

Review Article

Renal Protective Effects of Resveratrol

Munehiro Kitada and Daisuke Koya

Diabetology and Endocrinology, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Kahoku, Ishikawa 920-0293, Japan

Correspondence should be addressed to Daisuke Koya; koya0516@kanazawa-med.ac.jp

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Resveratrol (3,5,4'-trihydroxystilbene), a natural polyphenolic compound found in grapes and red wine, is reported to have beneficial effects on cardiovascular diseases, including renal diseases. These beneficial effects are thought to be due to this compound's antioxidative properties: resveratrol is known to be a robust scavenger of reactive oxygen species (ROS). In addition to scavenging ROS, resveratrol may have numerous protective effects against age-related disorders, including renal diseases, through the activation of SIRT1. SIRT1, an NAD⁺-dependent deacetylase, was identified as one of the molecules through which calorie restriction extends the lifespan or delays age-related diseases, and this protein may regulate multiple cellular functions, including apoptosis, mitochondrial biogenesis, inflammation, glucose/lipid metabolism, autophagy, and adaptations to cellular stress, through the deacetylation of target proteins. Previous reports have shown that resveratrol can ameliorate several types of renal injury, such as diabetic nephropathy, drug-induced injury, aldosterone-induced injury, ischemia-reperfusion injury, sepsis-related injury, and unilateral ureteral obstruction, in animal models through its antioxidant effect or SIRT1 activation. Therefore, resveratrol may be a useful supplemental treatment for preventing renal injury.

1. Introduction

Chronic kidney disease (CKD), which is characterized by a chronic reduction in the glomerular filtration rate (GFR) and the presence of proteinuria or albuminuria, is recognized as an independent risk factor for both end-stage renal disease (ESRD) and cardiovascular disease, leading to a decrease in quality of life and an increased risk of mortality [1]. Acute kidney injury (AKI) is common in the setting of critical illness and is associated with a high risk of death [2]. In addition, AKI can directly cause ESRD and can increase the risks of the development of incident CKD and the worsening of underlying CKD [3]. Therefore, additional treatment to prevent both chronic and acute kidney injury is necessary.

Resveratrol (3,5,4'-trihydroxystilbene) is a polyphenolic phytoalexin that occurs naturally in many plant parts and products, such as grapes, berries, red wine, and peanut skins [4], and has numerous beneficial health effects. Previous epidemiological studies have revealed an inverse correlation between red wine consumption and the incidence of cardiovascular disease, a phenomenon known as the "French Paradox." The French population has relatively low rates of

cardiovascular disease despite traditionally eating a diet rich in saturated fat [5]. Resveratrol, which is present in red wine, has been postulated to explain the protective effects on the cardiovascular system observed in the French Paradox, and the effects of this compound are exerted through several mechanisms, including antioxidant effects [6]. SIRT1, an NAD⁺-dependent deacetylase, has been identified as one of the molecules through which calorie restriction (CR) extends the lifespan and delays age-related diseases [7–9]. The activation of SIRT1 exerts cytoprotective effects through multiple mechanisms, such as antiapoptosis, antioxidative, and anti-inflammation effects and the regulation of mitochondrial biogenesis, autophagy, and metabolism in response to the cellular energy and redox status [10]. Resveratrol has been shown to be a SIRT1 activator [11], and numerous previous studies have shown that the administration of resveratrol can prevent many diseases, such as diabetes, neurodegenerative disorders, cognitive disorders, cancer, kidney diseases, and cardiovascular disease through SIRT1 activation [9, 10, 12]. Thus, resveratrol exerts its cytoprotective effects through at least two mechanisms, antioxidant activity and SIRT1 activation (Figure 1). In the present review, we summarize the

