol

In vitro and in vivo evidence thus far indicates that many mechanisms underlie the renoprotective and therapeutic effects of resveratrol against DN. The present review provides a

critical overview on key signaling pathways/mechanisms that are modulated by resveratrol and thought to be responsible for its beneficial effects. These include oxidative stress and AGEs, autophagy, lipotoxicity, endoplasmic reticulum (ER) stress and inflammation, the AMP kinase (AMPK) pathway, and angiogenesis.

Nephroprotective effect of resveratrol via modulating oxidative stress and AGEs

Microvascular complications of DM are mainly attributed to hyperglycemia, which has been identified as a primary factor responsible for the pathogenesis and progression of DN through metabolic derangements. Hyperglycemia-mediated oxidative stress is one such derangement (37), and reports suggest that elevated glucose flux can increase reactive oxygen species (ROS) production by the mitochondrial electron transport chain. ROS accumulation can overwhelm the cellular antioxidant defense system and thus induce renal damage via different mechanisms, including activation of the polyol pathway and hexosamine biosynthesis pathway, increased production of AGEs, and activation of protein kinase C (PKC) (38, 39). Meanwhile, it was also reported that blockade of ROS overproduction or interfering with ROS signaling could significantly attenuate these pathways and the associated complications (40). Therefore, natural products like resveratrol with potential antioxidant capacity are of high priority in the search for promising therapeutic agents for the control of DN. In fact, the capability of resveratrol to elicit antioxidant protection against DN has been demonstrated in a number of cell culture studies and preclinical investigations (**Table 1**). For instance, in a diabetic rat model (streptozotocin-induced DM), resveratrol treatment [5 and 10 mg/(kg · d)] significantly attenuated pre-DN symptoms including reduced clearance of creatinine and urea, proteinuria, and oxidative stress (elevated lipid peroxidation and decreased antioxidant enzyme activity) via its antioxidant activity (18). Kitada et al. (41) reported that resveratrol treatment (0.3% mixed with a nonpurified diet) ameliorated renal injury and decreased mitochondrial oxidative stress and biogenesis followed by normalization of manganese-superoxide dismutase (MnSOD) in DM mice (male *db/db* mice). Hence, resveratrol could protect against renal damage induced by oxidative stress in DM conditions by improving the antioxidant defense system and decreasing lipid peroxidation (41). Tubulointerstitial fibrosis is a primary predictor of renal dysfunction and a major feature of DN. Accumulating reports suggest that the induction of epithelial-to-mesenchymal transition (EMT) in renal tubular epithelial cells is a probable factor involved in the irreversible progression of tubulointerstitial fibrosis. Of note, high-glucose–induced (30 mmol glucose/L) EMT in renal tubular epithelial cells could be prevented by resveratrol treatment (5–20 μmol/L) via its ROS-scavenging capacity. Downregulation of the NAD(P)H oxidase (NOX) subunits NOX1 and NOX4 and extracellular signal-regulated kinase (ERK) 1/2 signaling pathway has been identified to account for the inhibition of ROS production by resveratrol (42).

AGEs, originating from binding of glucose with amino groups of proteins, lipids, and/or nucleic acids in circulation via an irreversible and nonenzymatic process, have been reported to be increased under hyperglycemic conditions (43). Increased production of AGEs and their accumulation in individuals with T2D could induce specific renal lesions, which eventually contribute to the loss of renal function (44). In particular, AGE formation was found to be doubled in DM individuals with ESRD compared with individuals with DM with no renal complications. AGE accumulation in individuals with DN is likely a result of their increased formation and decreased renal clearance (45). The primary pathway responsible for AGEs to exert their pathological effects is the interaction of AGEs with the receptor for AGEs (RAGE), and in kidney cells these interactions can lead to NF-κB activation. The activation of NF-κB can further enhance ROS production, leading to oxidative stress. AGEs can also increase the expression of growth factors and cytokines including TGF-β and connective tissue growth factor (CTGF). They were also reported to increase ECM component production and interact with the renin-angiotensin system (46). These biological activities largely account for the role of AGEs and RAGE in the pathogenic process of DM, including the development of tubulointerstitial damage in DN (46). Resveratrol treatment [1, 5, or 10 mg/(kg · d)] in DM rats (T2D) was shown to attenuate deleterious effects of AGEs by downregulating RAGE expression and reducing oxidative stress, despite not having a significant effect on AGE accumulation in kidney (47). In another study, it was reported that resveratrol treatment [5 mg/(kg · d)] in type 1 diabetes rats significantly ameliorated renal hypertrophy and structural changes, including tubular atrophy, mesangial expansion, diffused glomerulonephritis, and renal fibrosis. The authors also observed reduced AGE accumulation, oxidative stress, and DNA damage, without any significant change in RAGE expression (48). The discordance in these previous studies suggests the involvement of other pathway(s) rather than RAGE alone.

The nuclear factor erythroid 2–related factor 2 (Nrf2)–Kelch-like ECH-associated protein 1 (Keap1) signaling pathway is well known for its role in the regulation of antioxidant defense (49). Resveratrol exhibited antioxidative effects during DM through modulation of Nrf2–Keap1 and associated antioxidant response elements (AREs) and improved renal function. Hyperglycemia-induced oxidative stress increased the renal production of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 in DM rats. However, oral administration of resveratrol [5 mg/(kg · d)] significantly improved kidney dysfunction and decreased the expression of these proinflammatory cytokines, which was accompanied by an enhancement in the antioxidant defense system via normalizing the expression of Nrf2–Keap1 and its downstream regulatory proteins in DM rats (T2D) (50). Resveratrol (10 μM) treatment in mesangial cells has been shown to decrease high-glucose–induced (25 mmol glucose/L) cell proliferation and fibronectin expression through inhibition of c-Jun N-terminal kinase (JNK) and

