Resveratrol in Kidney Disease

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Different diseases and disorders that affect the kidneys include, but are not limited to, glomerulonephritis, diabetic nephropathy, polycystic kidney disease, kidney stones, renal fibrosis, sepsis, and renal cell carcinoma. Kidney disease tends to develop over many years, making it difficult to identify until much later when kidney function is severely impaired and undergoing kidney failure. Epidemiological studies have suggested that a diet rich in fruits and vegetables is associated with health benefits including protection against kidney disease and renal cancer. Resveratrol, a polyphenol found in grapes and berries, has been reported to have antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, neuroprotective, and anti-cancer properties.

Keywords: resveratrol ; kidney disease ; mesangial cells ; renal epithelial cells ; fibroblasts ; glomerulosclerosis ; renal cancer

1. Introduction

1.1. Kidney Function in Health and Disease

The kidneys are a pair of organs located below and posterior to the liver in the peritoneal cavity whose main function is blood filtration and salt and water homeostasis[1]. The kidney is divided into three regions: the outer cortex, medulla, and inner hilum. The renal cortex contains the functional unit of the kidney known as the nephron, with approximately one million nephrons located within each kidney (**Figure 1**)[2]. Each nephron is responsible for filtration as blood enters the kidney, which migrates through the length of the nephron where specialized regions reabsorb water and small molecules before it is secreted as urine. The nephron can be further divided into the renal corpuscle (Bowman's capsule) and renal tubule[2]. Located within the Bowman's capsule is the glomerulus, a filtering unit of blood vessels which is responsible for the majority of filtration within the kidney. Throughout all these structures, the kidney is connected to a highly vascularized network of arteries, veins, and nerves, entering and exiting at the renal hilum[2]. In addition to filtration and reabsorption, the kidneys also produce hormones such as renin, erythropoietin, and calcitriol/vitamin D_3, that regulate blood pressure, help control red blood cell production, and maintain bone metabolism and health[3][4].

Chronic kidney disease (CKD) is defined as kidney damage, or decreased kidney function present for longer than three months. In addition, CKD requires an estimated GFR of less than 34.68 mL/min/m2 and abnormalities in biopsy/renal imaging results[5]. Kidney disease tends to develop over many years, making it difficult to identify until much later when kidney function is severely impaired. Physiologically, CKD arises due to many pathological injuries that destroys some of the nephrons, resulting in the nephrons overcompensating by hyperfiltration. Over time, glomerular hypertension, albuminuria, and loss of renal function develop[6]. The increase in glomerular capillary pressure leads to glomerular capillary wall destruction, dysfunction of podocytes that cover the capillaries, and increased macromolecule permeability[6][7]. In conjunction, increased pro-inflammatory mediators are released that stimulate the proliferation of fibrotic cells. In addition, accumulation of ECM molecules results in scar formation and renal failure[6][7][8]. Currently, treatment strategies exist for CKD, with all options aimed at relieving or preventing the condition from worsening, including conservative care, medication, dialysis, or transplantation[9][10].

CKD is not the only form of kidney disorder that can severely affect an individual, with many other disorders severely afflicting the kidney and renal system, such as polycystic kidney disease (PKD), a genetic disorder, either autosomal dominant or recessive, characterized by cyst formation in the kidneys[11]. Glomerulonephritis is term used to describe a range of immune-mediated disorders resulting in inflammation of the glomerulus and other regions of the kidney [12]. The inflammation within the kidney disrupts blood filtration, leading to decreased urination, high blood pressure, hematuria, and albuminuria[12]. Diabetic nephropathy characterized by glomeruli damage and impaired blood filtration develops in more than 50% of people with type 2 diabetes mellitus (T2DM)[13]. In addition, renal cell carcinoma (RCC), also known as cancer of the kidney, is the sixth and tenth most common cancer in men and women, respectively, accounting for more than 140,000 deaths yearly and ranking as the 13th most common cause of cancer death worldwide[14][15]. RCC

originates in the lining of the proximal convoluted tubule and encompasses approximately ninety percent of all kidney cancer cases in adults[16]. RCC is characterized by decreased kidney filtration, anemia, and increased blood pressure, resulting in complete kidney failure[17]. Current treatment strategies of RCC include surgery (partial or radical nephrectomy), chemotherapy, immunotherapy, and radiation therapy[18].

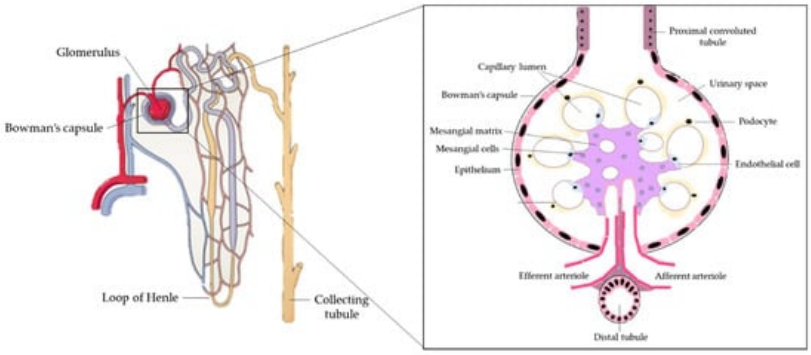

Figure 1. The structure of the glomerulus and nephron.

1.2. Resveratrol

Resveratrol (RSV) (3,5,4′-trihydroxy-trans-stillbene) is a polyphenol belonging to the family of stilbenes, based on shared common structure of two phenyl moieties connected by a two-carbon methylene bridge[19] [42]. RSV is found in the skin of grapes, in berries, and peanuts, with considerably high levels in grape juice (0.19–0.96 mg/L), and red wine (1.9 ± 1.7 mg/L)[20][21][22]. RSV has been studied for its pharmacological effects, including antioxidant, anti-inflammatory, immunomodulatory, hepatoprotective, anti-cancer, anti-atherosclerotic, and anti-diabetic properties[19][23][24][25][26][27][28].

The bioavailability of RSV is relatively low due to its low absorption, rapid metabolism, and elimination. A number of past reviews have focused on resveratrol's bioavailability[29][30][31] and interested readers are recommended to consult these reviews[29][30][31]. Initial studies in humans, showed low levels of unmetabolized RSV in the plasma upon a single oral administration dose of 5 to 25 mg[31][32][33]. Administration of 25 mg trans-RSV resulted in total resveratrol peak blood concentration of 1.8–2 µM after 60 min[33]. This was similar to another study which showed that increasing doses (500 mg to 5000 mg) of oral administered trans-RSV resulted in plasma levels of 0.3–2.3 µM within 50–90 min[32].