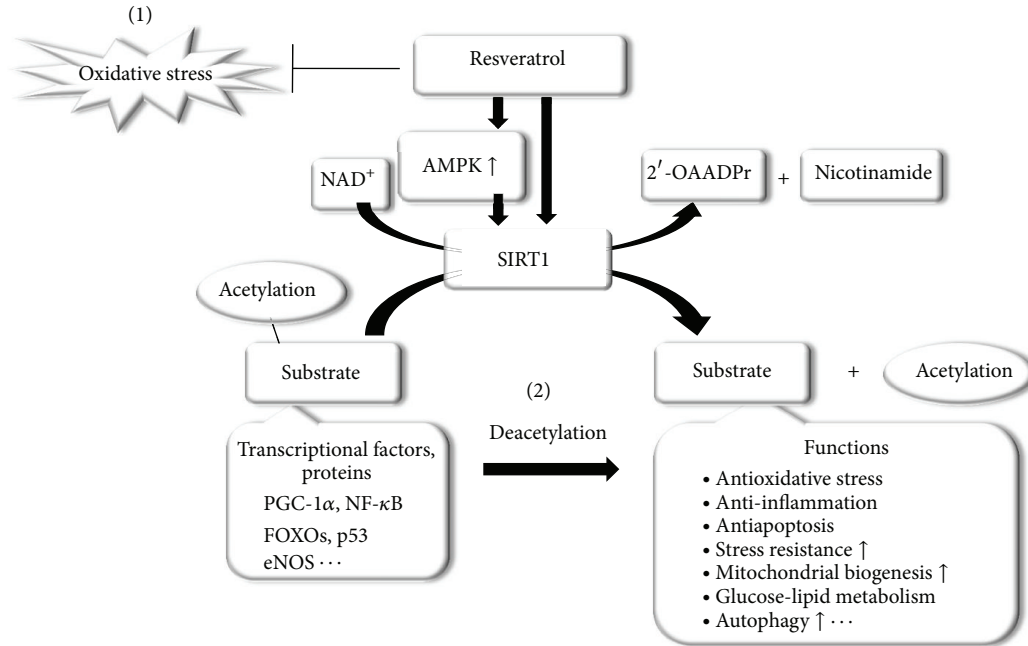


FIGURE 1: Proposed mechanisms by which resveratrol exerts cytoprotection. (1) Resveratrol attenuates oxidative stress. (2) Resveratrol activates SIRT1, which is an NAD^+ -dependent deacetylase, directly or indirectly via AMPK activation. SIRT1 plays an important role in the regulation of oxidative stress, inflammation, apoptosis, stress resistance, mitochondrial biogenesis, autophagy, and glucose-lipid metabolism, via the deacetylation of many substrates.

protective effects of resveratrol against several types of renal injury and discuss the mechanisms involved.

2. Mechanisms of the Cytoprotective Effects of Resveratrol

2.1. Resveratrol as an Antioxidant. An excess of reactive oxygen species (ROS) is involved in a variety of diseases, the aging process, and numerous cellular response pathways [13, 14]. ROS include superoxide (O_2^-), the hydroxyl radical (OH^*), and peroxynitrite (ONOO^-), and these compounds attack cellular proteins and DNA. Oxidative stress is induced by an imbalance between ROS production and antioxidant defenses; therefore, exogenous antioxidants or the modulation of antioxidant enzymes can be expected to reduce oxidative stress. Resveratrol is a natural antioxidant. Previous studies have shown that resveratrol can directly scavenge ROS, such as O_2^- , OH^* , and ONOO^- [15, 16]. In addition to scavenging ROS, exogenously administered resveratrol modulates the expression and activity of antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase (GPx), and catalase, through transcriptional regulation via nuclear factor E2-related factor 2 (Nrf2), activator proteins (AP)-1, forkhead box O (FOXO), and SP-1 or through enzymatic modification [17–20].

2.2. Resveratrol Activates SIRT1. Aging is a universal process that affects all organs, and age-related disruptions in cellular homeostasis result in a reduction in responsiveness to physiological stress and organ dysfunction. Numerous

studies have revealed that CR retards aging or extends the lifespans of yeast, worms, flies, and rodents [7]. Colman et al. also reported that CR delayed the onset of age-associated pathologies, including diabetes, cancer, cardiovascular disease, and brain atrophy and decreased mortality in rhesus monkeys [21]. In addition, Fontana et al. showed that CR for an average of 6 years improved metabolism in humans, as measured by the levels of serum insulin, cholesterol, C-reactive protein (CRP), and tumor necrosis factor (TNF)- α as well as the thickness of the carotid intima media [22]. This group also observed that long-term CR ameliorated declines in left ventricular diastolic function and decreased the levels of serum tumor growth factor (TGF)- β 1, TNF- α , and high-sensitivity CRP [23]. Thus, CR induces these antiaging effects by improving insulin sensitivity and reducing inflammation and oxidative stress, and CR is accepted as the only established experimental antiaging paradigm.