TABLE 1 Nephroprotective effect of resveratrol during DN[1]

Reference	Description	Outcome	Significance
Nephroprotective effect of resveratrol via modulating oxidative stress and AGEs			
He et al., 2015 (42)[2]	In vitro: Resveratrol (5–20 μmol/L) on high-glucose–induced EMT in renal tubular epithelial cells	Resveratrol inhibited high-glucose–induced EMT by decreasing intracellular ROS via downregulation of NOX1, NOX4, and blockade of ERK1/2	The study suggests resveratrol is potent agent against high-glucose–induced EMT in renal tubular cells via inhibiting the NOX/ROS/ERK1/2 pathway
Zhang et al., 2012 (51)[2]	In vitro: Resveratrol (10 μmol/L) on high-glucose–induced mesangial cell proliferation and fibronectin expression	Resveratrol prevented high-glucose–induced mesangial cell proliferation and fibronectin expressions through inhibiting JNK and NF-κB activation, NAD(P)H oxidase activity elevation, and ROS production	This study suggests the JNK/NF-κB/NOX/ROS pathway may be a novel therapeutic target of resveratrol for DN
Xu et al., 2012 (52)[2]	In vitro: Resveratrol (10 μmol/L) against high-glucose–induced oxidative damage to mitochondria of rat mesangial cells	Resveratrol pretreatment ROS production and mitochondrial superoxide generation, as well as stimulated MnSOD activity; resveratrol also reversed the decrease in mitochondrial complex III activity in mesangial cells, which is a major source of mitochondrial oxidative stress	Resveratrol efficiently reduces oxidative stress and maintains mitochondrial function related to activating SIRT1 in glucose-treated mesangial cells
Wang et al., 2017 (53)[2]	In vitro: Effect of resveratrol treatment (25 μmol/L) on hyperglycemia-induced oxidative stress in human kidney epithelial cells	Resveratrol increased SIRT1 deacetylase activity, decreased the expression of acetylated-FOXO3a, and inhibited oxidative stress; silencing SIRT1 blocked the resveratrol action against oxidative stress	Resveratrol modulates the SIRT1/FOXO3a pathway by increasing SIRT1 deacetylase activity, subsequently ameliorating hyperglycemia-induced renal tubular oxidative stress damage
Zhang et al., 2019 (54)[2]	In vitro: Resveratrol (10 μmol/L) effect on high-glucose–induced oxidative stress and apoptosis in podocytes	Resveratrol attenuated high-glucose–induced ROS production and cell apoptosis, and increased the expression of SIRT1, PGC-1α, and its downstream genes NRF1 and mitochondrial transcription factor A, respiratory chain complex I and III activity, and mitochondrial membrane potential	Resveratrol ameliorates high-glucose–induced oxidative damage and apoptosis in podocytes via SIRT1/PGC-1α–mediated mitochondrial protection
Zhang et al., 2019 (55)[2]	In vitro: Resveratrol (10 μmol/L) on high-glucose–induced oxidative stress and apoptosis in mouse podocytes and renal tubular epithelial cells	Resveratrol inhibited excessive ROS production and apoptosis, improved respiratory chain complex I and III activity, elevated mitochondrial membrane potential	The study indicates that the renoprotective effect of resveratrol in DN is via SIRT1/PGC-1α–mediated attenuation of mitochondrial oxidative stress
Sharma et al., 2006 (18)	In vivo: Resveratrol [5 and 10 mg/(kg · d)] on renal function and oxidative stress in diabetic rats	Resveratrol attenuated pre-DN symptoms including reduced clearance of creatinine and urea, proteinuria, and oxidative stress (elevated lipid peroxidation and decreased antioxidant enzyme activity)	The study reinforces the importance of antioxidant capacity of resveratrol against renal dysfunction in DN
Kitada et al., 2011 (41)	In vivo: Resveratrol treatment (0.3% with nonpurified diet) on DN in *db/db* mice	Resveratrol treatment reduced urinary albumin excretion and attenuated renal pathological changes in *db/db* mice; it also decreased mitochondrial oxidative stress and biogenesis in the kidneys	Renoprotective effect of resveratrol in DN is through improvement of oxidative stress via normalization of MnSOD function

(*Continued*)

TABLE 1 (*Continued*)