2. Resveratrol's Effects on Kidney Disease

2.1. In Vitro Studies: Effects of Resveratrol on Mesangial Cells

Glomerular mesangial cells occupy a central position in the renal glomerulus forming the central tuft-like structure of the glomerular microvasculature, involved in the generation of inflammatory mediators (such as cytokines, macromolecules and immune complexes), and are responsible for the contractile function. Mesangial cells contract or relax to modify glomerular filtration locally in response to vasoconstrictive or vasorelaxant agents, respectively[34]. Mesangial matrix expansion and vaso-mediator release result in decreased glomerular surface area and hemodynamics, reducing GFR. Mesangial cell function is affected by immunologic injury and metabolic disease, resulting in impaired filtration[35].

Overall, the studies show that the treatment of mesangial cells with RSV attenuated the basal, PDGF-, high glucose- and TGF-β1-induced cell proliferation. In addition, RSV treatment reduced the high glucose- and TGF-β1-induced oxidative stress and inflammation, reduced mitochondrial superoxide and ROS production, and increased MnSOD and mitochondrial complex III activity. The production of the extracellular matrix protein, fibronectin, was significantly inhibited by RSV treatment. RSV treatment significantly reduced the high glucose-induced effects by regulating NF-κB, JNK, Akt, and p38 signaling (**Table 1**).

Table 1. Effects of resveratrol on kidney mesangial cells.

Cell	Resveratrol Concentration/Duration	Effect	Reference
Rat primary mesangial cells and LLCPK1 cells	50–75 µM; 24 h	↑NF-κB activation	[36]

Cell	Resveratrol Concentration/Duration	Effect	Reference
Rat primary mesangial cells	10 μM; 1 h	↓Gentamicin-induced contraction	[37]
Rat mesangial cells	10 μM; 1 h	↓PDGF-induced cell proliferation ↓PDGFR Y-751 phosphorylation ↓PDGFR Y-761 phosphorylation ↓PDGF-induced PI3K, Akt, ERK1/2, c-Src activity ↑PTP1B activity	[38]
Rat primary mesangial cells	10 μM; 6 h	↓High glucose-induced • ROS production • Mitochondrial superoxide ↑ MnSOD activity ↑ Mitochondrial complex III activity ↑ ΔΨm hyperpolarization ↑ SIRT1 activity	[39]
CRL-2573 and primary mesangial cells	5–10 μM; 24 h	↓ High glucose-induced • Cell proliferation • Fibronectin protein • JNK and NF-κB activation • NADPH oxidase activity • ROS production	[40]
HBYZ-1 cells	20 μM; 72 h	↑High glucose-induced AdipoR1 mRNA and protein ↑FOX01 activity ↓FOX01 phosphorylation	[41]
Rat mesangial cells	25 μM; 48 h	↓High glucose-induced • Cell proliferation • PAI-1 protein • Ph-Akt • NF-κB	[42]

Cell	Resveratrol Concentration/Duration	Effect	Reference
CRL-2573 cells	10 μM; 48 h	↓High glucose-induced • p38 MAPK activation • TGF-β1 expression • Fibronectin	[43]
SV40 MES 13 cells	10 μM; 46 h	↓TGF-β1-induced ROS production ↑TGF-β1-induced • Mitochondrial membrane potential • ATP • Complex I/III activity • NDUFB8 and ATP β protein • SIRT1 • PGC-1α deacetylation	[44]

NF-κB: nuclear factor kappa light-chain-enhancer of activated B cells; PDGF: platelet-derived growth factor; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; ERK1/2: extracellular signal-regulated kinases 1/2; c-Src: proto-oncogene tyrosine-protein kinase Src; PTP1B: tyrosine-protein phosphatase non-receptor type 1B; MnSOD: manganese superoxide dismutase; ROS: reactive oxygen species; SIRT1: sirtuin 1; JNK: c-Jun N-terminal kinase; NADPH: nicotinamide adenine dinucleotide phosphate; FOX01: forkhead box 01; PAI-1: plasminogen activator inhibitor 1; MAPK: mitogen-activated protein kinase; TGF-β1: transforming growth factor-β1; ATP: adenosine triphosphate; NDUFB8: NADH:ubiquinone oxidoreductase subunit B8; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator. ↓: decrease; ↑: increase.

2.2. In Vitro Studies: Effects of Resveratrol on Renal Epithelial Cells

Injury in renal epithelial cells results in renal dysfunction and necrosis associated with renal failure[45]. Overall, the studies suggest that the treatment of renal epithelial cells with RSV attenuated the cisplatin-, high glucose-, oxalate- and TGF-β1-induced oxidative stress, reduced mROS production, and increased antioxidant enzyme activities. In addition, RSV treatment prevented EMT and fibronectin production. Renal epithelial cell apoptosis was reduced by RSV treatment through increased anti-apoptotic protein levels and reduced pro-apoptotic protein expression. Furthermore, RSV treatment increased mitochondrial membrane potential and complex III activity to attenuate the mitochondrial dysfunction and metabolic stress (**Table 2**).

Table 2. Effects of resveratrol on renal epithelial cells.

Cell	Resveratrol Concentration/Duration	Effect	Reference
Rodent glomerular epithelial cells	30 μM and 50 μM; 72 h	↓High glucose-induced • de novo protein synthesis • Acetylation of LKB1 • Ph-eIF4E protein • eIF4G, eEF2, and p70S6K protein	[46]
Mouse proximal tubular epithelial cells	100 μM; 30 min	↓Cisplatin-induced • Apoptosis • p53(S379) acetylation • PUMA-α and caspase-3 protein • Bax translocation ↑SIRT1 siRNA-acetylation ↑Bcl-xL, Bax, and Bak protein	[47]
Human renal epithelial cells	0, 40 and 80 μM; 24 h	↓Oxalate-induced • Colonization • Hyaluronan • ROS production • NADPH p22 and p47 mRNA • MCP-1 and osteopontin mRNA • TGFβ1, TGF-RI/II • Malondialdehyde	[48]
mpkCCD$_{C14}$ cells	25–400 μM; 30 min to 24 h	↓Sodium transport ↑GFP-AKT-PH redistribution ↑AMPKα protein	[49]
NRK-52E cells	10 and 100 μM; 24 h	↓TGF-β1-induced • Cellular proliferation • EMT • EM synthesis • Shh and Gli1 mRNA	[50]

