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Review

Resveratrol and endothelial function: A literature review

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ABSTRACT

Endothelial dysfunction is a major contributing factor to diseases such as atherosclerosis, diabetes mellitus, obesity, hypertension, acute lung injury, preeclampsia, among others. Resveratrol (RSV) is a naturally occurring bioactive polyphenol found in grapes and red wine. According to experimental studies, RSV modulates several events involved in endothelial dysfunction such as impaired vasorelaxation, eNOS uncoupling, leukocyte adhesion, endothelial senescence, and endothelial mesenchymal transition. The endothelial protective effects of RSV are found to be mediated by numerous molecular targets (e.g. Silent Information Regulator 1 (SIRT1), 5′ AMP-activated protein kinase (AMPK), endothelial nitric oxide synthase (eNOS), nuclear factor-erythroid-derived 2-related factor-2 (Nrf2), peroxisome proliferator-activated receptor (PPAR), Krüppel-like factor-2 (KLF2), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB)). Herein, we present an updated review addressing pharmacological effects and molecular targets of RSV in maintaining endothelial function, and the potential of this phytochemical for endothelial dysfunction-associated disorders.

1. Introduction

Resveratrol (RSV or 3, 5, 40-trihydroxystilbene), mostly found in red wine, peanuts, apples and grapes, is a polyphenolic compound [1,2]. These compounds regulate lipid profile, blood pressure, oxidative stress, inflammation, cell adhesion, and endothelial function. RSV is also considered a strong antioxidant with numerous biological and therapeutic properties such as hepatoprotective, anticancer, cardioprotective, anti-atherosclerotic, endothelial protective, anti-thrombotic, anti--angiogenic, lipid-modulating, mitochondria biogenesis, anti-diabetic, and anti-hypertensive effects [3,4]. Endothelial dysfunction is defined as impaired vasodilation, pro-inflammatory and pro-thrombotic predilection of endothelium [5]. Up-regulation of vascular adhesion molecules (such as intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1(VCAM-1)), chemokine generation, and plasminogen activator inhibitor-1 are implicated in the inflammatory response leading to a pro-thrombotic condition [6]. The precise mechanism of RSV on inhibition of oxidative stress-induced inflammation is unknown, and RSV could cause a dose/cell type-dependent activation of pro- and anti-apoptotic pathways [7,8]. A single-dose of RSV in obese patients with untreated borderline hypertension (HTN) was shown to increase flow-mediated dilation (FMD). Also, RSV treatment in healthy individuals substantially lowered the concentration of pro-inflammatory cytokines and expression of adhesion molecules (i.e. ICAM-1 and VCAM-1). In a study by Tomé-Carneiro et al., the beneficial effects of RSV on reduction of pro-inflammatory and soluble cell

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adhesion molecules was demonstrated [9,10]. Moreover, RSV prevented endothelial cell activation and monocyte adhesion by suppressing NF-kB pathway and resulted in decreased proinflammatory gene expression in coronary arterial endothelial cells [11]. It is documented that RSV plays an important role in lipid catabolism, cell clearance and several physiologic processes [12] (Fig. 1). Herein, we discuss the various effects of RSV on improving endothelial cell dysfunction as below.

2. Cardioprotection

Cardiovascular disease (CVD) including numerous blood and/or heart vessels disorders like coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease, congenital heart disease and deep vein thrombosis [13]. Fortunately, there are a number of "traditional" pharmacotherapies for heart failure (HF) that have been found to reduce HF-related mortality. Considering that resveratrol is anticipated to have favorable effects in a variety of CVD that might lead to HF and/or are HF comorbidity. Importantly, various animal models of ischemia and non-ischemic HF have indicated that RSV enhances diastolic or systolic performance, prolongs survival, and both [14]. Notably, RSV has been demonstrated to enhance systolic or diastolic performance, minimize negative atrial and left ventricular remodeling, promote cardiac energetics and hemodynamics, and/or increase exercise capacity in a variety of animal models of ischemia and non-ischemic HF [15–17]. Considering these preclinical trials of RSV effect in HF patient is still uncertain. Furthermore, in patients with angina pectoris, 20 mg of resveratrol per day for 60 days led to a significant drop in b-type natriuretic peptide (BNP), indicating enhanced left ventricular performance [18]. The use of RSV as a pretreatment 15 min before inducing ischemia with coronary artery ligation (for 30 min) has been found to reduce LV systolic pressure and infarct size [19]. Other study showed that RSV decreased infarct size after ischemia and then reperfusion when administered 5 min prior reperfusion in vivo [20]. It was also observed that administering RSV (0.05 and 1 mg/kg) 60 min before inducing ischemia in rat and then reperfusion for 3 h can reduce infarct size and the frequency of ischemia/reperfusion caused ventricular fibrillation (VF) and ventricular tachycardia (VT) [21]. Moreover, clinical studies involving patients with HF have started as a result of the growing interest in the field. The REV-HF (clinicaltrials.gov, #NCT03525379) is a randomized, double-blind, placebo-controlled experiment that focuses at how skeletal muscle function changes following 8 weeks of RSV treatment in heart failure patients [22]. Furthermore, the RES-HF trial (clinicaltrials.gov, #NCT01914081) is a randomized, double-blind, placebo-controlled experiment that aims to evaluate the clinical safety and effectiveness of RSV for in patients with HF. Improvements in echocardiographic and patient outcome, endothelial function, biomarker of inflammation and oxidative stress, and nitric oxide (NO) function are among the major and secondary aims [23].

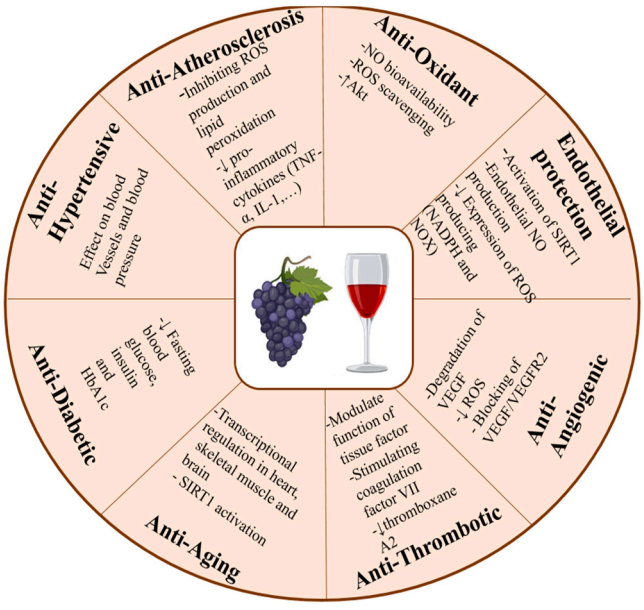

Fig. 1. Cardiovascular actions of resveratrol. Resveratrol exerts pleiotropic cardiovascular actions against cardiovascular diseases by its anti-oxidant, anti-atherosclerotic, anti-hypertensive, anti-diabetic, anti-aging, anti-thrombotic, anti-angiogenic, and endothelial protective effects.