Reference	Description	Outcome	Significance
Moridi et al., 2015 (47)	In vivo: Resveratrol [1, 5, 10 mg/(kg · d)] on RAGE and oxidative stress in diabetic rat kidney	Resveratrol treatment reduced malondialdehyde concentrations, plasma glucose, and expression of RAGE; the total antioxidant and insulin concentrations were significantly increased in resveratrol-treated rats	Renoprotective effect of resveratrol during DM is via attenuating oxidative stress and downregulation of RAGE expression
Al-Hussaini and Kilarkaje, 2018 (48)	In vivo: Resveratrol [5 mg/(kg · d)] on diabetes-induced oxidative DNA damage and AGEs in rat kidneys	Resveratrol reduced renal hypertrophy and structural changes such as tubular atrophy, mesangial expansion or shrinkage, diffuse glomerulonephritis, and fibrosis in diabetic rats; it also reduced AGE accumulation, oxidative stress, and DNA damage	The study suggests that resveratrol significantly alleviates diabetes-induced glycation, oxidative damage, and apoptosis to inhibit DN progression
Palsamy and Subramanian, 2011 (50)	In vivo: Renoprotective effect of resveratrol [5 mg/(kg · d)] during diabetes	Resveratrol normalized the levels of oxidative stress, inflammatory markers, renal expression of Nrf2/Keap1, and its downstream regulatory proteins in diabetic rats	This study demonstrates resveratrol's renoprotective effect via attenuating oxidative stress markers and normalizing antioxidative Nrf2–Keap1 signaling in renal tissues of diabetic rats
Hussein et al., 2016 (56)	In vivo: Resveratrol [5 mg/(kg · d)] on development and progression of DN in rats	Resveratrol improved the antioxidant defense mechanism and normalized renal mRNA expressions of TGF-B1, fibronectin, NF-κB/p65, Nrf2, Sirt1, and FOXO1	Resveratrol's anti-DN effect is mediated through improving glycemic control and attenuating oxidative damage in kidneys
Wang et al., 2017 (53)	In vivo: Resveratrol treatment [30 mg/(kg · d)] on hyperglycemia-induced oxidative stress in renal tubules in diabetic rats	Resveratrol ameliorated renal dysfunction and glomerulosclerosis; it also increased SIRT1 deacetylase activity, while decreasing acetylated-FOXO3a expression and oxidative stress induced by hyperglycemia	Resveratrol modulates the SIRT1/FOXO3a pathway by increasing SIRT1 deacetylase activity, and ameliorates renal tubular oxidative damage
Wu et al., 2012 (57)	In vivo: Protective effect of resveratrol against DN in rats	Resveratrol increased the expression of SIRT1 and FOXO1 activity; this was correlated with increased SOD activity, and decreased malondialdehyde, collagen IV, and fibronectin protein concentrations	Resveratrol-mediated modulation of SIRT1/FOXO1 pathway may be a useful therapeutic target for treatment of DN
Zhang et al., 2019 (55)	In vivo: Renoprotective effect of resveratrol [30 mg/(kg · d)] in diabetic mice	Resveratrol alleviated proteinuria, decreased malondialdehyde content while increasing MnSOD activity in renal cortex of diabetic mice; it also restored the expression of SIRT1 and PGC-1α	The study indicates that the renoprotective effect of resveratrol in DN is via SIRT1/PGC-1α–mediated attenuation of oxidative stress
Bashir, 2019 (58)	In vivo: Combined administration of resveratrol [20 mg/(kg · d)] and insulin against DN in rats	Resveratrol and insulin synergistically increased renal cortex antioxidant enzyme activities, inhibited lipid peroxidation, and upregulated Na^+/K^+-ATPase, independent of each other	This study suggests that combined therapy with insulin and resveratrol may be an excellent therapeutic option for DN
Nephroprotective effect of resveratrol via stimulating autophagy			
Ma et al., 2016 (59)[2]	In vitro: Resveratrol on autophagy under hypoxic conditions in renal proximal tubular cells	Resveratrol promoted SIRT1 expression, while SIRT1 knockdown attenuated the concentrations of autophagic proteins Atg7, Atg5, and LC3 and impaired the beneficial effect of resveratrol on autophagy	This study suggests SIRT1-mediated autophagy induction is a promising protective mechanism of resveratrol against DN
Huang et al., 2017 (60)[2]	In vitro: Resveratrol on autophagy in human podocytes	Resveratrol induced autophagy and suppressed apoptosis in podocytes through regulating microRNA-383-5p (miR-383-5p); autophagy inhibition reversed the protective effects of resveratrol	Renoprotective effect of resveratrol in DN is via the activation of autophagy in podocytes, which involves miR-383-5p

(*Continued*)

TABLE 1 (*Continued*)

Reference	Description	Outcome	Significance
Xu et al., 2017 (61)[2]	In vitro: Effect of resveratrol (10 μmol/L) on autophagy-related genes in mouse podocytes	Resveratrol increased LC3-II/LC3-I and decreased cleaved caspase expression, likely via upregulating miRNA-18a-5p, which targeted the atactic telangiectasis mutated (ATM) gene	Regulation of autophagy via miR-18a-5p/ATM pathway is a potential therapeutic target for DN
Ma et al., 2016 (59)	In vivo: Resveratrol [5 mg/(kg · d)] on kidney function in diabetic rat	Resveratrol promoted SIRT1 expression and improved metabolic state of kidneys; SIRT1 knockdown in NRK-52E cells downregulated expression of autophagic proteins Atg7, Atg5, and LC3 and impaired its beneficial effect on autophagy under hypoxic conditions	The study reinforces the role of SIRT1 in resveratrol's therapeutic effect on DN via the induction of autophagy
Huang et al., 2017 (60)	In vivo: Resveratrol [10 mg/(kg · d)] on autophagy in *db/db* mice	Resveratrol regulated autophagy in *db/db* mice through suppressing microRNA-383-5p (miR-383-5p) expression	Activation of autophagy via miR-383-5p contributes to resveratrol's renoprotective effect in *db/db* mice
Xu et al., 2017 (61)	In vivo: Resveratrol [100 mg/(kg · d)] on autophagy in DN in *db/db* mice	Resveratrol increased LC3-II/LC3-I and synaptopodin expression while decreasing cleaved caspase 3; increased expression of autophagy related genes was positively correlated with miRNA-18a-5p expression	Resveratrol-mediated autophagy induction via upregulation of miR-18a-5p/ATM is a potential therapeutic option for DN
Nephroprotective effect of resveratrol via reducing lipotoxicity			
Kim et al., 2013 (19)[2]	In vitro: Resveratrol (1, 5, 50 ng/mL) on glucotoxicity in mesangial (NMS2) cells	Resveratrol prevented high-glucose–induced apoptosis in mesangial cells through inducing AMPK phosphorylation and activation of SIRT1–PGC-1α/PPARα–ERR-1α–SREBP1	Resveratrol might protect against glucotoxicity via activation of the AMPK/SIRT1–PGC-1α signaling pathway
Ji et al., 2014 (62)[2]	In vitro: Effect of resveratrol on AdipoR1 expression in mesangial cells (HBYZ-1)	Resveratrol treatment elevated the activity of FOXO1 and increased the expression of AdipoR1 in mesangial cells cultured in high-glucose conditions	Induction of FOXO1 activity and AdipoR1 expression may be a therapeutic target for treatment of DN
Park et al., 2016 (63)[2]	In vitro: Resveratrol on lipotoxocity in human glomerular endothelial cells (HGECs)	Resveratrol prevented high-glucose–induced oxidative stress and apoptosis in glomerular endothelial cells by ameliorating lipotoxicity, which was evidenced by increased expression of AdipoR1 and AdipoR2	Resveratrol protects against lipotoxicity by inhibiting oxidative stress, apoptosis, and endothelial dysfunction
Kim et al., 2013 (19)	In vivo: Resveratrol treatment on renal lipotoxicity and kidney function in *db/db* mice	Resveratrol lowered lipid concentrations, which were correlated with increased AMPK phosphorylation and activation of SIRT1–PGC-1α signaling and of the key downstream effectors, PPARα–ERR-1α–SREBP1	Resveratrol helps prevent lipotoxicity-induced apoptosis and oxidative stress in the kidneys via activation of AMPK/SIRT1–PGC-1α signaling
Ji et al., 2014 (62)	In vivo: Nephroprotective effect of resveratrol in diabetic rats	Resveratrol increased AdipoR1 expression in kidneys of rats with DN, which was correlated with decreased malondialedehyde, collagen IV, and fibronectin proteins while improving kidney pathological indicators	Induction of FOXO1 activity and AdipoR1 expression is an important therapeutic target of resveratrol against DN in rats
Park et al., 2016 (63)	In vivo: Preventive effect of resveratrol against DN in *db/db* mice	Resveratrol increased phosphorylation of AMPK and SIRT1, decreased downstream effectors FOXO1 and FOXO3a via increasing AdipoR1 and AdipoR2 in renal cortex; it also increased expression of PPARγ coactivator-1α and estrogen-related receptor-1α, and decreased sterol regulatory element-binding protein 1	The study suggests that resveratrol prevents DN by ameliorating lipotoxicity, oxidative stress, apoptosis, and endothelial dysfunction via increasing AdipoR1 and AdipoR2 expressions in kidney