Cell	Resveratrol Concentration/Duration	Effect	Reference
HK-2 cells	5–20 μM; 4 h	↓High glucose-induced • EMT • ROS levels • NOX1 and NOX4 protein • ERK1/2 activation	[51]
HK-2 cells	20 μM; 48 h	↓EMT ↓β-catenin nuclear translocation ↑E-cadherin and SIRT1 mRNA and protein ↓MMP7, α-SMA, and COLIA1 mRNA and protein	[52]
HK-2 cells	12.5 μM; 48 h	↓Ioxitalamate-induced • Cytotoxicity • Cytosolic DNA fragmentation • 8-OHdG formation • ROS production ↑Bcl-2 and survivin protein ↑ Caspase 3 activity	[53]
OX161 and UCL93 human renal epithelial cells; MDCK canine renal epithelial cells	2–50 μM; 48 h	↓Cyst number ↓MCP-1 protein and activity ↓TNF-α protein and activity ↓CFB protein and activity ↑SOD2 protein	[54]
HK-2 cells	20 μM; 12 h	↑Cell viability ↓Ph-NFκB protein ↓TNF-α, IL-1β, and IL-6 mRNA and protein ↓IRE1 activation	[55]

Cell	Resveratrol Concentration/Duration	Effect	Reference
HK-2 cells	25 μM; 72 h	↓High glucose-induced oxidative stress ↓MDA and ROS activity ↑CAT and SIRT1 protein ↑SIRT1 activity ↓Acetyl-FOXO3a protein	[56]
TCMK-1 cells	25 μM; 72 h	↓Cadmium-induced apoptosis ↓mROS production ↑mSIRT3 protein and activity ↑PGC-1α and SOD2 mRNA	[57]
HK-2 cells	5–20, 40 μM; 72 h	5–20 μM RSV: ↓TGF-β-induced EMT ↓Cytotoxicity ↑SIRT1 and E-cadherin protein ↓α-SMA and fibronectin protein ↓Ph-Smad3 ↓SIRT1-Smad3/4 40 μM RSV: ↑Cytotoxicity ↑mtROS release ↑Bax, fibronectin, and α-SMA protein ↓Bcl-2 protein ↓ATP production ↓PGC-1α and TFAM protein	[58]

LKB1: liver kinase B1; eIF: eukaryotic translation initiation factor; eEF2: eukaryotic translation elongation factor 2; p70S6K: ribosomal protein S6 kinase beta-1; AMPKα: AMP-activated protein kinase alpha; PUMA: pro-apoptotic p53 upregulated modulator of apoptosis; siRNA: small interfering RNA; GFP: green fluorescent protein; EMT: epithelial-to-mesenchymal transition; MDA: malondialdehyde; TFAM: mitochondrial transcription factor A; Bcl-xL: B-cell lymphoma-extra-large; Bax: Bcl-2-associated X; Bak protein: BCL2-antagonist/killer protein; α-SMA: α-smooth muscle actin; COLIA1: collagen type I alpha 1; NOX: NADPH oxidase; MMP: matrix metalloproteinase; MCP-1: monocyte chemoattractant protein 1; CAT: catalase; CFB: complement factor B; mROS: mitochondrial ROS; IL: interleukin; TFAM: mitochondrial transcription factor A.

2.3. In Vitro Studies: Effects of Resveratrol on Cells of the Renal Corpuscle

Renal podocytes are cells that wrap around the capillaries of the glomerulus in the Bowman's capsule. Functionally, podocytes, together with renal endothelial cells, form the filtration barrier and interact with mesangial cells to regulate glomeruli function[59]. Mouse podocytes treated with TGF-β1 to induce transdifferentiation followed with RSV treatment resulted in significantly reduced albumin permeability across the podocyte monolayer, indicating reduced podocyte death and increased percentage of E-cadherin expressing cells[60]. Additionally, adhesion molecules P-cadherin, zonula occludens-1 (ZO-1), and kin of IRRE-like protein 1 (NEPH1) protein levels were significantly increased, while α-SMA protein levels were decreased with RSV treatment, indicating preserved podocyte function[60]. In conjunction, treatment of podocytes with RSV resulted in attenuation of the high glucose-induced mitochondrial stress, decreased mROS production and increased membrane potential, all involved in diabetic nephropathy development[61]. In addition, RSV treatment increased respiratory chain complex I and III activities, while release of pro-apoptotic proteins (cytochrome C and diablo) from the mitochondria was reduced, suggesting improved mitochondrial functioning and reduced podocyte damage. Additionally, SIRT1, PGC-1α, nuclear respiratory factor 1 (NRF-1), and TFAM mRNA and protein levels were increased with RSV treatment[61].

Overall, the studies suggest that treatment of cells of the renal corpuscle (podocytes) with RSV preserves membrane integrity and metabolic flux. RSV treatment reduces albumin permeability and α-SMA protein levels, suggesting preserved renal functioning. Increased mitochondria complex activities and decreased mROS production indicate increased metabolic flux and decreased oxidative stress with RSV treatment. These data show that treatment of cells of the renal corpuscle with RSV exhibit a kidney oxidative protective effect and improved function (**Table 3**).

Table 3. Effects of resveratrol on cells of the renal corpuscle.

Cell	Resveratrol Concentration/Duration	Effect	Reference
Mouse podocytes	2–5 µM; 30 min	↓Albumin permeability ↓Podocyte death ↑E-cadherin expression ↑P-cadherin, ZO-1, and NEPH1 protein ↓α-SMA protein	[60]
Immortalized podocytes	10 µM; 48 h	↓High glucose-induced • Mitochondrial stress • mROS production • Cyto C and diablo release ↑Complexes I and III activities ↑Mitochondrial membrane potential ↑SIRT1, PGC-1α, NRF1, TFAM mRNA and protein	[61]

ZO-1: zonula occludens-1; NEPH1: kin of IRRE-like protein 1; NRF1: nuclear respiratory factor 1.