Based on initial studies on aging in yeast, silent information regulator 2 (Sir2), an NAD^+ -dependent deacetylase, was identified as one of the molecules through which CR extends the lifespan and delays age-related diseases [24]. Homologues of Sir2 in higher eukaryotic organisms are known as sirtuins. SIRT1, the sirtuin most closely related to Sir2, is one of seven sirtuins in mammals [9]. The beneficial effects of CR involve the function of SIRT1, which is induced by CR in various tissues [21]. The importance of SIRT1 in the effects of CR has been demonstrated using genetically altered mice [25, 26]. SIRT1 is an important regulator of a wide variety of cellular processes, including stress responses, cell survival, mitochondrial biogenesis, and metabolism in

response to the cellular energy, as well as the redox status, via the deacetylation of many substrates [9, 12]. Therefore, SIRT1 activators are expected to function as CR mimetics, and the screening of compounds for their ability to activate SIRT1 led to the discovery of 18 small molecules, including resveratrol [11]. Resveratrol can activate SIRT1 through multiple mechanisms. Although resveratrol was originally thought to directly activate SIRT1 through an allosteric effect, AMPK is required for the activation of SIRT1 by resveratrol. AMPK plays an important role in the regulation of metabolism in response to the energy balance [27]. In addition, Park et al. found that resveratrol activates SIRT1 through the activation of AMPK via the inhibition of phosphodiesterase 4 (PDE 4) and the elevation of cAMP in cells, thereby providing a new mechanism to explain SIRT1 activation by resveratrol [28]. A recent study reported by Price et al. also demonstrated a direct link between SIRT1 and the metabolic benefits of resveratrol [29]. These authors reported that a moderate dose of resveratrol (25–30 mg/kg/day to mice treated with high fat diet) first activated SIRT1 and then induced the deacetylation of liver kinase B (LKB) 1 and the activation of AMPK, leading to increased mitochondrial biogenesis and function. In addition, a high dose of resveratrol (215–235 mg/kg/day to mice treated with high fat diet) may directly activate AMPK, independently of SIRT1. Moreover, Hubbard et al. demonstrated that sirtuin-activating compounds (STACs), including resveratrol, can increase the catalytic activity of SIRT1 toward certain substrates through an allosteric mechanism involving an amino terminal domain near the catalytic core and through direct binding to SIRT1 [30].

3. Renal Protective Effects of Resveratrol

3.1. Diabetic Nephropathy. Diabetic nephropathy is one of the more serious complications of diabetes and is the most common cause of ESRD. Oxidative stress has been implicated in the pathogenesis of diabetic vascular complications, including nephropathy [31]. Previous studies have clearly demonstrated that resveratrol can improve diabetic nephropathy in several animal models of types 1 and 2 diabetes through its antioxidative effects resulting from direct radical scavenging or the modulation of antioxidant enzymes.

Sharma et al. reported that treatment with resveratrol (5 mg or 10 mg/kg orally) for 2 weeks improved urinary protein excretion, renal dysfunction, and renal oxidative stress in streptozotocin- (STZ-) induced diabetic rats [32]. In addition, Palsamy and Subramanian reported that resveratrol treatment (5 mg/kg orally for 30 days) resulted in significant normalization of the creatinine clearance and the levels of plasma adiponectin, C-peptide, and renal oxidative stress and inflammation in STZ-nicotinamide-induced diabetic rats [33]. Furthermore, resveratrol treatment ameliorated the dysfunction of antioxidant enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione-S-transferase (GST), and glutathione reductase (GR), and the reduction in the levels of vitamin C, vitamin E and reduced glutathione (GSH) in diabetic kidneys. In addition, they found that the expression levels of Nrf2