(*Continued*)

TABLE 1 (*Continued*)

Reference	Description	Outcome	Significance
Nephroprotective effect of resveratrol via attenuating ER stress and inflammation			
Xu et al., 2014 (20)	In vitro: Resveratrol on hyperglycemia-induced mesangial cell proliferation and inflammation	Resveratrol attenuated high-glucose–induced PAI-1 expression and mesangial cell proliferation while inhibiting Akt and NF-κB activation	Anti-inflammatory effect of resveratrol in mesangial cells is likely mediated via inhibition of Akt/NF-κB pathway
Yuan et al., 2018 (64)[2]	In vivo: Resveratrol [50 mg/(kg · d)] on DN in diabetic rats	Resveratrol decreased ER stress–associated signaling molecules p-PERK, GRP78, ATF4, and CHOP in kidneys, and these were correlated with amelioration in indicators of DN	Resveratrol is a highly safe and effective agent against DN through its modulatory action on ER response in kidney cells
Xu et al., 2014 (20)	In vivo: Resveratrol [10 mg/(kg · d)] on DN in diabetic mice	Resveratrol decreased the expression of PAI-1 and intercellular adhesion molecule 1 while decreasing p-Akt/Akt ratio and NF-κB in the kidneys of diabetic rats; it also significantly decreased the density of PCNA-positive cells in glomeruli	This study indicates that resveratrol helps prevent DN by inhibiting renal inflammation via Akt/NF-κB pathway
Nephroprotective effect of resveratrol via activating AMPK signaling pathway			
Ding et al., 2010 (16)[2]	In vitro: Resveratrol treatment (5, 10, 20 μmol/L) on rat renal mesangial cell proliferation	Resveratrol blocked high-glucose–induced dephosphorylation of AMPK and phosphorylation of 4E-BP1 and S6 and strongly inhibited both the DNA synthesis and proliferation of rat mesangial cells	This study suggests that resveratrol may protect against DN by inhibiting AMPK signaling pathway
He et al., 2016 (65)[2]	In vitro: Resveratrol (20 μmol/L) on high-glucose–induced proliferation of rat kidney fibroblast cells	Resveratrol inhibited high-glucose–induced cell proliferation that was accompanied by increased p-AMPK and decreased NOX4 expression	Resveratrol is a potential therapeutic agent against fibroblast proliferation and activation via AMPK signaling pathway
Ding et al., 2010 (16)	In vivo: Resveratrol treatment [10 mg/(kg · d)] on renal hypertrophy in early-stage diabetes in rats	Resveratrol activated AMPK in rat kidneys and inhibited eukaryotic translation initiation factor 4E-BP1, and phospho-ribosomal protein S6 (S6), which was correlated with reduced plasma creatinine, urinary albumin excretion, and improved renal function	This study suggests that resveratrol protects against DN by activating AMPK and reducing 4E-BP1 and S6 phosphorylation
He et al., 2016 (65)	In vivo: Resveratrol treatment [40 mg/(kg · d)] on renal interstitial fibrosis in DN of *db/db* mice	Resveratrol treatment in *db/db* mice attenuated renal fibrosis, which was accompanied by an evident increase in p-AMPK and decrease in NOX4	Resveratrol is a potential therapeutic agent against diabetic renal fibrosis via regulation of AMPK/NOX4/ROS signaling
Nephroprotective effect of resveratrol via modulating angiogenesis			
Wen et al., 2013 (66)[2]	In vitro: Antiangiogenic activity of resveratrol in mouse podocytes and endothelial cells	Resveratrol downregulated high-glucose–induced VEGF and Flk-1 expression in cultured mouse glomerular podocytes and endothelial cells	Resveratrol has the potential to suppress angiogenesis by downregulating VEGF/Flk-1 signaling
Wen et al., 2013 (66)	In vivo: Antiangiogenic activity of resveratrol [20 mg/(kg · d)] against DN in rats	Resveratrol decreased expression of VEGF, Flk-1, and angiopoietin 2, and increased expression of Tie-2 in rat kidneys, which was accompanied by improved kidney function	This study reinforces an important role of resveratrol's antiangiogenic activity in its beneficial effect on DN