2.4. In Vitro Studies: Effects of Resveratrol on Embryonic Kidney Cells

The development of the embryonic kidney begins with the invasion of the metanephric mesenchyme by the ureteric bud. Under a series of morphogenetic events that convert the mesenchyme to epithelium, the basis of the mature nephron is formed[62]. The human embryonic kidney (HEK) 293 cell line is commonly used in research as a model of kidney cell differentiation[63]. In a study by Rössler et al. (2015), treatment of HEK293 cells with RSV resulted in increased early growth response 1 (Egr-1) protein levels and the transcription of the Egr-1 responsive reporter gene, indicating increased activity[64]. In addition, RSV treatment increased ERK1/2 phosphorylation and Raf activation, while MAP kinase phosphatase-1 (MKP-1) activity was impaired[64]. ETS like-1 protein (Elk-1) transcriptional activity was significantly

increased with RSV treatment. Importantly, inhibition of ERK or use of dominant negative Raf prevented the RSV induced increased Egr-1 levels. These data suggest that RSV induces the expression of Egr-1 by ERK and Raf activation and MKP-1 repression[64].

Ochratoxin A (OTA) is a nephrotoxin that results in the destruction of renal tubular epithelium resulting in progressive renal failure, effects associated with decreased antioxidant activity and increased ROS production[65]. Treatment of HEK293 cells with RSV resulted in significantly decreased intracellular ROS production; however, when co-treated with OTA, RSV was unable to mitigate the increased ROS production[66]. DNA damage was decreased in HEK293 cells treated with RSV alone and co-treated with OTA, suggesting improved epithelium preservation. Additionally, OTA-induced 8-oxoguanine glycosylase (OGG1) mRNA levels were significantly increased with RSV, indicating increased DNA repair. OTA-induced glutathione (GSH) levels were significantly increased in cells treated with RSV, compared to OTA treated cells[66]. Overall, these data indicate that RSV treatment protects against nephrotoxin-induced DNA damage through decreased ROS production and increased antioxidant GSH level.

Treatment of HEK293 cells with RSV resulted in significantly decreased high glucose-induced aging marker, β-galactosidase, mRNA levels, indicating reduced aging. RSV treatment also increased high glucose-induced SIRT1 and thioredoxin (Trx) mRNA levels while Trx interacting protein (TXNIP) mRNA levels were reduced indicating improved intracellular antioxidant expression[67].

Overall, these studies suggest that treatment of embryonic kidney cells with RSV reduced toxin or aging-induced DNA-damage and increased DNA-repair, indicative of improved cellular activity and longevity. In addition, RSV treatment reduced OTA- and high glucose-induced oxidative stress with increased GSH enzyme activity and decreased ROS production. These data show that RSV treatment protects embryonic kidney cells from DNA damage (**Table 4**).

Table 4. Effects of resveratrol on embryonic kidney cells.

Cell	Resveratrol Concentration/Duration	Effect	Reference
HEK293 cells	20 μM; 24 h	↑Egr-1 protein ↑Egr-1 reporter mRNA ↑Ph-ERK1/2 protein ↓MKP-1 activity ↑Elk-1 transcriptional activation potential	[64]
HEK293 cells	25 μM; 24–48 h	↓OTA-induced • Oxidative stress • DNA damage • ROS production ↑OGG1 expression ↑GSH levels	[66]
HEK293 cells	2.5, 5, and 10 μM; 12–48 h	↓High glucose-induced Aging β-galactosidase mRNA TXNIP mRNA ↑SIRT1 mRNA ↑Trx mRNA	[67]

Egr-1: early growth response 1; MKP-1: MAP kinase phosphatase-1; Elk-1: ETS transcription factor; OTA: ochratoxin A; OGG1: OTA-induced 8-oxoguanine glycosylase; GSH: glutathione; Trx: thioredoxin; TXNIP: Trx interacting protein.

2.5. In Vitro Studies: Effects of Resveratrol on Kidney Fibroblasts

Kidney fibroblasts are found in the interstitium, are involved in the production of ECM components, such as fibronectin and collagen, and act to maintain ECM homeostasis by producing ECM-degrading proteases. With dysfunction, fibroblasts continue to produce ECM components resulting in tubulointerstitial fibrosis and renal failure[68]. Only one study exists (by He et al. (2016)) on the effects of RSV treatment on kidney fibroblast cells[69]. Treatment of NRF-49F fibroblasts with RSV resulted in the attenuation of the high glucose-induced cell proliferation and dose-dependently reduced ROS production. Additionally, RSV treatment increased phosphorylated AMPK and acetyl-CoA carboxylase (ACC) protein levels, while NOX4, α-SMA, and fibronectin protein levels were decreased back to levels similar to control cells (**Table 5**) [69]. These data suggest that RSV treatment increased phosphorylated AMPK and ACC reduces oxidative stress marker NOX4 activity and results in the reduction of ROS production.

Table 5. Effects of resveratrol on kidney fibroblasts.

Cell	Resveratrol Concentration/Duration	Effect	Reference
NRF-49F cells	5, 10, and 20 µM; 1 h	↓High glucose-induced • Cell proliferation • Fibronectin protein • α-SMA protein • ROS production • NOX4 protein ↑High glucose-induced • Ph-AMPK • Ph-ACC	[69]

ACC: acetyl-CoA carboxylase.

2.6. In Vitro Studies: Effects of Resveratrol on Renal Cancer Cells

Renal cancer accounts for more than 140,000 deaths/year, ranking as the 13th most common cause of cancer death worldwide[14][15]. Renal cancer is characterized by decreased kidney filtration, anemia, and increased blood pressure, resulting in impaired functioning and complete kidney failure[17]. Increased expression of vascular endothelial growth factor (VEGF) is associated with poor prognoses and increased metastasis[70]. Treatment of human renal cancer cells (786-0) with RSV resulted in reduced cell growth that was associated with reduced VEGF mRNA and protein levels[70]. Signal transducers and activators of transcription (STAT) proteins are upregulated in various malignancies, including renal cancer. Treatment of Caki-1 and 786-0 renal cancer cells with RSV promoted cell apoptosis and reduced cell survival as seen by the reduced colony formation[71]. RSV inhibited phospho-STAT3 (tyrosine 705 and serine 727), phospho-STAT5 (tyrosine 684 and tyrosine 699), and nuclear STAT3 and STAT5 protein levels, while protein tyrosine phosphatase (protein tyrosine phosphatase (PTP)ε and Src homology- 2 domain containing phosphatase (SHP-2)) mRNA and protein levels were increased[71]. Additionally, the protein levels of phosphorylated upstream kinases (Janus kinase (JAK)1, JAK2, and Src) were significantly inhibited by RSV. Bcl-2, bcl-xL, survivin, inhibitor of apoptosis (IAP)-1, and IAP-2 protein levels were reduced, while caspase-3 protein level and poly (ADP-ribose) polymerase (PARP) cleavage were increased by RSV treatment in both renal cancer cell lines[71].