RSV may protect against myocardial reperfusion/ischemia and myocardial infarction by upregulating NO production, improving antioxidant effectiveness and, antagonizing fractalkine, or promoting angiogenesis mediated by vascular endothelial growth factor (VEGF). Furthermore, RSV decreases hypertension and consequent cardiac hypertrophy in mice caused by different hypertrophic stimuli like pressure overload, deoxycorticosterone acetate (DOCA)-salt or Angiotensin (Ang) II [24,25]. These responses are linked to an increase in NO, AMPK stimulation, a reduction in oxidative stress, and a decrease in ET-1 and Ang II levels [26]. In this regard, RSV inhibits prohypertrophic effect and functional deterioration in chronic heart failure through modulating the p70S6 kinase and LKB1/AMPK signaling pathways in hypertensive rats [26–28]. Recently reports showed that RSV is a new inhibitor of immunoproteasome that prevents PTEN degradation and reduces cardiac hypertrophy in animal model of pressure overload. Suppression of immunoproteasome catalytic subunit expression and activity, which lowers PTEN degradation and inhibits AKT/mTOR and activates AMPK signaling pathways, was linked to the positive effect. The positive result was related with suppression of immunoproteasome catalytic subunit activation, which decreases PTEN degradation leading to activation of AMPK and inhibition of AKT/mTOR signaling pathways [29,30] (Table 1).

3. Anti-thrombotic effects

Thromboembolic events caused by excessive platelet accumulation are involved in disorders such as myocardial infarction, stroke or acute limb ischemia [31]. Studies on RSV have demonstrated its antiplatelet effect both in vitro and in vivo, which is due to its potential to modulate tissue factor (TF) function and gene/protein expression [32–34]. TF, is a well-known thromboplastin, which activates thrombosis through binding to and further stimulation of coagulation factor VII as a principle initiator of extrinsic coagulation cascade [36]. TF is mainly expressed in neutrophils, monocytes, perivascular cell membranes, and platelets. It is also upregulated in endothelial cells in response to stimulation by cytokines such as tumor necrosis factor-alpha (TNF-α) [35,36]. To date, the association between RSV and TF production, protein accumulation, or mRNA expression is not addressed. The effects of RSV on platelets appear to be mediated through cyclooxygenase-1 (COX-1) repression rather than cyclooxygenase-2 (COX-2) [37]. Selective COX-1 inhibition results in decreased TxA2 (thromboxane A2) production, which normally drives platelet aggregation [37]. Conversely, COX-2 synthesizes prostacyclins as antiplatelet factors in vascular endothelium [38]. In a study by Dutra et al., a hybrid Resveratrol-furoxan product mediated the release of NO (nitric oxide) and inhibited platelet aggregation in the process of the Adenosine diphosphate (ADP) agonist, collagen and arachidonic agonist [39]. Compared to acetylsalicylic acid (ASA), administration of Resveratrol-furoxan was associated with decreased bleeding time on mice models. These findings illustrated the importance of further research and developing new forms of RSV with even improved properties.

4. Anti- angiogenic effects

Angiogenesis is a tightly regulated mechanism in which new vessels

Table 1
Cardiovascular effects of resveratrol.

Model	Resveratrol treatment (Conc./Time)	Finding	Proposed mechanism	Reference
In vitro/H9c2 cells	25 μM for 24 h	↑Cell viability	- ↓BAX/p53 - ↑Phosphorylation of AMPK - - ↑BCL-2	[194]
In vitro/H9c2 cells	20 μM for 24 h	↓Cardio-toxic effects	- ↓Apoptosis via - ↑Autophagy-AMPK activation - ↑LC3 (particularly LC3-II)/ BCL-2 - - ↓BAX expression	[195]
In vitro/H9c2 cells	25 μM for 24 h	Anti-apoptotic effect in cardiomyocytes	- ↑Sirt1 activation - ↑SOD - - ↓MDA expression	[196]
In vitro/H9c2 cells	20 μM for 24 h	- ↓Apoptotic ratio and activated autophagy process	- Blocking induction of E2F1/mTORC1 and E2F1/AMPKα2 pathway	[197]
In vitro/Cardiomyocytes cell from old Sprague-Dawley rats	20 μM for 24 h	- ↑VDAC1 deacetylation in - cardiomyocytes - Cardioprotective effect - ↓Cardiomyocyte apoptosis	- ↑SIRT1 - ↓Bax - ↑Bcl-2 expression	[198]
In vivo/Female F344 rats	2.5 mg/kg/day for 2 weeks	- ↓Fibrosis and fibroblast activation - ↓Mortality rate - -↓Fibrosis/Fibroblast activation	- ↑SIRT1 - ↓TGF-β/pSMAD3/SMAD3 levels - ↑Mn-SOD	[199]
In vivo/Male Wister rats	20 mg/kg for 6 weeks	- Improving cardiac function - -minimize cardiotoxic side effects	- ↓Caspase 3 - ↓Myocardial apoptosis/Fibrosis - - ↓Bax/NFAT3 expression	[200]
In vivo/Wister rats	80 mg/kg for 8-week	- Improved LVF - ↓Myocardial hypertrophy - ↓Fibrosis - ↓Severity of heart failure	- ↑Akt-1,GSK-3β - ↓p38-MAP, ERK1/2, MKP-1,COX-2, iNOS	[201]
In vivo/C57BL/6 mice	146 mg kg/day and 320 mg kg/day for 1 week	- Normalized molecular markers of cardiotoxicity - Restored the heart ability in response to hypertension	- Modulate p38 in the heart - ↑p21, Igfbp3, Gadd45g, TP53 Perp	[202]
In vivo/Wistar albino rats	20 mg/kg	- ↓Heart weight/body weight ratio	- ↑SOD - ↑Cardiac caspase-3 protein expression - ↑Glutathione/↑troponin-I - -↑CK-MB	[203]
In vivo/Wistar rats	10 μM	- ↓Infract size - ↓Arrhythmia - ↓CK-MB - ↓ LDH - - ↓Troponin I	↑Cardiac release NO	[204]
In vivo/Albino Wistar rats	50 mg/kg for 30 day	↓Cardiac marker enzymes,lipid profile, LPO, anti-oxidant enzymes, transcripts of inflammatory markers	- ↑Superoxide dismutase/catalase - ↓NF-kB/TNF-α especially - ↓TG/LDLc/VLDLcl/LDH - ↑ HDLc - ↓CK-MB/ALP	[205]

AKT: Protein Kinase B; AMPK: Adenosine Monophosphate-Activated Protein Kinase; AngII: Angiotensin II; BAX: BCL (B Cell Lymphoma)-Associated X; DOX: Doxorubicin; E2F1, Transcription2 Factor 1; E2F1: Transcription2 Factor 1; ER: Endoplasmic reticulum; Foxo: Forkhead Box O; hCPCs: Human Cardiac Progenitor Cells; HO: Heme Oxygenase; Igfbp3: insulin-like growth factor binding protein 3; ISO: Isoproterenol; Gadd45g: growth arrest and DNA damage inducible gamma; GSH: Glutathione; LC3: LV: Light Chain 3; Left Ventricular; MAPK: Mitogen-Activated Protein Kinase; MDA: Malonaldehyde; Mn-SOD: Manganese Superoxide Dismutase; mTORC1: Mammalian Target of Rapamycin Complex 1; MuRF-1: MuscleRING-Finger Protein-1; NFAT3: Nuclear Factor of Activated T-Cells; NO: Nitric Oxide; oxLDL: oxidized Low-Density Lipoprotein; Perp: TP53 apoptosis effector; PI3K: Phosphatidylinositol 3-kinase; RES: Resveratrol; ROS: Reactiveoxygen Species; SA: Syringic Acid; sE-selectin: Soluble E-selectin-1; sICAM-1: Soluble Intercellular Adhesion Molecule-1; Sirt, Sirtuin; SIRT1, Sirtuin 1; SOD: Superoxide Dismutase; sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; S6k1: Ribosomal Protein S6 Kinase Beta-1; TGF-β: Transforming Growth Factor-β tPAI-1: Total Plasminogen Activator Inhibitor; ↑: Increase; ↓: Decrease.