[1] AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2; AGE, advanced glycation end-product; Akt, protein kinase B; AMPK, AMP kinase; ATF, activating transcription factor; ATG, autophagy related; CHOP, C/EBP homologous protein; DN, diabetic nephropathy; EMT, epithelial to mesenchymal transition; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ERR-1α, estrogen-related receptor 1α; Flk-1, fetal liver kinase; FOXO, forkhead box O; GRP78, glucose-regulated protein 78; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; LC3, microtubule-associated protein 1A/1B-light chain 3; MnSOD, manganese superoxide dismutase; NOX1, NAD(P)H oxidase 1; NOX4, NAD(P)H oxidase 4; NRF1, nuclear respiratory factor 1; NRF2, nuclear factor erythroid 2–related factor 2; p-, phosphorylated; PAI-1, plasminogen activator inhibitor 1; PCNA, proliferating cell nuclear antigen; protein kinase R-like ER kinase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PPARα, peroxisome proliferator-activated receptor α; PPARγ, peroxisome proliferator-activated receptor γ; RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; SREBP1, sterol regulatory element-binding transcription factor 1; TGF-B1, transforming growth factor B1; VEGF, vascular endothelial growth factor; 4E-BP1, 4E binding protein 1.

[2] In vitro studies were conducted using human-derived cell lines.

NF-κB activation. Moreover, ROS production was inhibited by resveratrol in mesangial cells by suppressing the activity of NOX, which is a pro-oxidant enzyme and a primary generator of superoxide anions (51). In a DM rat model (T2D), resveratrol treatment [5 mg/(kg · d)] improved renal dysfunction, which was shown by an appreciable decrease in serum creatinine, urinary protein, and urinary TGF-β1 expression compared with the control. It also resulted in a significant improvement in the antioxidant defense system, and further mRNA analysis indicated normalization of renal expressions of TGF-β1, fibronectin, NF-κB/p65, NRF2, sirtuin 1 (SIRT1), and forkhead box O (FOXO) 1 (FOXO1) (56).

The mammalian sirtuins belong to the family of NAD^+-dependent enzymes and reports suggest a close association between SIRT1 activity and metabolic diseases including DM (67, 68). SIRT1 can regulate FOXO transcription via direct binding or by deacetylation. Mesangial cells cultured in high-glucose conditions exhibited increased production of ROS, mitochondrial superoxide generation, and MnSOD activity. However, these hyperglycemia-induced conditions were inhibited in cells pretreated with resveratrol through the activation of SIRT1. SIRT1 inhibition using small interfering RNA targeting EX-527 inhibited resveratrol's protective effect against oxidative stress under hyperglycemic conditions, indicating the role of SIRT1 (52, 53). Under DM conditions, FOXO1 activity was significantly decreased with a concomitant reduction in FOXO1 targeted gene expression. The downregulation of FOXO1 correlated with increased production of malondialdehyde, increased expression of type IV collagen and fibronectin proteins in renal cortex, and reduced superoxide dismutase (SOD) activity. These results support a role of FOXO1 in oxidative stress development. Meanwhile, these conditions were improved in resveratrol-treated rats, which underscores the importance of resveratrol's antioxidative properties in conferring its nephroprotection in DM and the involvement of the SIRT1/FOXO1 pathway in this effect (57). Apart from usage in single-agent therapy, the antioxidation-mediated protective effect of resveratrol against DN has also been tested in combination with conventional drugs such as rosuvastatin (56). Increased production of mitochondrial ROS is considered one of the initiating steps in the pathogenesis of DN. The peroxisome proliferator-activated receptor (PPAR) γ co-activator 1α (PGC-1α) and its downstream transcription factors nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM) are primary regulators of mitochondrial biosynthesis. Upregulation of PGC-1α expression was found to delay the onset of DM complications along with improvement in mitochondrial function. Moreover, studies also revealed that PGC-1α could be activated by SIRT1 (54). The cells attached to the outside of the glomerular basement membrane are known as visceral epithelial cells of the renal capsule and also referred to as podocytes. Podocytes are critical for maintaining the glomerular filtration barrier and for prevention of proteinuria (54). Studies have demonstrated that incubation of glomerular podocytes and renal tubular epithelial cells with resveratrol (10 μM) inhibited apoptosis. In the renal tissues of mice with DN (CD-1 mice), resveratrol [30 mg/(kg · d)] ameliorated the pathological manifestations along with restoration of SIRT1 and PGC-1α expression. In addition to these effects, resveratrol treatment also resulted in decreased production of mitochondrial ROS, improvement in respiratory chain complex I and III activity, and enhanced mitochondrial membrane potential. Taken together, these findings reveal that oxidative stress is a pharmacological target of resveratrol and it is likely that its potent antioxidant properties contribute largely to its protective effect against podocyte damage in DN mice, which was mediated through the SIRT1–PGC-1α pathway (54, 55). Apart from the damaging effects on various cellular macromolecules, ROS overproduction also impacts nephron ion transport. The Na^+/K^+-ATPase is a predominant membrane-bound enzyme complex that has a crucial role in the maintenance of Na^+ and K^+ gradient across the cellular plasma membrane. Enhanced production of ROS has been shown to inhibit Na^+/K^+-ATPase enzyme activity, and some studies found that impairment in renal function and degenerative complications during DM were correlated with Na^+/K^+-ATPase concentrations and subsequent decreased activity (58). Administration of resveratrol [20 mg/(kg · d)] with insulin to diabetic rats (streptozotocin-induced DM) protected them against renal damage via promoting their antioxidant defense system and Na^+/K^+-ATPase activity (58). Thus, it is clear that resveratrol inhibits hyperglycemia-induced ROS generation and associated oxidative stress through multiple pathways and a subsequent reduction in oxidative stress largely contributes to its nephroprotective effects in DN (Table 1).