Treatment of ACHN and A498 renal carcinoma cells with RSV resulted in significantly impaired cell growth, cell-to-cell contact, and migration[72]. RSV treatment inhibited the formation of filopodia, which are actin-rich microspikes that project out of the cell cytoplasm and are involved in migration. Additionally, RSV treatment reduced EMT markers (N-cadherin

and vimentin), transcriptional repressor (Snail), tumor metastasis markers (MMP-2 and MMP-9), phosphorylated Akt, and ERK1/2 protein levels, while cell invasion suppressor marker (E-cadherin and tissue inhibitors of metalloproteinase 1 (TIMP-1)) protein levels were increased[72].

Overall, these studies suggest that treatment of renal carcinoma cells with RSV resulted in reduced cell proliferation, survival, and migration. RSV treatment promoted cell apoptosis and pro-apoptotic protein expression. These limited studies indicate protective effects of RSV against renal cancer (**Table 6**).

Table 6. Effects of resveratrol on renal cancer cells.

Cell	Resveratrol Concentration/Duration	Effect	Reference
786-0 cells	0, 10, 20 and 40 µM; 24, 48 and 72 h	↓Cell growth ↓VEGF mRNA and protein	[70]
Caki-1 and 786-0 cells	0, 10, 30 and 50 µM; 6 h	↑Apoptosis ↓Survival ↓Migration ↓STAT3 and STAT5 activation ↑PTPε and SHP-2 protein ↓JAK1, JAK2, and c-Src protein ↓Bcl-2, bcl-xL, survivin, IAP-1, and IAP-2 protein ↑Caspase-3 protein	[71]
ACHN and A498 cells	50 µM; 12 h	↓Cell growth ↓Cell-to-cell contact ↓Migration ↓Filopodia formation ↓N-cadherin, vimentin, snail, MMP-2, MMP-9, ph-Akt and ph-ERK1/2 protein ↑E-cadherin and TIMP-1 protein	[72]

VEGF: vascular endothelial growth factor; STAT: Signal transducers and activators of transcription; PTP: protein tyrosine phosphatase; SHP-2: Src homology- 2 domain containing phosphatase; JAK: Janus kinase; IAP: inhibitor of apoptosis; TIMP: tissue inhibitors of metalloproteinase 1.

2.7. In Vivo Animal Studies: Effects of Resveratrol on Diabetic Nephropathy

Diabetic nephropathy is a major complication of T2DM, that results in glomeruli damage and an inability to correctly filter the blood[13]. Multiple models of diabetic nephropathy including genetic models *db/db* and C57BL/KsJ db/+ mice and chemical-induced streptozotocin (STZ) administered rats and mice were utilized to determine the effects of RSV treatment.

Overall, the studies suggest that treatment of animals suffering from diabetic nephropathy with RSV attenuates hyperglycemia, hyperlipidemia and improves kidney structural integrity and kidney function. RSV administration decreased urinary albumin and serum creatinine levels, indicating improved kidney functioning. In addition, renal oxidative stress, inflammatory cell infiltration, cytokine production, and MDA content were reduced with RSV administration, while

antioxidant enzyme activity and SIRT1 expression were increased. These data show that RSV treatment has protective effects against diabetic nephropathy (**Table 7**).

Table 7. Effects of resveratrol on diabetic nephropathy (animal studies).