are physiologically developed [40]. This is an intricate process driving multiple physiologic events including embryogenesis, wound healing, corpus luteum development, among others [41]. A number of growth factors and cytokines secreted by matrix cells, endothelial cells and tumor cells, regulate the synchronization of specific reactions involved in angiogenesis (i.e. endothelial cell proliferation, differentiation, migration and protease activation) [42]. Many ligands, namely placental growth factor (PlGF), platelet-derived growth factor (PDGF), angiopoietins (mostly Ang-1 and −2), acid and basic fibroblast growth factors (aFGF and bFGF), platelet-derived-endothelial cell growth factor (PD-ECGF) and hepatocyte growth factor (HGF) are needed for a proper angiogenesis process [43,44]. Vascular endothelial growth factor (VEGF) is the most important signal protein that improves survival and mitogenic potential of vascular endothelial cells. Two VEGF receptors (VEGFR1 and VEGFR2) are present; VEGFR2 has been shown to regulate much of the effects of VEGF on angiogenesis and their interaction is approximately 50 times greater than VEGFR1/VEGF binding. The VEGFR2 activation significantly contributes to initiation of downstream transduction signaling in angiogenesis, such as Akt, A mitogen-activated protein kinase (MAPK), and Jun N-terminal kinases (JNKs). Hu et al., showed that RSV inhibited VEGF-induced VEGFR2 phosphorylation without any impact on VEGFR2 protein expression. Lack of a phosphorylated VEGFR2 protein may explain the reduction in VEGF-derived phosphorylation of extracellular-signal-regulated kinase (ERK), Akt, Jun N-terminal kinase (JNK), and eNOS [45]. In addition, RSV could facilitate degradation of VEGF and hence reduces the interaction of VEGF with its receptor. Other potential causes are also known to inhibit VEGF association with VEGFR2, including development of a VEGF gradient, half-life of the signaling process or matrix adhesion molecules [45,46]. Reactive oxygen species (ROS) are found in the downstream VEGFR2 signaling and adversely affect endothelial function [47]. With using RSV in VEGF treated cells, the amount of ROS were evidently reduced which

may be due to hypophosphorylated VEGFR2 protein [45] (Table 3).

5. Anti-atherosclerotic effects

Atherosclerosis is precipitated by chronic inflammation and dysregulated angiogenesis. However, the role of these processes in atherosclerosis has not yet been elucidated. While it may protect endothelial cells by inducing the anti-apoptotic protein expression and NO production, VEGF also as a pro-atherogenic factor stimulates the endothelial cell proliferation and growth, thus inducing angiogenesis, increasing endothelial permeability and upregulating cell adhesion proteins. An increased serum concentration of VEGF has been reported in patients afflicted with coronary artery disease, myocardial infarction, and atherosclerosis. RSV is a cardioprotective phytoalexin; it hinders oxidative damage by affecting the superoxide and hydroxyl radical anion, preventing ROS formation and lipid peroxidation. Also, NF-kB, an inflammation-inducing transcription factor, is associated with increased serum levels of pro-inflammatory cytokines including chemokine ligand 3, interleukin 1 beta (IL-1β), and TNF-α [48,49]. Porotra et al., showed that RSV decreased the expression and secretion of VEGF and the cellular hyper permeability induced by high glucose in aortic cultured endothelial monolayers [50]. It also prevented the upregulation of VEGF in incubated macrophages with 7-oxo cholesterol reinforcing the possible therapeutic role of this polyphenol to counteract pro-atherogenic signaling of oxysterols within an atherosclerotic plaque [51]. RSV possibly impede the secretion of VEGF in vivo, resulting in less migration, permeability and proliferation of endothelial cells [51]. Nevertheless, the exact effect of RSV on serum VEGF concentration during the development and evolution of atherosclerosis is not yet clear; therefore, the relationship between VEGF and inflammation and VEGF evolution throughout the atherogenic process is not yet known as well.

6. Anti-diabetic effects

Insulin resistance is a strong risk factor for the development of T2D, however, there is no effective therapeutic strategy to counteract this condition. There are only some general guidelines for diet and exercise which are rarely implemented and the results differ from patient to patient. The studies on the role of naturally-occurring products such as RSV in reversing insulin resistance are constantly evolving [52–54]. Two meta-analysis indicated that RSV decreased fasting blood glucose, insulin and glycated hemoglobin (HbA1c) [55]. Movahed et al., reported that administration of RSV supplement to adults with T2D (1000 mg/day for 45 days) decreased HbA1c by 15% and Homeostatic Model for Assessment of Insulin Resistance (HOMA-IR) by 50% [56]. Similarly, in the lack of glucose-lowering influence, insulin level in T2DM patients with periodontal disease decreased by 5% to 480 mg/day after 4 weeks of receiving RSV [57]. However, in a meta-analysis consisting nine T2D trials, the beneficial impact of RSV was only reported for HOMA-IR reduction. Some clinical studies evaluating the effect of RSV on biomarkers of diabetes were inconclusive [58]. No apparent difference was observed in insulin level in T2D patients who received 10 mg/day and 3000 mg/day of RSV in two separate trials. It was then suggested that there could be an appropriate dosage range for RSV to affect metabolic pathways [59]. In a randomized double-blind crossover study, seventeen individuals with T2D received placebo or RSV (150 mg/day) for 30 days and insulin sensitivity was assessed through hyperinsulinemic-euglycaemic [60]. Following RSV treatment, an ex vivo improvement in muscle mitochondrial activity and decreased systolic blood pressure were observed while hepatic and peripheral insulin sensitivity remained unchanged [61,62]. In another experiment, a comparative high dosage of metformin by patients led to higher plasma levels of RSV; the dihydro-resveratrol metabolite, signals a higher RSV breakdown that could impair its bioavailability. Moreover, in T2DM patients with severe complications such as lower extremity ulcers, there was little evidence of insulin reduction. This research identified no improvements in diabetic's biomarker; hence, Resveratrol's ability to overcome severe T2D needs to be verified [63]. Several studies have highlighted the antidiabetic effects of RSV on non-T2D patients. Witte et al., reported that RSV treatment in obese but stable elderly people, decreased HbA1c within 6 months [64]. Similarly, Timmers et al., found a moderate 14% insulin reduction with 150 mg/day RSV for 30 days in the same group. The increase in insulin sensitivity was attributed to the rise in mitochondrial activity in the skeletal muscle, and reduced levels of leptin and triglyceride. thus it grows the performance of substrate usage [60,61]. Conversely, a 4-week study on obese/mildly overweight elderly patients using the same dosage (150 mg/day) did not indicate any improvements in lipids, glucose metabolism or inflammatory markers [65]. Likewise, in elderly glucose-intolerant individuals without T2D, 6 weeks of 2–3 g/day RSV failed to improve insulin sensitivity or glucose tolerance [66]. In a meta-analysis on non-T2D patients by Liu et al., no significant antidiabetic effects was observed following RSV treatment [55]. The high concentration of RSV was shown to adversely impact insulin function by excessive stimulation of peroxisome proliferator-activated receptor-γ coactivator-1af (PGC1af), a key regulator of mitochondrial biogenesis and metabolism [67]. This result [68] contradicts another report on patients with metabolic syndrome who received 90 days of 1500 mg/day Resveratrol therapy and a substantial decrease was observed in postprandial insulin dose [69] (Table 2).