and its downstream enzyme, including γ -glutamyl cysteine synthetase (GCS), m-GST, and hemoxygenase-1 (HO-1) were significantly decreased in the renal tissues of diabetic rats. However, the administration of resveratrol modulates the expression of Nrf2 in the context of diabetes-induced oxidative stress by upregulating γ -GCS, m-GST, and HO-1. We also reported that resveratrol treatment (400 mg/kg, orally, administered at concentration of 0.3% resveratrol) alleviated albuminuria and histological mesangial expansion and reduced the increased levels of renal oxidative stress and inflammation in the kidneys of db/db mice through the scavenging of ROS and normalizing manganese (Mn)-SOD function by decreasing its levels of nitrosative modification [20]. Kim et al. demonstrated that resveratrol prevents diabetic nephropathy in db/db mice by the phosphorylation of AMPK and SIRT1- peroxisome proliferator-activated receptor γ coactivator (PGC)-1 α signaling, which appear to prevent lipotoxicity-related mesangial cell apoptosis and oxidative stress in the kidney [34]. Zhang et al. showed that high glucose levels enhance mesangial cell proliferation and fibronectin expression through the c-Jun N-terminal kinase (JNK)/nuclear factor κ B (NF- κ B)/NADPH oxidase/ROS pathway, which was inhibited by resveratrol in cultured mesangial cells [35].

In addition to antioxidant effects, resveratrol has other properties that can ameliorate diabetes or high glucose-induced kidney injury by activating AMPK or SIRT1. Ding et al. reported that resveratrol treatment attenuates renal hypertrophy and urinary albumin excretion in the early stage of diabetes in STZ-induced diabetic rats without affecting the blood glucose levels [36]. They found that resveratrol activates AMPK and inhibits the phosphorylation of 4E-BP1 and S6 in diabetic kidneys. Moreover, in cultured mesangial cells, resveratrol has been shown to block the high glucose-induced dephosphorylation of AMPK and the phosphorylation of 4E-BP1 and S6, inhibiting both the DNA synthesis and proliferation. In addition, Lee et al. reported that resveratrol ameliorates high glucose-induced protein synthesis in glomerular epithelial cells [37]. Resveratrol increases AMPK phosphorylation and abolishes high glucose-induced reductions in the AMPK phosphorylation level. In addition, resveratrol inhibits the high glucose-induced phosphorylation of eIF4E, eEF2, eEF2 kinase, and p70S6 kinase, which have significant roles in the initiation and elongation steps of mRNA translation. Resveratrol prevents the high glucose-induced hyperacetylation of LKB-1, which is an upstream regulator of AMPK, leading to AMPK activation, and the deacetylation of LKB-1 is independent of SIRT1. However, Tikoo et al. showed that resveratrol (55 mg/kg, intraperitoneal injection) prevents the decrease in SIR2 expression and the increases in the p38MAPK and p53 levels and the dephosphorylation of histone H3 in the kidney of STZ-induced diabetic rats, suggesting that SIR2 is involved in the beneficial effects of resveratrol in the kidneys [38]. Furthermore, Wu et al. demonstrated that resveratrol has protective effects on diabetic kidneys by modulating the SIRT1/FOXO1 pathway [39]. They demonstrated that FOXO1 activity is reduced, with a concomitant decrease in the expression of catalase, a FOXO1 target gene, and that

SIRT1 expression decreased in the renal cortex of STZ-induced diabetic rats, resulting in enhanced renal oxidative stress. Treatment with resveratrol increased the renal FOXO1 activity, catalase expression, and SIRT1 expression, leading to a reduction in oxidative stress. Moreover, in cultured mesangial cells, Xu et al. demonstrated that resveratrol exerts protective effects on high glucose-induced mitochondrial oxidative stress and mitochondrial dysfunction [40]. All of these protective effects of resveratrol were blocked by the knockdown of SIRT1 and by EX-527, a specific inhibitor of SIRT1.

Chen et al. reported that resveratrol treatment improved diabetes-induced glomerular hypertrophy and urinary albumin excretion; reduced the expression of glomerular fibronectin, collagen IV, and transforming growth factor (TGF)- β ; reduced the thickness of the glomerular basement membrane; and reduced nephrin expression in the kidneys of STZ-induced diabetic rats, possibly through the inhibition of the phosphorylation of Smad2, Smad3, and ERK1/2 [41]. However, the mechanism by which resveratrol inhibits Smad2, Smad3, and ERK1/2 phosphorylation remains unknown.