Nephroprotective effect of resveratrol via stimulating autophagy

Autophagy is a tightly controlled and well-coordinated multicellular process that plays a fundamental role in cellular homeostasis through lysosomal degradation of protein aggregates and damaged organelles (69). Studies have demonstrated that autophagy is a stress-adaptive response that is stimulated during nutrient starvation in order to extend support to cells by providing nutrients and energy through recycling of endogenous materials (70). Activation of autophagy results in degradation and recycling of entrapped cytosolic components (71). Under conditions such as hypoxia, ER stress, and/or nutrient starvation, autophagy can be activated and acts as a protective mechanism for kidney cells, which helps in delaying the progression of DN. Furthermore, many studies revealed that finding a primary target to activate and restore the autophagy activity in the kidneys could be renoprotective during the disease condition (72, 73).

SIRT1-stimulated autophagy activation has recently been demonstrated to have a renoprotective effect during DN (74). Furthermore, key findings on SIRT1 clarified that SIRT1 can interact with essential components of the autophagy mechanism, including autophagy gene (Atg) 5 (Atg5),

Atg7, and microtubule-associated protein 1A/1B–light chain 3 (LC3). LC3 is crucial for autophagosome formation, and the conversion of LC3I to LC3II is considered as a hallmark of autophagy (75, 76). In vitro and in vivo studies showed that resveratrol could activate SIRT1 and promote autophagy activity via improving the adaptation of renal cells to hypoxia and inhibiting apoptosis in diabetic rats (Table 1). Resveratrol treatment in renal proximal tubular cells (NRK-52E) upregulated the autophagic proteins such as Atg5, Atg7, and LC3 along with a beneficial influence on hypoxia-induced proteins including Foxo3 and BCL2/adenovirus E1B 19kDa interacting protein 3 (Bnip3) (59). These findings suggest that resveratrol-mediated activation of SIRT1 and thus induction of autophagy is a promising therapeutic strategy for DN.

Inhibiting podocyte apoptosis through the activation of autophagy has been recommended as a strategic target for the treatment of DN. Resveratrol [10 mg/(kg · d)] has been reported to attenuate apoptosis in podocytes of *db/db* mice by stimulating autophagy via the inhibition of microRNA (miRNA)-383–5p. Resveratrol also induced autophagy in human podocytes cultured in high-glucose medium (30 mmol glucose/L). Furthermore, the beneficial effect of resveratrol in podocytes was reversed when the autophagy was inhibited by 3-methyladenine (3-MA) and Atg5 short hairpin RNA (shRNA). This finding indicates that resveratrol-induced autophagy plays a crucial role against podocyte damage during DN (60). A study by Xu et al. (61) found a decreased ratio of LC3II to LC3I in the kidneys of *db/db* mice compared with normal mice, indicating an insufficient level of autophagy in the former. Likewise, treatment with resveratrol [100 mg/(kg · d)] was able to attenuate the disease condition by promoting autophagy while reducing apoptosis in podocytes in the renal cortex of the *db/db* mice. In vitro mechanistic analysis confirmed that resveratrol enhanced LC3II expression in podocytes cultured in high-glucose medium accompanied by reduced expression of cleaved caspase-3 protein, a known apoptosis executioner (61).

Increasing attention has been paid to miRNAs as key regulatory factors of autophagy. Upregulation of miRNA-18a-5p, for instance, was reported to stimulate autophagy and inhibit apoptosis in podocytes cultured in high-glucose medium upon treatment with resveratrol. This indicates that resveratrol-induced autophagic activity was at least partly mediated via the upregulation of miRNA-18a-5p. In this study, the authors identified protein kinase ataxia-telangiectasia (ATM) as a target gene for miRNA-18a-5p, which was evidenced by reduced activity of luciferase reporter vector of ATM following miR-18a-5p treatment in podocytes. Subsequent in vivo experiments demonstrated a suppressive effect of resveratrol on ATM expression in the renal cortex of *db/db* mice. Silencing the ATM gene also up-regulated LC3II/LC3I and reduced the expression of cleaved caspase-3 in cultured podocytes. The authors concluded that the proautophagic and antiapoptotic activity of resveratrol in podocytes is closely associated with the upregulation of miRNA-18a-5p and inhibition of its target gene ATM (61). These studies provide compelling evidence that induction of autophagy by resveratrol as part of its nephroprotective effect is likely mediated via multiple signaling pathways (Table 1).

Nephroprotective effect of resveratrol via reducing lipotoxicity

The accumulation of fatty acids and their metabolites in cells could compromise cellular functions and eventually lead to cellular injury or even death. This process has been termed "lipotoxicity." Lipotoxicity can also lead to DM-associated renal injury in genetically predisposed individuals (77). The exact mechanism of lipid accumulation in the kidneys has not been clearly elucidated. In the meantime, few reports suggest that, during conditions such as DM, an increase in the sterol regulatory element binding protein 1 (SREBP-1) results in exacerbated de novo fatty acid synthesis and thus lipid accumulation, which eventually leads to compromised renal function followed by mesangial expansion, proteinuria, and glomerulosclerosis (78). SREBP-1 is a transcription factor that regulates fatty acid and triglyceride synthesis. Compromised renal function could interrupt fatty acid catabolism, causing lipid accumulation in the kidneys (79). In vitro (mesangial cells) and in vivo (*db/db* mice) assays by Kim et al. (19) not only confirmed that DN was associated with lipid/triglyceride accumulation in the kidneys but also exemplified the capability of resveratrol to ameliorate lipotoxicity-mediated DN, including reversal of renal lipid accumulation, apoptosis-mediated cell injury, and oxidative stress. This study identified the downregulation of SREBP-1 and the activation of AMPK–SIRT1–PGC-1α signaling pathway and subsequent activation of PPARα–estrogen-related receptor 1α (ERR-1α) and FOXO3a to be a major mechanism responsible for the observed beneficial effect of resveratrol treatment (Table 1) (19).