Cardiovascular complications are the primary cause of mortality and morbidity in type 2 diabetic (T2D) patients especially women [72]. The risk of myocardial infarction in T2D women is five times higher compared to those free of diabetes, this risk is only increased by two-folds in men [73]. Also, myocardial infarction is associated with greater risk of death in women with T2D as opposed to male. There is scant data regarding the correlation between female gender and adverse cardiovascular events [74]. Notably, Des rois et al., described an advanced coronary endothelial damage in female rats without any ischemic insult, which may increase cardiovascular complications in T2D females. Currently, most antidiabetic therapies do not alleviate these complications highlighting the role of dietary supplements in combination with the present treatments. In numerous studies on T2D or metabolic syndrome models, RSV reduced chronic inflammation, oxidative stress and increased insulin sensitivity. Also, the impact of RSV on endothelial activity particularly through nitric oxide (NO) and sirtuin pathways, has been previously documented [75,76]. RSV has shown beneficial effects on mitochondrial activity by growing mitochondrial DNA and biogenesis [77]. It may also be an interesting candidate for optimizing cardiac metabolism and cardiovascular status in T2D females [78,79]. The dosage of RSV used in literature is variable between 0.1 and 500 mg/day to even 4 g/day [68,80].

7. Anti-hypertensive effects

Endothelial dysfunction is defined as a direct or indirect decline in NO bioavailability [81]. Estrogen modulates NO release by endothelium through enhancing its bioavailability and development via genomic and non-genomic variables [82,83]. Its effect on estrogen receptor alpha (ERα) and reduction of oxidative stress have been previously discussed [84]. During menopause, a fall in estrogen levels contributes to endothelial dysfunction and hypertension. Hormone replacement therapy (HRT) is often recommended to minimize the adverse effects of estrogen deficiency. RSV is a phytoestrogen with similarities to diethylstilbestrol (a synthetic estrogen) which could be a safer alternative to HRT. It also exerts its effects on estrogen receptors and serves as a selective estrogen receptor modulator (SERM). Both phytoestrogens and SERMs are identified as endothelium-vasodilators [84–87]. In addition, Dolinsky et al., indicated that high dose RSV attenuates blood pressure in rats [88]. In a study by Vanhoute et al., other endothelium factors such as endothelium-derived hyperpolarizing factor were proposed as vasodilators [84,89]. Although there are literature supporting the

Table 2
Effects of resveratrol in diabetes.

Model	Resveratrol treatment (Conc./Time)	Finding	Proposed mechanism	Reference
In vitro/BRECs	1, 5, 10, 20 μM for 48 h	- Induction suppresses apoptosis - ↓BG	- ↓ROS - Inhibition of caspase-3 activation - Modulating the AMPK/Sirt1/PGC-1α Pathway	[119]
In vitro/Muller cells	10, 20, and 30 mmol/L for 1- to 7-month	- ↓BP - Prevent from DR	- ↓Glutamate uptake/GS activity/GLAST/ - GS expression	[206]
In vitro/H9c2 cell	20 μmol/L for 16 weeks	↓Cardiac injury in diabetic rats	- ↓Expression ANP/BNP/β-MHC - ↑SOD - Regulation of mitochondrial function via: SIRT1 activation	[207]
In vitro/Retinal Müller cells	10, 20, and 30 mmol/L for 1–7 months	Anti-apoptosis effect	- miR-29b inhibitor - ↓Caspase-3/Bax protein expression	[208]
- In vivo/C57BL/db/db mice- In vitro/HUVECs	5, 30, 50 mg/kg/day for 4 weeks	- Diabetic wound healing Acceleration through its endothelial - ↓Fasting BP/Plasma insulin levels/ Hyperglycemia/Angiogenesis	- ↑Number of PCNA-positive endothelial cells (↓apoptosis) - ↓ ROS - ↓Caspase-3 - ↑SIRT1/Inhibition of FOXO1/Further de-repression of c-Myc	[209]
In vivo/SD rats (STZ/DR model)	10, 20 and 30 mmol/L for1–7 months	- Prevention of DR - ↓BG	- ↓ Glutamate uptake by - Upregulation of GS activity - ↓Expression of GLAST/GS - - ↓Weight	[206]
In vivo/Male Wistar rats (STZ/DM model)	10 mg/kg/d for 120 days	- Treatment of T2D - - Neuroprotective	- ↓Oxidative/Nitrosative stress - - Prevented neuronal loss	[210]
In vivo/Female NOD mice (T1DM model)	200 mg/kg/day for 28 days	- ↓BG - Improves renal function	- ↓The expression of the inflammatory factors RAGE/ NF-κB (P65)/NOX4 - ↓BUN, SCr, 24 h UMA - Improved the renal pathological structure - Improvement in the metabolic memory of hyperglycemia	[211]
In vivo/Male albino rats (STZ model)	10 mg/kg/day for 45 days	- Relative kidney protection in diabetic nephropathy - Better outcome compared to losartan	- ↓GS/Profibrotic TGF-β levels - ↓IL-6/TNF-α/NF-κB - ↑SOD	[212]
In vivo/Rat (HFD/STZ model)	16 weeks	- Improved the insulin resistance - Cardiac function in diabetic rat	- ↓Cardiomyocyte apoptosis - Ameliorating mitochondrial - UCP2 mediated the protective effects - ↓ROS	[213]
In vivo/SD male rats (STZ model)	0.1,1, 5, 10, 50 μg/kg/d	- Reducing the severity of DR - Suppresses HG-induced apoptosis	- Upregulation active caspase-3 - ↓IL-1β/IL-6/TNFα/VEGF/IFNγ/MCP-1 - Several inflammatory factors IL-1/ IL-6/TNF/ VEGF/IFN/MCP-1 - ox-LDL in the retina. - - Upregulation active caspase-3	[214]
In vivo/Male SD rats (STZ model)	5 and 10 mg/kg/day 1–7 months	- Potential therapeutic option for DR - ↓Plasma glucose/fructosamine - ↓Apoptosis	- Suppressed apoptosis of retinal cells - Regulated miR-29b and SP1 expression	[215]
In vivo/Epididymal adipose tissue of mice (STZ model)	10–100 mM	- ↓Inflammation and adipose tissue dysfunction in diabetic	- ↓Inflammation/Cell apoptosis/ATP production/ Oxygen tension in 3T3-L1 cells - ↓HIF-1 by: Regulation of AMPK/SIRT	[216]
In vivo/C57BL/6 male mice (T2DM model)	- RES/400 mg/kg for 45 days	↓Hyperglycemia diabetic/T2DM	- ↓PLIN5 gene expression	[217]
In vivo/Wistar albino rats (STZ model)	20 mg/kg/day for 28 days	↑IR	- ↓Body weights - ↓TNF - - ↑SIRT1 and AMPK immunoreactivity	[218]
In vivo/db/m mice (STZ/DR model)	5 mg/kg	- Improve glycemic control resulting in Renoprotection - - Attenuating renal oxidative stress damage	- ↓High glucose-induced NRK cell activation by: - ↓NOX4- derived ROS - Inhibits high glucose-induced NOX4 expression in NRK cells via: - Activation of AMPK - ↓ROS/Oxidative stress - -Activated/ERK1/2 - Attenuated renal fibrosis via: - Regulation of AMPK/NOX4/ROS signaling	[219]
In vivo/Male mice (T2DM model)	50 mg/kg	↓Insulin resistance in obesity/T2D	- ↓Lipid metabolism via: - Prevention of PKA/HSL activation - ↓the accumulation of cAMP via preserving PDE3B - ↓FFAs influx /DAG accumulation - - Inhibition of PKCθ translocation improved insulin signaling in the muscle	[220]
In vivo/db/db mice (STZ/DR model)	10 mg/kg/day/12 weeks	Treatment of DN	- ↓High glucose-induced apoptosis via: Autophagy in podocytes, (miR-383-5p)	[221]
In vivo/Wistar rats (STZ model)	10 mg/kg/day/10 weeks	Protective role of diabetic kidneys	↓Expression of TNF-α/IL-6	[222]
In vivo/Rat (T2DM model)	50 mg kg/16 weeks	↓Cardiac injury in DN rats	Mitochondrial function regulation of, with: - SIRT1 activation - - ↑PGC-1α deacetylation	[207]