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
db/db mice	0.3% diet; 8 weeks	↓Glucose levels ↓Insulin levels ↓Triglyceride levels ↓FFA levels	↓Albuminuria ↓Mesangial expansion ↓Fibronectin accumulation ↓Macrophage infiltration ↑O^{2-} scavenging ↑MnSOD activity ↓Mitochondrial biogenesis mRNA	[73]
Male Wistar rats	5 mg/kg/day; 16 weeks	↓Glucose levels ↓SOD activity ↓TBARS levels ↓TNF-α ↓IL-6	↓Apoptosis rate of kidney cells ↓NF-κB activity	[74]
Male Wistar rats	20 mg/kg/day; 8 weeks	↓Glucose levels ↓Creatinine levels	↓Urinary protein excretion ↓Renal hypertrophy ↓Mesangial matrix expansion ↓Mesangial cell hyperplasia ↓GSTM expression	[75]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
db/db mice	20 mg/kg/day; 12 weeks	No measured effects	↓Kidney albuminuria ↓Kidney NEFA and triacylglycerol ↓Mesangial area ↓Oxidative stress ↓Type IV collagen ↓TGF-β1 ↓F4/80 positive cells ↑Ph-AMPK ↑SIRT1 protein ↓PI3K-Akt protein and activity ↓Ph-FOXO3a ↓BAX protein ↑BCL-2 production ↓Renal and Urinary 8-OHdG	[76]
FVB mice	10 mg/kg/day; 12 weeks	No measured effects	↓Glomerular area ↓Extracellular matrix ↓Albumin levels ↓Ph-Akt protein ↓PAI-1 protein ↓ICAM-1 protein ↓PCNA mRNA	[42]
Sprague–Dawley rats	200 mg/kg/day; 12 weeks	No measured effects	↓Glomerular area ↓Mesangial cell expansion ↓Glomerular basement membrane thickness ↓Collagen IV ↓Fibronectin ↑AdipoR1 expression ↓MDA production	[41]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
Male Wistar rats	10 mg/kg/day; 30 days	↓Glucose levels ↓Urea nitrogen levels	↓Glomeruli sclerotic changes ↓Epithelial desquamation ↓Tissue swelling ↓Intracytoplasmic vacuolization ↓Brush border loss ↓Kidney TGF-β1 ↑SOD and CAT activities ↓MDA levels	[77]
db/db mice	40 mg/kg/day; 12 weeks	↓BUN levels ↓Creatinine levels	↓Glomerulosclerosis ↓Tubulointerstitial fibrosis ↓Albuminuria ↑Kidney SOD, Mn-SOD, Catalase protein ↓Renal MDA ↓α-SMA protein ↓E-cadherin protein ↓TGF-β, pSmad3, ph-Akt, ph-ERK ↓IGF-1R expression ↑HRD1 expression	[78]
db/db mice	20 mg/kg/day; 12 weeks	↓Triacylglycerol levels ↓NEFA levels ↑Adiponectin levels	↓Glomerular matrix expansion ↓Albuminuria ↑AdipoR1 and AdipoR2 ↑Ph-AMPK, SIRT1, total FoxO1, total FoxO3a ↑PGC-1α, ERR-1α, ph-ACC ↓SREBP-1c ↓Bax ↑Bcl-2 ↓8-OHdG levels ↓8-isoprostane levels	[79]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
db/db mice	40 mg/kg/day; 12 weeks	No measured effects	↓Mesangial area ↓Albuminuria ↓Collagen deposition ↓FSP-1, α-SMA, and fibronectin protein ↓NOX4 protein ↑Ph-AMPK, ph-ACC	[69]
Sprague-Dawley rats	5 mg/kg/day; 4 months	↓Glucose levels ↓Cholesterol levels ↓Triglyceride levels ↓HbA1c levels ↓Creatinine levels ↓Urea nitrogen levels ↓Cycstatin C levels ↓TNF-a, IL-6, IL-1B, and IL-10 levels	↓Albuminuria ↓Renal 8-OHdG ↑SIRT1 mRNA and protein ↑Atg5 and Atg7 mRNA	[80]
Male Wistar rats	30 mg/kg/day; 16 weeks	↓Creatinine levels	↑Renal function ↓Kidney weight ↑Kidney SOD activity ↓Kidney MDA content ↑CAT protein ↓SIRT1 protein ↑SIRT1 activity ↓Acetylated-FOXO3a	[56]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
Sprague-Dawley rats	20 mg/kg/day; 4 weeks	↓Glucose levels ↓Creatinine levels	↓Kidney weight ↓Glomerular thickening ↓Interstitial fibrosis ↓Epithelial cellular vacuolar degeneration ↓Hyaline casts ↓Arteriolopathy ↓Ph-p38 and p38 protein ↓TGF-β1 protein ↓Fibronectin protein ↓Urinary albumin	[43]
Male Wistar rats	5 mg/kg/day; 45 days	No measured effects	↓Renal hypertrophy ↓Mesangial expansion ↓Fibrosis ↓Oxidative damage ↓Kidney AGE accumulation ↓DNA damage ↓4-HNE protein ↓Caspase-3 protein ↓Cleaved caspase-3 protein	[81]
C57BL/KsJ db/+ mice	10 mg/kg/day; 8 weeks	↓Glucose levels ↓Insulin levels ↓IL-1β, IL-17, IL-10 and TNF-α levels ↑IL-6 and VEGF levels	↓Renal cell apoptosis ↓Apaf-1, caspase-3, caspase-8 and caspase-9 mRNA ↓Ph-AMPK ↓Total thiol level ↑GSH level	[82]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
CD-1 mice	30 mg/kg/day; 12 weeks	↓Glucose levels ↓Cholesterol levels ↓Urea nitrogen levels	↓Glomerular thickening ↓Mesangial area ↑Podocyte mitochondria ↓Renal cell apoptosis ↑Nephrin, SIRT1, PGC-1α, NRF1, TFAM protein ↓Kidney MDA content ↓Kidney Mn-SOD activity	[61]

FFA: free-fatty acid; TBARS: thiobarbituric acid reactive substances; GSTM: glutathione S-transferase Mu; NEFA: non-esterified fatty acid; 8-OHdG: 8-hydroxydeoxyguanosine; PAI: plasminogen activator inhibitor; ICAM: intercellular adhesion molecule; PCNA: proliferating cell nuclear antigen; SOD: superoxide dismutase; Mn-SOD: manganese superoxide dismutase; BUN; blood urea nitrogen; IGF-1R: insulin-like growth factor 1 receptor; HRD1: 3-hydroxy-3-methylglutaryl reductase degradation; ERR: estrogen-related receptor; SREBP: sterol regulatory element-binding protein; FSP: fibroblast-specific protein; HbA1c: hemoglobin A1c; Atg: autophagy related; AGE: advanced glycation end production; 4-HNE: 4-Hydroxynonenal; Apaf: Apoptotic protease activating factor.

2.8. In Vivo Animal Studies: Effects of Resveratrol on Renal Fibrosis

Renal fibrosis is often characterized by glomerulosclerosis and tubulointerstitium damage and is the final symptom manifestation of CKDs. Additionally, renal fibrosis can be pathologically described with inflammatory infiltration, loss of renal parenchyma due to tubular atrophy, capillary loss, and podocyte depletion[83].

Overall, the studies suggest that administration of RSV to animal models of renal fibrosis reduced extracellular matrix protein deposition, reduced tubulointerstitium damage, and mesangial cell proliferation. RSV reduced serum creatinine levels and kidney oxidative stress, while kidney antioxidant enzymes (SOD, CAT, GPx, and GSH) were increased. In addition, RSV treatment improved mitochondrial biogenesis, mitochondrial complex I and III activities, and electron transport protein expression, while mPTP opening and fission protein expression were reduced. RSV treatment also exerted anti-inflammatory effects, by reducing mRNA and protein expression of pro-inflammatory signaling molecules and cytokines. These data demonstrate that RSV treatment exerts protective effects against renal fibrosis (**Table 8**).

Table 8. Effects of resveratrol on renal fibrosis (animal studies).