Other studies reported that activation of PPARα can induce fatty acid uptake, utilization, and catabolism. Zhou et al. (80) reported that resveratrol [400 mg/(kg · d)] treatment significantly improved renal damage induced by a high-fat diet in mice (C57BL/6J) via activation of PPARα and AMPK (80). These findings might also be applied to DN in light of previous reports on the activation of PPARα by resveratrol in diabetic mice (19). Lipotoxicity-induced oxidative stress has also been critically studied due to its potential role in the pathogenesis of chronic kidney disease (63). Adiponectin has been found to inhibit oxidative stress and inflammation and exhibit renoprotective effects by regulating albuminuria and podocyte function in mice (81). The biological effect of adiponectin can be mediated through its receptors such as AdipoR1 and AdipoR2. AdipoR1 is known to activate AMPK and AdipoR2 has been reported to activate PPARα. AMPK is known for its potential role against oxidative stress and apoptosis, whereas PPARα is a transcription factor that controls the transcription of genes encoding fatty acid oxidation enzymes (82, 83). A study by Ji et al. (62) demonstrated the promising effect of resveratrol against DN by increasing the expression of AdipoR1 via

activating FOXO1 in diabetic kidneys and in mesangial cells exposed to high glucose (62). When the diabetic mice and the human glomerular endothelial cells (HGECs) cultured in high-glucose medium were treated with resveratrol, a similar phenomenon was observed that included upregulated expression of AdipoR1 and AdipoR2 and their downstream signaling molecules such as AMPK, FOXO1, and FOXO3a. Therefore, the authors suggested that the renoprotective effect of resveratrol during DN was mediated through the activation of AMPK–SIRT1–PPARα via AdipoR1 and AdipoR2 (Table 1). These modifications by resveratrol treatment not only ameliorated the renal lipotoxicity but also oxidative stress, apoptosis, and endothelial dysfunction (63).

Nephroprotective effect of resveratrol via attenuating ER stress and inflammation

The ER is the largest and dynamic organelle of the cell and is crucial for many cellular functions such as protein synthesis, lipid and carbohydrate metabolism, and calcium storage (Ca^{2+}). These versatile functions of the ER are controlled and performed by distinct domains, including tubules, sheets, and the nuclear envelope. The process of protein folding in the ER is controlled by a group of Ca^{2+}-dependent molecular chaperones and enzymes (84). The protein-folding enzymes include glucose-regulated protein 78/immunoglobulin binding protein (GRP78/BiP), glucose-regulated protein 94, and protein disulfide isomerase. It was reported that certain pathological conditions could interfere with normal protein-folding processes of the ER and eventually lead to ER stress due to the accumulation of misfolded and toxic proteins. Conversely, the homeostatic response of the ER to stress constitutes the so-called unfolded protein response (UPR) (85). The process of UPR comprises 3 major intrinsic signaling pathways including protein kinase R-like ER kinase (PERK), inositol-requiring enzyme-1 (IRE-1), and activating transcription factor (ATF) 6 (ATF-6), which involve transmembrane stress sensors (85).

It has been well established that ER stress is one of the major contributing factors in the onset and progression of various pathological conditions including DN (86). In this regard, abnormal glucose concentrations are among the primary stimulators for the initiation of ER stress in renal cells and thus DN (87). In fact, ER stress has been documented in the kidneys of humans with DN (88) and in experimental models of DN (89, 90). Excessive production of ROS and thus oxidative stress is an important pathological event in hyperglycemia- and proteinuria-induced ER stress. To compensate for the loss of antioxidants and membrane proteins and the associated cellular damage due to cumulative oxidative stress, the synthesis of these defense molecules would be increased. However, excess oxidative stress would ultimately overwhelm the capacity of the ER, leading to ER stress (88). In addition to oxidative stress, activation of renal epidermal growth factor receptors (EGFRs) has also been reported to induce ER stress in DN (91). Hence, proper maintenance of the ER in renal cells is essential to handle misfolded proteins and this has been appreciably accepted as a therapeutic strategy to combat kidney damage during hyperglycemia-mediated cellular injury and apoptosis.

Although there are multiple lines of evidence indicating the role of resveratrol in protection against DN, data on its activity against ER stress in renal cells are scarce. In a recent study, expression of phosphorylated PERK (p-PERK), GRP78, ATF4, and C/EBP homologous protein (CHOP) was significantly increased in kidneys of rats with diabetes (64). Expression of these ER stress factors was significantly reduced by resveratrol treatment, suggesting a nephroprotective effect of resveratrol in rats with DN that was mediated through the PERK signaling pathway involving attenuation of ER stress (Table 1) (64). More studies are urgently needed in this area to gain a better understanding of the roles of other signaling pathways that are known to be involved in the induction of ER stress in renal cells during DN.