(*continued on next page*)

Table 2 (*continued*)

Model	Resveratrol treatment (Conc./Time)	Finding	Proposed mechanism	Reference
In vivo/Male SD rats (STZ model)	25 mg/kg/day	- Prevented all these cardiac changes - Improves cardiac health	- Activates SIRT-3/Regulates the acetylation status of TFAM - ↓Mitochondrial OXPHOS	[223]
Clinical trial NCT02502253	500 mg/Twice daily/5-week	Does not control glycemia/BG	- No effect on GLP-1 secretion - No changes in HbA1c/Daily energy intake/Body weight/Postprandial BG	[224]
Clinical trial NCT04117022	10 μM/72 h	SIRT1 is protective in patients with proliferative DR	Inhibiting the production of IL-17 in PBMCs	[225]
Clinical trial NCT03436992	500 mg/Twice daily/60 days.	- ↓Levels of FBS/HbA1c and oxidative stress	- ↓Inflammation/Oxidative stress/MDA	[226]
Clinical trial NCT02502253	500 mg/90 days	↓Urinary albumin excretion in patients with DN	- ↓Urinary albumin excretion/Urine albumin/Creatinine ratio - - ↑Antioxidant (polyphenols)/Anti-inflammatory	[227]

BP: Blood Pressure; COH: Chronic Ocular Hypertension; DBP: Diastolic Blood Pressure; DM: Diabetic Mellitus; eNOs, Endogenous Nitric Oxide Synthase; ERK: Extracellular Signal Regulated Kinases; FMD: Flow-Mediated Dilation; HF: High fat; HFD: High Fat Diet; HPVR: Hypoxic Pulmonary Vascular Remodeling; IL 1: Interleukin; LDL: Low Density Lipoprotein; IL-6: Interleukin-6; MAPK, Mitogen Activated Protein Kinase; NO: Nitric Oxide; RGC-5: Retinal Ganglion Cells; ROS: Reactive Oxygen Species; SD: Sprague-Dawley; SBP: Systolic Blood Pressure; SHR: Spontaneously Hypertensive Rats; SIRT1: Sirtuin 1; SIRT1: Silent Information Regulator 1; SOD: Sodium Oxide Dismutase; SOD: Superoxide Dismutase; TC: Total Cholesterol; TNF-α: Tumor Necrosis factor-a; VSM: Vascular Smooth Muscles; ↑: Increase; ↓: Decrease.

Table 3
Effects of resveratrol in angiogenesis.

Model	Resveratrol treatment (Conc./Time)	Finding	Proposed mechanism	Reference
Human endometrial growth/In vitro	1, 10, 50, 100 and 200 μM for 21 days	- ↓Growth and treatment of endometriosis	- Apoptotic genes (Bax, P53, caspase 3 and Bcl2) and SIRT1 - ↓NO	[228]
Human colon cancer HCT 116 and HT-29 cell lines/In vitro	1, 10 or 100 μM for 72 h	- Anti-proliferation - Anti-tumoral effect	- ↑Apoptosis in cancer cells via activation of the ERK1/2 pathway - ↓COX-2 nuclear accumulation and anti-proliferation	[229]
HUVECs/In vitro	100 μL 0.5 μM solution	- Anti-angiogenic in attenuating the VEGF-mediated responses	- ↓Proliferation of VEGF-mediated endothelial cell, cell migration and invasion and tube formation - Blocks VEGF-induced phosphorylations of Akt, Erk and eNOS	[45]
HUVECs/In vitro	10 μM for 72 h	Positive role in diabetic wound healing	- SIRT1-dependent endothelial protection - Inhibition of FOXO1 - De-repression of c-Myc expression	[209]
HUVECs/In vitro	10 mg/kg, 20 mg/kg tail vein injection for 1 to day 7	- ↓VEGF - ↓Aerobic glycolysis via modulation of PKM2 nuclear translocation	- ↓mRNA and protein level of GLUT1, HK2, PFK1, PKM2	[230]
HUVECs/In vitro	50 mg of powder at 100 mg and 2 mL of 50% methanol for 72 h	- Anti-tumor effect - ↓Microvessel density	- ↓VEGF - ↓Expressions of COX-2 and inflammatory cytokines	[231]
MBCDF cell line (primary breast cancer cell)/In vitro	2.5–20 μM for 6 days	- Anticancer effects in vitro and in vivo - Inhibition of tumor neoangiogenesis	- ↑Endothelial cell death - ↑Sub-G1 cells accumulation - ↓Tumor vessel number	[232]
HUVECs/In vitro	50 mg of powder at 100 mg and 2 mL of 50% methanol for 72 h	↓Proliferation of VEGF-mediated endothelial cell, cell migration and invasion and tube formation	- ↓Phosphorylation of VEGF-triggered VEGF receptor-2 and JNK - ↓Phosphorylation eNOS, Akt and Erk	[45]
RT-2 glioma cells in rat/In vivo	40 mg/kg/day and 100 mg/kg/day for 5 days	- ↑Cytotoxic effects and apoptosis - Antitumor effect on both	- ↓Expression of VEGF by two tyrosine kinase receptors, KDR and Flt-1 - ↓Microvessel densities	[233]
EPCs	25 μmol/L to 75 μmol/L for 2 days	↑Anti-angiogenic function	- ↓Expression of miR-542-3p - ↑ANGPT2 protein level	[234]
PCOS patients	800 mg per day for 40 days	- ↑Quality oocyte and embryorate - ↓Serum total testosterone level and LH - ↑TSH and FSH levels	↓VEGF & HIF1 genes expression in the granulosa cells of follicles	[235]

ANGPT2: Angiopoietin-2; COX: Cyclooxygenase; FOXO1: Forkhead box protein O1; eNOS: Endothelial NOS; EPCs: Endothelial progenitor cells; ERK: Extracellular-signal-regulated kinase; FSH: Follicle stimulating hormone; GLUT1: Glucose transporter-1, HIF: Hypoxia-Inducible Factor; HUVECs: Human umbilical vein endothelial cells; HK2: Hexokinase II; JNK: c-Jun N-terminal kinase; KDR: kinase domain region; Flt-1: Fms-like tyrosine kinase 1, LH: Luteinizing hormone; PFK1: Phosphofructokinase-1, PKM2: Pyruvate kinase M2; TSH: Thyroid stimulating hormone; VEGF: Vascular Endothelial Growth Factor.

antihypertensive role of RSV, evidence on its direct impact on both blood pressure and endothelial function in animals with estrogen deficiency alone is still scarce.