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
Sprague–Dawley rats	10 mg/kg/day; 21 days	↓MDA levels	↓Urine calcium oxalate crystals ↓Hyaluronan protein ↓Osteopontin protein ↑GPx protein ↑CAT protein ↑SOD protein	[48]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
Male Wistar rats	8 mg/kg/alternating days; 8 days	↓Creatinine levels ↓Urea nitrogen levels	↓Oxidative stress ↓Renal tubular epithelial cell necrosis ↓MDA, BUN, CRE, and ROS levels ↑SOD and GPx levels ↑Selenium content	[84]
C57BL/6J mice	20 mg/kg/day; 14 days	No measured effects	↓Extracellular matrix deposition ↓Tubulointerstitium damage ↓Oxidative stress ↓ICAM-1 mRNA ↓TNF-α mRNA ↓TGF-β mRNA ↓Acetyl-Smad3 ↓Fibronectin	[85]
UUO-Sprague-Dawley rats	20 mg/kg/day; 7–14 days	↓Creatinine levels	↓Renal interstitial damage ↓Tubular dilation and atrophy ↓Collagen deposition ↓Inflammation cell infiltration ↓α-SMA and type III collagen mRNA and protein ↑E-cadherin protein and mRNA ↓TGF-β1 expression	[50]
I/R and UUO C57BL/6 mice	20 mg/kg/day; 6 weeks	↓Creatinine levels ↓BUN levels	↑α-SMA protein ↑COL1A1 protein	[52]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
Sprague–Dawley rats	50 mg/kg; 8 h	↓Creatinine levels ↓Urea nitrogen levels	↓Apoptosis ↑SIRT1 activity and protein ↑SIRT3 activity and protein ↑SOD2 protein ↓Acetyl-SOD2 ↑GSH and ATP content ↑GSH/GSSG ratio ↑CAT activity ↓mPTP opening	[86]
Male cystic (Cy/+) rats	200 mg/kg/day; 5 weeks	↓BUN levels ↓Creatinine levels	↓Cyst density ↓Macrophage infiltration ↓MCP-1 ↓TNF-α ↓CFB ↓Ph-p65, ph-S6K and p50	[54]
Sprague–Dawley rats	3 and 10 mg/kg/injection; 70 h	↓BUN levels ↓Creatinine levels ↓Nitrogen levels	↑Survival ↓Cystatin C ↓KIM-1 ↓TNF-α ↓IL-1B ↓IL-6 ↓Renal injury index	[87]
Kunming mice	10 mg/kg/day; 1 week	↓BUN levels ↓Creatinine levels	↓Apoptosis ↓Caspase-3 activity ↓Bax protein ↓ERK1/2 protein	[57]

Animal	Resveratrol Concentration/Duration	Serum Effects	Other Effects	Reference
Male AKI rats	30 mg/kg; 12 h	↓Creatinine levels ↓Urea nitrogen levels ↓TNF-α, IL-1β, IL-6 levels	↑Renal function ↓Tubular epithelial cell injury ↑Survival ↓p-65 positive cells ↓Renal TNF-α, IL-1β, IL-6 mRNA ↓IRE1 protein	[55]
5/6 Nephrectomized Sprague–Dawley rats	20 mg/kg/day; 4 weeks	No measured effects	↓Mesangial cell proliferation ↓Glomeruli matrix expansion ↓TGF-β ↑ATP production ↓ROS production ↑Activities of complex I and III ↑ATP synthase B ↑COX I, Opa1, Mfn2 ↓Drp1	[44]
C57BL/6 mice	25 and 100 mg/kg/day; 2 weeks	↓Creatinine levels	25 mg/kg RSV: ↓Renal fibrosis ↓Tubular lesion score ↓Interstitial collagen deposition ↓α-SMA protein ↓Snail protein ↓Fibronectin protein ↑SIRT1 ↓Phospho-Smad3 100 mg/kg RSV: ↑Renal fibrosis ↑α-SMA and TFAM	[58]

CRE: creatinine; GPx: glutathione peroxidase; mPTP: mitochondrial permeability transition pore; KIM-1: kidney injury molecule 1; IRE-1: Inositol-requiring enzyme 1; Opa1: optic atrophy 1; Mfn2: mitofusin 2; Drp1: dynamin related protein 1.

3. Effects of Resveratrol on Human Kidneys

Only two clinical studies exist measuring the effects of RSV in humans with kidney disease. In a randomized, double-blinded pilot study by Saldanha et al. (2016), administration of RSV (500 mg/day) for 4 weeks to non-dialyzed chronic kidney disease (CKD) patients (GFR between 15 and 60 mL/min/m^2) resulted in no significant effects. Antioxidant and anti-inflammatory marker levels were the same in RSV and placebo supplemented participants[88]. It should be emphasized that administration of RSV (500 mg/day) for 4 weeks had low toxicity.

In another randomized, double-blinded study by Lin et al., low-dose (150 mg/day) or high-dose (450 mg/day) of RSV intake for 12 weeks by peritoneal dialysis (PD) patients resulted in significant improvements in mean net ultrafiltration (UF) volume and rate[89]. In addition, angiogenesis markers, VEGF, fetal liver kinase-1 (Flk-1), and angiopoietin (Ang)-2 levels in peritoneal dialysate effluent (PDE) were significantly reduced in the high-dose RSV group. The levels of angiopoietin receptor (Tie-2) and thrombospondin-1 (Tsp-1) in the PDE were increased with RSV treatment[89]. These data suggest that RSV treatment has angiogenesis-ameliorating effects in PD patients and improves ultrafiltration kidney function. It should be mentioned that in the study by Saldanha et al.[88] administration of 500 mg RSV/day for 4 weeks resulted in no significant effects, while in the study by Lin et al.[89] administration of 450 mg RSV/day for 12 weeks resulted in significant improvements and health benefits, suggesting that longer duration of administration of a specific dose of RSV (450 or 500 mg/day) may be required to see/elicit beneficial effects.

Other clinical studies exist showing beneficial effects of RSV administration in cardiovascular disease, diabetes mellitus and cancer, however, the effect of RSV supplementation in kidney disease patients has not been extensively studied[90] [91]. In a randomized, double-blinded study by Brasnyo et al. (2011), oral administration of RSV (10 mg/day) in type 2 diabetic (T2DM) individuals (following the WHO diagnostic guidelines), significantly increased insulin sensitivity and reduced serum glucose and cholesterol levels[92]. In addition, RSV treatment significantly reduced serum creatinine levels and maintained GFR, suggesting improved kidney function[92]. In a similar randomized, open-label, controlled study, administration of RSV (250 mg/day) for 4 months in T2DM patients (3 year duration of T2DM and minimum 6 months oral hypoglycemic treatment) resulted in significantly improved lipid profile, with reduced total cholesterol and triglyceride levels[93] [117]. Serum creatinine, urea nitrogen levels, and total protein excretion were reduced with RSV treatment, suggesting improved kidney function[93]. These studies[92][93] show that treatment of individuals with T2DM and impaired kidney function with RSV resulted in improved glucose, insulin, and lipid homeostasis and better kidney function.

Although there are numerous studies measuring the effects of RSV in diabetes, the studies mentioned above were performed in individuals with established CKD and diabetic nephropathy and show a kidney-protective effect of RSV administration. These data highlight the importance of future clinical trials required to investigate the exact effects of RSV in individuals with kidney disease (**Table 9**).