3.2. Drug-Induced Renal Injury Model. Cisplatin is a chemotherapeutic agent that is widely used to treat malignant tumors. As the most common adverse effect of cisplatin, nephrotoxicity is an important dose-limiting factor in cisplatin treatment. The nephrotoxicity of cisplatin is induced directly by DNA damage, inflammation, and oxidative stress in the proximal tubules of the S3 segment in the outer medulla and the corticomedullary region of the kidney [42]. Amaral et al. reported that pretreatment with resveratrol (25 mg/kg, intraperitoneal injection) attenuated signs of cisplatin-induced renal injury, such as tubular cell apoptosis and inflammation and renal dysfunction, by reducing the level of oxidative stress and inhibiting inflammation [43]. In addition, Kim et al. showed that SIRT1 activation by resveratrol reduces the cisplatin-induced acetylation of p53, apoptosis, and cytotoxicity in cultured mouse proximal tubular cells [44]. SIRT1 expression and activity after 3 days of cisplatin treatment have been shown to decrease in the kidneys; however, the administration of resveratrol ameliorated the decreases of SIRT1 activation and the glomerular filtration rate and the increases of tubular cell apoptosis and urinary Kim-1 excretion, which is induced by cisplatin.

Other studies have shown that resveratrol attenuated renal injury caused by several drugs, including glycerol [45, 46], gentamicin [47, 48], and cyclosporine [49], by reducing oxidative stress, as one of the mechanisms of the renal protective effect of resveratrol.

3.3. Aldosterone-Induced Kidney Injury. Aldosterone and its activation pathway through mineralocorticoid receptor contribute to podocytes injuries and progression of proteinuric kidney disease. Yuan et al. reported that SIRT1/PGC-1 α axis in mitochondria ameliorated aldosterone-induced podocytes injuries [50]. They found that aldosterone suppressed SIRT1 and PGC-1 α activation in cultured podocytes,

resulting in increased podocytes apoptosis and the loss of slit diaphragm proteins, including nephrin and podocin, accompanied with mitochondrial dysfunction. SIRT1 activation protected against aldosterone-induced podocytes injuries with mitochondrial dysfunction, by inhibiting both apoptosis and loss of slit diaphragm proteins, through deacetylation and activation of PGC-1 α . Treatment with resveratrol prevented aldosterone-induced podocytes apoptosis and mitochondrial dysfunction and restored expression of nephrin and podocin in vitro and in vivo model, through activation of the SIRT1/PGC-1 α axis.

3.4. Ischemia-Reperfusion and Sepsis-Induced Kidney Injuries.

Renal ischemia is a common course of AKI. Reperfusion is essential for the survival of ischemic renal tissue; however, reperfusion also contributes to additional renal damages [51]. Oxidative stress plays a crucial role in ischemia-reperfusion injury of the kidney. Several studies have demonstrated that resveratrol exerts protective effects against ischemia-reperfusion injury in the kidneys, as well as the heart and brain injury, by reducing oxidative stress and several other mechanisms. Giovannini et al. reported that the pretreatment of rats with resveratrol (0.23 μ g/kg) reduced the mortality rate of ischemic rats from 50% to 10% and reduced the extent of renal damage, as reflected by glomerular dysfunction, tubular cell necrosis, inflammatory cell infiltration, glomerular thrombosis, urinary IL-6 excretion, and oxidative stress [52]. Peroxynitrite (ONOO⁻), which is generated by the reaction of NO with superoxide, is a powerful oxidizing RNS and causes protein nitration, DNA damage, and mitochondrial dysfunction, leading to endothelial and epithelial dysfunction. Treatment with NG-nitro-L-arginine methyl ester (L-NAME), which is a nitric oxide synthase inhibitor, abolished the effects of resveratrol on ischemic kidneys, suggesting that resveratrol protects the kidneys from ischemia-reperfusion injury through a nitric oxide-dependent mechanism. Chander and Chopra also showed that pretreatment with resveratrol (5 mg/kg) attenuates renal ischemia-reperfusion injury through NO release in rats [53]. Resveratrol may enhance the enzymatic activity of endothelial NOS (eNOS) through phosphorylation by AMPK [54] or deacetylation by SIRT1 [55], possibly leading to the production of NO and protecting vascular tissues, including the kidneys. The transcriptional activity of eNOS is also increased by resveratrol-induced FOXO activation via SIRT1 [56].