8. Pharmacological effects and molecular targets of resveratrol in endothelial dysfunction

Endothelial integrity is essential for vascular homeostasis. Endothelial cells are a semi-permeable layer that monitor fluid movement,

leukocyte/platelet adhesion, electrolytes/macromolecules, coagulation, angiogenesis and hemostasis factors, and LDL transcytosis.

8.1. Anti-oxidant effects of resveratrol

The deleterious effect of prolonged endothelial exposure to elevated glucose on increased vascular permeability has been well established; it alters endothelium-dependent relaxation (EDR) by inducing ROS formation or dysfunction of voltage-gated K+ channels in vascular SMCs [90,91]. Acute high glucose (AHG) could inhibit acetylcholine (ACh)--mediated EDR in isolated aortic rings of both rabbits and rats through production of free radicals [92]. RSV interaction with multiple molecular targets exerts antioxidant and anti-inflammatory downstream effects [93]. Its cardioprotective effect is of much interest explaining the focus on chronic trans-Resveratrol (t-RSV) exposure, which is commonly applied to the intake, and mitigate such levels of stress [94]. Guzman et al., introduced RSV as a protective agent against AHG-induced degradation of EDR. They proposed that under pharmaceutical situations,100 μM t-RSV can resemble the optimal reaction of t-RSV as a defensive agent due to similarity of the dose-response curves to ACh in the presence of 10 and 100 μM tRSV [95]. Since NO mediates vasodilatation induced by ACh, it is speculated that t-RSV may exert its function by preventing NO degradation. Latest studies in rats indicated that intravenous t-RSV functions as a strong renal vasodilator which increases NO production/bioavailability and superoxide scavenging [96]. Consequently, similar to quercetin, RSV can increase NO bioavailability by direct ROS scavenging via Akt/ eNOS signaling, which results in NO production or cellular-enzymatic antioxidant defense [97,98]. In addition, RSV has been suggested as a direct antioxidant with stilbene skeleton in its hydroxyl group [99].

8.2. Resveratrol enhances endothelial NO production

Preeclampsia is a condition characterized by a pregnancy-induced hypertension, caused by reduced bioavailability of NO due to oxidative stress and subsequent endothelial dysfunction [100,101,102]. However, there is no strong evidence to validate that antioxidants may decrease the risk of developing preeclampsia [103]. In one study, RSV was found to be efficient as an adjunct to oral nifedipine in the management of preeclampsia, whereas other research indicated that RSV may aggravate trophoblast and endothelial dysfunction in human cells [104]. Moreover, RSV targets multiple antioxidant molecules by physical activity or potential impact, including Nrf2 and eNOS [105]. Nrf2 binds to the promoter sequence of antioxidant response element (ARE) and controls the production of antioxidant proteins such as glutathione reductase (GSR) and heme oxygenase-1 (HO-1) [105,106]. Hyperglycemia also induces ROS formation that decreases NO bioavailability contributing to endothelial dysfunction. It has been suggested that RSV could even protect NO from degradation [107]. Latest studies have indicated that intravenous RSV functions as a strong renal vasodilator by enhancing NO bioavailability/production and superoxide scavenging in animal models [108]. Similar to quercetin, RSV can increase NO bioavailability by direct ROS scavenging via Akt/eNOS signaling, which results in NO production or cellular-enzymatic antioxidant defense [109,110]. In addition, RSV has been proposed as a direct antioxidant [111,112]. Pektas et al., showed that acute exposure of aortic segments to high-glucose decreased endothelial relaxation and downregulated gene expression in the pathway of insulin signaling [113]. Thus, the effect of RSV on eNOS was observed at enzymatic level and protein/gene expression. RSV co-incubation facilitated acetylcholine-mediated relaxation in aortic rings exposed to high glucose, reversed p-Akt/Akt ratio and inhibited Akt mRNA and p-eNOS/total eNOS mRNA [113]. RSV also considerably elevated IRS-1, PI3K, FOXO3a and mTOR mRNA levels [113]. The ubiquitin-proteasome system plays an essential role in protein degradation by eliminating misfolded, damaged or oxidized peptides. It also maintains cell growth, division and differentiation, and regulates stress response and signal transduction [114,115]. Li et al. showed that RSV increased NO release and improved endothelial function in vivo, via PTEN-dependent Akt activation. It improved PTEN protein degradation in human umbilical vein endothelial cells (HUVECs) through stimulation of the 26S proteasome [116,117]. While RSV significantly elevates 26 S proteasome activity, MG132, a proteasome inhibitor, blocks its action. Such results support the main role of the PTEN-Akt-eNOS-NO proteasome pathway in defensive effects of RSV during hyperglycemia [116]. Moreover, RSV has been known to generate cellular effects by controlling the activity of AMPK which in turn induces vasodilation in aortic arteries [118]. Notably, RSV therapy does not alter blood glucose indicating that the positive effects of RSV are independent of reducing blood glucose [119] (Fig. 2).

8.3. Resveratrol reduces oxidative stress in endothelial cells

One of the main contributors to endothelial damage is oxidative stress caused by highly reactive molecules such as superoxide radical ion (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH) [120,121]. RSV directly and indirectly acts as an antioxidant due to the existence of phenolic rings characterized by three hydroxyl groups at positions 3, 4 and 5, conjugated double bonds and also the capacity for electron delocalization [122]. NADPH oxidase pathway generates ROS and RSV down-regulates NADPH oxidase 1 (NOX1), NOX2, NOX4, p22phox, and p47phox expression, and also modulates NADPH oxidase complex activity. Advancing age is related to impaired mitochondrial biogenesis which induces ROS formation and further vascular disruption [123, 124]. Experiments on cultured human coronary artery endothelial cells (HCAECs) in the presence of RSV indicated higher DNA content, upregulation of proteins involved in electron transport chain, and enhanced mitochondrial biogenesis [125,126]. RSV also decreased the oxidative response in endothelial progenitor cells (EPCs) and prevented their apoptosis through PPAR-γ/HO-1 pathways [127]. H_2O_2 is considered the most powerful form of ROS and disrupts intracellular signaling cascades. RSV provides protection against H_2O_2-induced oxidative stress through activating SIRT1-dependent autophagy pathway by regulating LC3-II, Beclin-1 and p62 in endothelial cells [128]. Sirtuins are a protein group with a significant level of evolutionary conservation. SIRT1, the most studied sirtuin, plays a critical role in the prevention and progression of numerous disorders [129]. Deacetylation of transcription factors such as p53, FoxO family members, NF-kB, and PGC-1α affects the cell's life cycle and its energy metabolism [130]. RSV is an activation of SIRT1, that is a NAD+-dependent deacetylase via several bioactive roles [131]. SIRT1 activation can protect cells against ROS-induced damage by deacetylating a number of transcriptional factors that control the numerous genes expression, such as SOD2 [132]. SIRT1 enzyme function could be regulated by redox-dependent posttranslational changes and providing potential molecular explanation for how RSV, that can affect cellular redox status, might indirectly trigger SIRT1 [133, 134]. AMPK is known to be activated by RSV and other polyphenols, possibly through inhibiting mitochondrial ATP generation [135]. AMPK signaling induces a rise in cellular NAD levels, that could indirectly stimulate SIRT1, which utilizes NAD as a substrate [136]. The finding that AMPK-deficient animals are resistant to RSV's positive metabolic impacts lend support to this theory [137]. AMPK is also necessary for the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) deacetylation, a mitochondria-biogenesis key regulator, in mice given RSV [138]. Because the signaling pathways of SIRT1 and AMPK are partially overlapping or interwoven, AMPK activation possibly explain several of the benefits seen following RSV therapy. AMPK pharmacological suppression showed no effect on RSV's SIRT1-dependent activation of the transcription factor KLF2 in endothelial cells [138]. Given that RSV interacts with a diverse variety of intracellular targets, identifying 'the principal target or the mechanism of action of RSV could be challenging [138].