Inflammation has also been implicated in the development and progression of DN (92). In a study aiming to investigate the nephroprotective effect of resveratrol against hyperglycemia-induced inflammation and mesangial cell proliferation in vitro and in vivo, resveratrol was found to significantly inhibit PAI-1 expression and mesangial cell proliferation. It also inhibited the activation of protein kinase B (Akt) and NF-κB. Furthermore, resveratrol treatment [10 mg/(kg · d)] in diabetic mice [male Friend Virus B (FVB) mice] significantly decreased PAI-1 and intercellular adhesion molecule 1 (ICAM-1) expression along with the phosphorylated AKT (p-AKT) to AKT ratio and NF-κB in the kidneys (20). These data, therefore, suggest that AKT/NF-κB signaling is involved in the anti-inflammatory and antiproliferative activity of resveratrol against hyperglycemia-induced nephro-pathological damage (Table 1).

Nephroprotective effect of resveratrol via activating the AMPK signaling pathway

AMPK is known for its role in important biological functions such as cellular growth and proliferation. It functions as a sensor of fuel and energy status in eukaryotes (93). The mammalian target of rapamycin (mTOR) pathway is one of the major downstream signaling pathways regulated by AMPK (94). Under glucose-deprived and/or -elevated AMP:ATP conditions, AMPK would be activated, which subsequently leads to phosphorylation and inhibition of mTOR (93). In vitro (kidney glomerular epithelial cells exposed to high glucose concentrations) and in vivo (streptozotocin-induced hyperglycemic rats) assays demonstrated that hyperglycemia could induce glomerular hypertrophy and that prolonged hyperglycemia resulted in inactivation of AMPK, and thus activation of mTOR signaling (95). These findings, together with other reports, emphasize that the AMPK–mTOR signaling pathway could be a promising target for the management of DN.

In a study by Ding et al. (16) resveratrol treatment [10 mg/(kg · d)] in DM rats (streptozotocin-induced DM) ameliorated the renal hypertrophy via activation of AMPK and subsequent inhibition of phosphorylation of mTOR downstream effectors S6 and 4E binding protein 1 (4E-BP1) in the kidneys. Furthermore, resveratrol also inhibited the proliferation of renal mesangial cells cultured in high-glucose medium through the same signaling pathway (16). Few studies also reported AMPK as a negative modulator of NOX. Upregulation of NOX family members was found to contribute largely to intracellular ROS in the kidneys of DN models, suggesting a strong relation between NOX-mediated ROS overproduction and renal interstitial fibrosis (96). Moreover, activation of AMPK inhibited NOX4-mediated p53 activation and epithelial cell apoptosis under DM condition (97), and decreased the accumulation of fibronectin and collagen in the kidneys of mice with DN (98). Resveratrol treatment (20 μM) effectively reduced the proliferation of kidney fibroblast cells (NRK-49F) under high-glucose (30 mmol glucose/L) conditions by activating AMPK and inhibiting NOX4-mediated ROS overproduction (65). Similar effects and mechanism of action were also observed in a diabetic mouse model (C57BL/KS *db/db*) where resveratrol [40 mg/(kg · d)] significantly attenuated renal fibrosis, which was accompanied by increased AMPK phosphorylation and decreased NOX4 expression (65). These studies highlight a great potential of AMPK activation for suppressing the progression of renal interstitial fibrosis through mitigation of oxidative stress, and reveal that the inhibitory activity of resveratrol against this pathological change during DN can be mediated by modulating the AMPK–NOX4–ROS signaling pathway (Table 1).

Nephroprotective effect of resveratrol via modulating angiogenesis

A growing body of evidence supports an important role of angiogenesis in the pathogenesis of DN. In particular, neovascularization has been reported to be connected to the development of glomerular hypertrophy during DN (99). VEGF is a potent stimulator of angiogenesis, and studies suggest that there is an increase in the expression of VEGF and its type 2 receptor fetal liver kinase (Flk-1) in animals and humans during DN (especially early stage) (100). VEGF has also been reported to stimulate mitosis and migration of endothelial cells, increase the permeability of endothelial monolayers, and even promote tube formation (101). VEGF-associated increased vascular permeability is likely a key mechanism responsible for the increased glomerular permeability and subsequent albuminuria during DN. Therefore, VEGF and/or its receptor Flk-1 have been proposed to be promising therapeutic targets for attenuating complications of DN. In this context, a study by Wen et al. (66) demonstrated that resveratrol pretreatment inhibited VEGF-mediated increased permeability and cellular junction disruption of mouse glomerular podocytes and endothelial cells cultured in high-glucose medium (66). In vivo, resveratrol treatment [20 mg/(kg · d)] in rats with DN blunted the levels of pathological biomarkers such as urine albumin excretion, kidney weight, and creatinine clearance rate. The increase in glomerular diameter, accumulation of mesangium, thickening of glomerular basement membrane, and renal fibrosis were also attenuated following resveratrol treatment. Furthermore, the increased expression of VEGF, Flk-1, and angiopoietin 2, and reduced expression of angiopoietin-1 receptor (Tie-2), observed in diabetic kidneys were all reversed following resveratrol treatment (66). These findings suggest a role of anti-angiogenesis in the nephroprotective effect of resveratrol (Table 1).

Conclusions and Future Perspectives

DN is a multifactorial secondary complication of DM and is a primary cause of ESRD (102). Resveratrol treatment not only improves the antioxidant defense system but also modulates a number of signaling pathways including AMPK/mTOR, EMT, AGEs, Hypoxia-inducible factor (HIF), lipotoxicity, oxidative stress, ER stress, and autophagy that eventually help in maintaining optimum kidney function during DN. However, evidence in the literature is scarce to support the actual beneficial effects of resveratrol treatment during the course of the disease in humans. A recent clinical trial has shown that resveratrol may be an effective adjuvant to ARBs for reducing urinary albumin excretion in patients with DN (ClinicalTrials.gov: NCT02704494) (23). Based on the good number of preclinical evidence and emerging promising data from some clinical trials, more randomized controlled trials are warranted to verify the efficacy and to better understand the mechanisms of resveratrol against DN in humans.

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