The development of AKI is a common complication during severe sepsis and more than doubles the mortality rate to nearly 75% [57]. When severe sepsis develops, the dysfunction of the renal microcirculation, which is induced by increased oxidative stress, especially as the result of reactive nitrogen species (RNS), contributes to the progression of AKI [58–60]. Holthoff et al. investigated the effects of resveratrol on sepsis-induced AKI using the cecal ligation and puncture (CLP) murine model [61]. Resveratrol restored the renal microcirculation and scavenged reactive nitrogen species, thus protecting the tubular cells in the kidney during sepsis. Furthermore, the administration of resveratrol to septic mice

at 6, 12, and 18 hr resulted in a significant improvement in survival compared with that of the vehicle-treated mice.

3.5. Obstructed Kidneys. Renal fibrosis is the hallmark of progressive renal disease and is recognized as the final common pathway of glomerular sclerosis and tubule-interstitial fibrosis. The unilateral ureteral obstruction (UUO) model is widely used to investigate the mechanisms of renal fibrosis [62]. The TGF- β /Smad3 signaling pathway plays a central role in the pathogenesis of renal fibrosis. Li et al. reported that resveratrol reversed the acetylation of Smad3 and inhibited the TGF- β -induced upregulation of fibrosis-related genes, such as collagen IV and fibronectin, through SIRT1 activation in the interstitial lesion of the obstructed kidney [63].

3.6. Aging Kidney. Aging causes progressive postmaturational deterioration of tissues and organs, leading to impaired tissue function, increased vulnerability to stress, and death. Kidney is one of the typical target organs of age-associated tissue damage, and the high incidence of CKD in the elderly is a health problem worldwide.

Kume et al. found that mitochondrial damage in aged kidneys is associated with a decrease in SIRT1 activation [64]. In the renal proximal tubular cells of aged mice, autophagy in response to renal hypoxia is decreased, resulting in renal dysfunction and histological renal fibrosis. CR-mediated renal SIRT1 activation deacetylates and activates FOXO3a transcriptional activity, leading to the recovery of Bnip3-mediated autophagy, even in aged kidneys. These findings indicate that SIRT1 is a crucial target in aging kidneys; therefore, resveratrol is expected to prevent renal aging.

4. Conclusions

Resveratrol can exert protective effects against both acute and chronic kidney injuries through its antioxidant effects and ability to activate SIRT1 (Figure 2). Therefore, resveratrol should be a useful additional treatment for preventing renal injury. However, it remains unclear whether resveratrol has beneficial effects on kidney diseases in humans and other animal models of renal diseases. In addition, a number of recent studies indicate that many of the protective effects of resveratrol could be mediated by SIRT1-independent mechanisms. Among them, the activation of mammalian target of rapamycin (mTOR) signaling pathway is involved in the pathogenesis for several kidney diseases, such as diabetic nephropathy [65–67] and the autosomal dominant polycystic kidney disease [68]. Liu et al. reported that RSV increases the association between mTOR and the DEP-domain-containing and mTOR-interactive protein (DEPTOR), an identified negative regulator of mTOR [69]. Therefore, resveratrol is expected to protect the kidney by the inhibition of mTOR pathway. Further studies are necessary to verify the beneficial effects of this compound in humans and other animals of kidney diseases and to clarify the detailed mechanism for the renal protective effect of resveratrol.

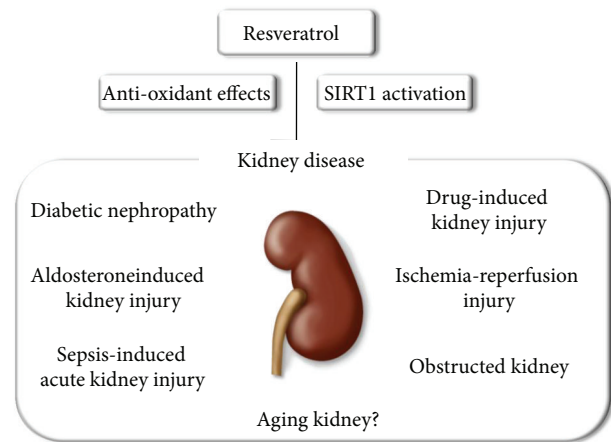


FIGURE 2: Resveratrol can prevent renal injury, including diabetic nephropathy, drug-induced renal injury, aldosterone-induced renal injury, ischemia-reperfusion injury, sepsis-induced kidney injury, and obstructed kidney, through its antioxidant effects and SIRT1 activation.

Conflict of Interests

The authors declare that there is no conflict of interests.

Acknowledgments

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