Furthermore, activation of SIRT1 by RSV protects mice from obesity

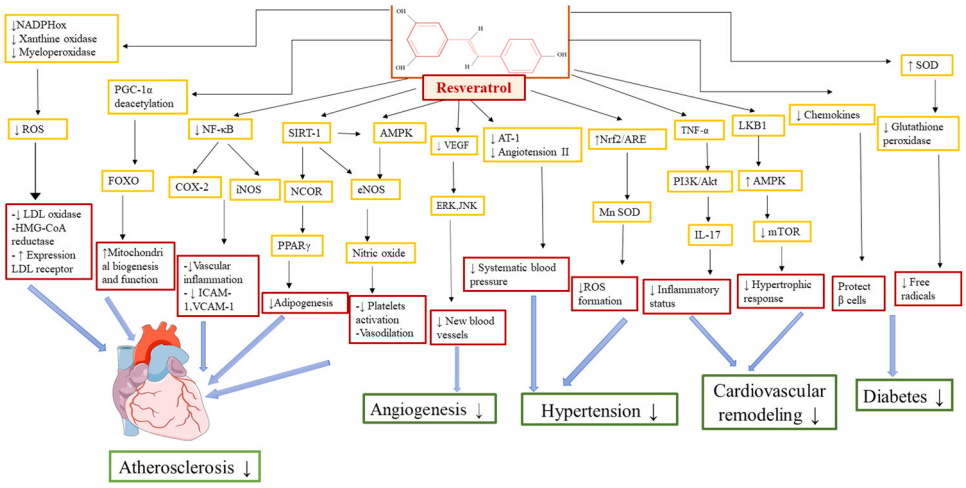

Fig. 2. Molecular targets of resveratrol in protecting against endothelial dysfunction. Resveratrol exerts its endothelial protective effects by modulating multiple targets in the vasculature, explaining its therapeutic potential in multiple diseases involving endothelial dysfunction, such as atherosclerosis, hypertension, diabetes and cardiac remodeling etc.

and insulin disturbances caused by high-fat diets [138,139]. The reported activation results in a decrease in PGC-1/acetylation and a rise in the same protein's function [140]. Incubation with RSV enhanced SIRT1 expression and activity by up to 50% in cultured HACECs [141]. SIRT1 stimulation plays an essential role for NO generation and also mediating various anti-inflammatory, anti-apoptotic, and anti-senescent actions of RSV [114,141].

SIRT1, also known as NAD^+-dependent deacetylase, plays an effective role in dealing with oxidative stress during aging. Studies have shown that increased SIRT1 expression helps to protect against cardiovascular disorders [142]. During activation of SIRT1 signaling pathway by RSV, P-selectin, PSGL-1, and Von Willebrand factor (vWF) were downregulated [75]. P-selectin and vWF are located inside Weibel-Palade bodies of endothelial cells and modulate inflammation and hemostasis. vWF is a glycoprotein involved in blood coagulation [143]. RSV also controls the autophagy mechanism and exerts antioxidant effects on HUVEC by upregulating the expression of transcription factor EB (TFEB) which in turn reduces ROS formation [77]. It induces the expression of HO-1 (encodes for heme oxygenase 1, also known as HMOX-1) and SOD2 (encodes for superoxide dismutase 2) genes, which have vital role in regulating ROS production in cells. Oxidized LDL (Ox-LDL) is the main culprit of vascular endothelial injury. In a study by Chen et al., it was found that RSV inhibits Ox-LDL-mediated mitochondrial dysfunction by enhancing the expression of Bnip3-related mitophagy in endothelial cells. AMP-activated protein kinas (AMPK) is an enzyme with anti-inflammatory and angiogenic properties [144]. In response to RSV, it is phosphorylated at tyrosine 172 and becomes activated. RSV increases the Bnip3-Related Mitophagy by upregulation of hypoxia-inducible factor 1 (HIF1) and AMPK. It can also modify placental endothelial oxidative stress by reducing sFlt1 and activin [145]. A study on preeclampsia by Natalie J. Hanna et al., showed that RSV suppressed sFlt-1 and soluble endoglin proteins which increase oxidative stress in endothelial cells [146].

8.4. *Anti-inflammatory mechanism of resveratrol*

Endothelium is a monolayer barrier with selective permeability, however, under the influence of external factors (i.e. chemical, physical, infectious) or hormones, the endothelium secretes vasoactive substances setting the stage for development of inflammation [147–149]. Endothelial cells acquire two types of active phenotypes during an inflammatory process. Type 1 is a transient but rapid response during which Weibel-Palade bodies and P-selectin are released and intercellular junctions are lost contributing to the endothelial interaction with leukocytes and platelets. Type 2 activation is a steady response which promotes the expression of inflammatory cytokines (e.g. interleukin-1 and TNF-α) and adhesion molecules [150]. Following activation of endothelial cells, there is an increase in permeability of endothelium to proteins, production of pro-inflammatory cytokines, and upregulation of adhesion molecules [151]. The NF-κB pathway also plays a very crucial role in this process. Similarly, lysophosphatidylcholine (LPC) is thought to be associated with coronary artery inflammation by increasing inflammatory cytokines (e.g. IL-8, IL-6 and TNF-α) [152]. RSV exhibits anti-inflammatory properties by inhibition of LPC through TLR - 4/MyD88/NF - κB signaling pathways [153,154]. RSV could decrease TNF-α by increasing the expression of KLF2 on both endothelial and endothelial progenitor cells [155]. It was also shown to reduce the expression and secretion of inflammatory factors such as IL-6, IL-1β and TNFα in the trophoblasts and HUVECs [156]. Several reports indicated that RSV can decrease TNF-α-activated production of MCP-1 through suppression of NF-κB transcription in adipocytes [155,157]. They suggested that RSV blocks the production of TNF-α-activated ICAM-1 and VCAM-1 in the endothelial cells [158]. Moreover, numerous studies have demonstrated that KLF2 can prevent inflammation through repression of various adhesion molecules including VCAM-1, E selectin and MCP-1 [159,160]. Consequently, Chu et al., reported that by inducing the expression of KLF2, RSV could downregulate the expression of ICAM-1 and MCP-1 in response to pro-inflammatory stimulation [161]. KLF2 is found to be involved in the prevention of atherosclerosis via anti-inflammatory activities and modulating eNOS expression [161]. Chen et al., identified that RSV alleviates LPC-induced inflammation and endothelial cell injury. These findings suggested that the effects of LPC on enzyme function, pro-inflammatory cytokine secretion, and expression of TLR-4, NF-kB p65 subunit and MyD88 was strongly decreased by RSV [162]. Also, transfection with TLR-4 shRNA inhibited LPC-induced injuries and inflammation by preventing TLR-4/MyD88/NF-1B signaling; alternatively transfection with TLR-4 cDNA increased LPC-induced injuries and inflammation and counteracted the defensive effects of RSV [162]. Gurusinghe et al., RSV substantially reduced placental oxidative stress and soluble fms-like tyrosine kinase-1 (sFlt1) and activin A production. It greatly mitigated endothelial activity of VCAM-1, ICAM-1, E-selectin and endothelin-1 induced by TNF-α and reduced endothelial permeability. Knockdown of Nrf2 eliminated some of the protective effects of RSV on endothelial cells, but not on crucial trophoblast cells [163].