Table 9. Effects of resveratrol on human kidneys.

Patients	Resveratrol Concentration/Duration	Effect	Reference
Nondialyzed CKD patients	500 mg/day; 4 weeks	No significant effects	[88]
PD patients	150 and 450 mg/day; 12 weeks	↓UF volume and rate ↓PDE VEGF, Flk-1 and Ang-2 ↑PDE Tie-2 and Tsp-1	[89]
T2DM patients	10 mg/day; 4 weeks	↑Kidney filtration ↑Insulin sensitivity ↓Glucose levels ↓Lipid levels ↓Serum creatinine	[92]

Patients	Resveratrol Concentration/Duration	Effect	Reference
T2DM patients	250 mg/day; 4 months	↑Kidney function ↓Cholesterol levels ↓Triglyceride levels ↓Serum creatinine ↓Total protein excretion ↓Urea nitrogen levels	[93]

CKD: chronic kidney disease; PD: peritoneal dialysis; UF: ultrafiltration; PDE: peritoneal dialysate effluent; Flk-1: fetal liver kinase 1; Ang: angiopoietin; Tie-2: angiopoietin receptor; Tsp-1: thrombospondin-1; T2DM: type 2 diabetes mellitus.

4. Effects of RSV at the Cellular/Molecular Level

Resveratrol has been found to affect a number of different signaling molecules in kidney cells (**Figure 2**). RSV inhibited the PDGF[38] and TGF-β1 response in mesangial[43][44][77] and epithelial[48][52][58] cells. It decreased oxidative stress[48][50][54][57][66][76][77], as shown by decreased ROS and MDA levels and increased antioxidant enzyme activity and improved mitochondrial biogenesis[39][44][58] (**Figure 2**). Activation of the energy sensor AMPK[46][49][69][76] and increased SIRT1[44][47][52][61][76] and PGC-1[57][61] levels were seen with RSV treatment. The deleterious effects of high glucose on kidney cells were diminished with RSV treatment[39][40][51][56][61][67][69] (**Figure 2**).

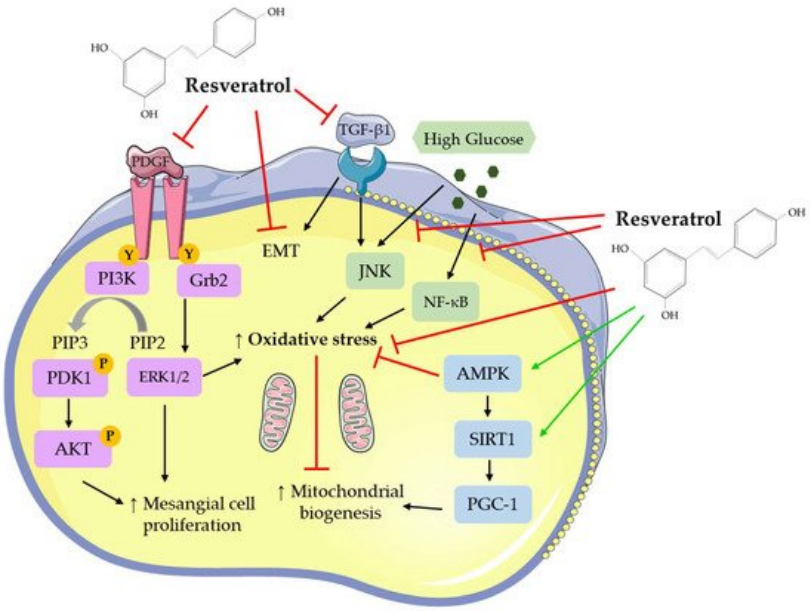

Figure 2. Effects of resveratrol on cellular signaling molecules. The figure was created based on the data of the studies[38][49][53][54][58][65][70][76][77]. AKT: protein kinase B; PDK: pyruvate dehydrogenase kinase; PIP3: phosphatidylinositol-3,4,5-triphosphate; PIP2: phosphatidylinositol 4,5-bisphosphate; ERK: extracellular signal-regulated kinase; PI3K: phosphoinositide 3-kinase; Grb: growth factor receptor-bound protein; PDGF: Platelet-derived growth factor; EMT: extracellular matrix transition; JNK: c-Jun N-terminal kinase; AMPK: AMP-activated protein kinase; SIRT: sirtuin; PGC: Peroxisome proliferator-activated receptor gamma coactivator; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TGF-β: transforming growth factor beta.

5. Conclusions and Future Directions

Overall, all available in vitro and in vivo animal and human studies examining the effects of RSV in kidney disease indicate that it can reduce fibrosis, mesangial expansion, oxidative stress, and inflammatory cytokine levels, while improving kidney structure and function. Treatment of renal mesangial, epithelial, and corpuscle cells with RSV resulted in

reduced structural changes and ROS production, while antioxidant and mitochondrial activities were improved. In addition, RSV treatment reduced fibroblast proliferation and activation to improve kidney structural maintenance. Renal cancer cells treated with RSV had reduced cell growth, cell-to-cell contact, and migration, and increased apoptosis.

In in vivo animal models of diabetic nephropathy treatment with RSV showed improved glucose homeostasis, reduced inflammation and increased antioxidant activity and kidney function. Animals with renal fibrosis administered RSV had reduced structural changes and inflammatory cell infiltration, cytokine expression, and decreased tubulointerstitium damage and oxidative stress.

The limited human studies indicate a protective effect of RSV administration on chronic kidney disease with increased kidney filtration rates and volume. The health benefits of RSV are widespread, and the low toxicity of the molecule makes it a prime candidate for medicinal use against kidney disease. However, more research and clinical studies are required to fully understand the effects of RSV on kidney disease.

Further investigation and clarification are required in the following areas: (1) dosage and bioavailability, (2) metabolism, tissue distribution, and biological effects of RSV analogs and metabolites, and (3) signaling mechanisms involved.

Only limited number of studies exist examining RSV administration in humans. More studies should be performed to determine the optimal dosage and route of administration of RSV and analogs with higher biological activity. RSV analogs (methylated and with other novel derivatives) may have great biological activity [54]. Most in vitro studies and evidence have used RSV and not its metabolites. The potential biological activity of RSV metabolites should be considered in future investigations.

Furthermore, future research should be conducted examining the exact signaling/cellular mechanisms affected by RSV and contributing to the attenuation of kidney disease.

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