8.5. Resveratrol mediated protective effects against endothelial apoptosis

Apoptosis is a programmed cell death that occurs under the influence of internal or external insults; it is essential for maintaining homeostasis. Dysregulated endothelial cell apoptosis is the main contributor to the pathogenesis of many diseases such as atherosclerosis (AS), allograft vasculopathy, congestive heart failure, diabetic retinopathy, emphysema, scleroderma, sickle cell disease (SCD), systemic lupus erythematosus and thrombotic thrombocytopenic purpura. Anti-apoptotic factors include cell– matrix interactions, growth and angiogenic factors, nuclear factor kappa B (NF-kB) and shear stress, whereas pro-apoptotic stimuli are death receptors, Toll-like receptors, ox-LDL, homocysteine, hypoxia and hyperoxia. RSV acts as an endothelial anti-apoptotic agent through different mechanisms. It prevented hyperglycemia-mediated endothelial injury by activating E2F3 pathway [164]. Similarly, upregulation of VEGF-B through an Akt-dependent pathway by RSV inhibited apoptosis in endothelial cells during hyperglycemia [165]. RSV can attenuate apoptosis in high glucose-treated endothelial cells by regulating SOCE-related proteins and NOTCH signaling. Li et al., found that RSV inhibited ROS-induced cell death by stimulating AMPK/Sirt1/PGC-1 α pathway in high-glucose treated retinal capillary endothelial cells. Hence, increased glucose concentration was associated with reduced AMP activated protein kinase (p-AMPK) and elevated Sirt1 and PGC-1 α levels [119,166]. It is shown that RSV can prevent ox-LDL-induced endothelial apoptosis by increasing Bcl-2 expression. Similarly, Liu et al., indicated RSV preventive effects on endothelial cell apoptosis caused ox-LDL by inhibiting mitochondria-derived oxidative stress [167].

8.6. Resveratrol prevents endothelial permeability and gatekeeps barrier integrity

Endothelial cells act as a major selective barrier between the circulating blood and surrounding tissues that only allow small molecules to cross based on their concentration gradient [166]. Dysfunction of this barrier due to LDL, growth factors, and inflammatory cytokines results in abnormal deposition of macromolecules and inflammatory cells in the intima which is a primary initiating event in atherosclerosis [168]. RSV has shown to promote endothelial function by reducing the effect of TNF on endothelial permeability through regulation of Nrf2 which is a transcription factor that enhances the expression of proteins with antioxidant properties [169]. A study by Aly Shamseddin et al., showed that RSV-lipid conjugates could inhibit the activation of MMP-9 activated by inflammatory cytokines. MMP-9 and to a lesser extent MMP-2 are two known enzymes that impair endothelial integrity [170].

8.7. Resveratrol mediated protective effects against endothelial mesenchymal transition (EndMT)

EndMT is a mechanism in which endothelial cells (EC) acquire mesenchymal cell properties while losing their EC features [171]. EndMT is similar to epithelial to mesenchymal transition (EMT). EndMT is most typically seen in the cardiovascular tissue intima. Endothelial-specific markers like vascular endothelial (VE)-cadherin and CD31 are downregulated during this transition, whereas fibroblast-specific protein 1 (FSP1), mesenchymal-specific markers like -SMA, and vimentin are upregulated [172]. EndMT is thought to play a role in the pathophysiology of a variety of diseases, including atherosclerosis, systemic sclerosis, cardiac fibrosis, myocardial infarction, pulmonary hypertension, cancer, and other fibrotic conditions [173]. As a result, EndMT regulation could be a possible treatment method for cardiac fibrosis. According to the literature, RSV suppresses EndMT via antagonizing the hedgehog signaling pathway in renal tubular cells. Similarly, Gao et al. reported that RSV inhibits the hedgehog pathway and EMT in cancer cells in vitro by preventing metastasis and invasion [174]. In addition, RSV inhibits EMT-inducing transcription factors (such as Zeb-1, Slug, and Snail) to prevent pancreatic cancer cells from migrating and invading. RSV suppress EGF-induced EMT via repressing EGF-stimulated ERK [175]. Moreover, renal damage is linked to the formation of renal fibrosis, with EMT playing an important role [176]. Similar as its effect on EMT, recent data have shown that RSV can ameliorate EndMT via in human retinal endothelial cells exposed to high glucose by reducing rrotein kinase C and ROS production [177]. Another study has shown that RSV can ameliorate advanced glycation end products- (AGEs-) induced EndMT in HUVECs via SIRT1 mediated suppression of TGF-β pathway [178]. Both lines of evidence provide the therapeutic basis for a resveratrol as an effective pharmacotherapy of vascular complications of diabetes. In addition, pharmacological activation of SIRT1 by RSV or SRT2104 attenuates EndMT and cardiac fibrosis via suppressing the TGF-β/Smad2/3 pathway [179].

8.8. Resveratrol prevents leukocyte adhesion to activated endothelium

The first step in inflammation is leukocyte adhesion mediated by specific glycoproteins including selectins, integrins and ICAMs,which play a pivotal role in leukocyte-endothelium interaction and induce the expression of inflammatory chemokines such as MCP-1 and CXCL8 [180]. RSV can suppress TNFα-induced expression of adhesive molecules such as ICAM-1, VCAM-1, and E-selectin that ultimately reduces inflammation [169]. A study on artery bypass graft showed that RSV could protect endothelial cell dysfunction by downregulating the expression of ICAM-1 [181]. Other than anti-inflammatory properties, RSV is found to have anti-microbial effects by reducing the infectivity of Staphylococcus aureus through downregulating the expression of VCAM-1 [182]. Preeclampsia is a condition in which anti-angiogenic molecules such as sFlt-1 and soluble endoglin (sEng)−1 are adversely increased and set the stage for endothelial dysfunction. Hannan et al., showed that RSV attenuated the secretion of these molecules and remarkably increased phosphorylation of eNOS while increased the production of VCAM-1 and adhesion of peripheral inflammatory cells. Altogether, RSV was introduced as a favorable candidate for treatment of preeclampsia. Also, Liu et al., showed that RSV improved endothelial inflammation by decreasing ICAM-1 expression through miR-221/222/AMPK/p38/NF-kB pathway. According to these findings, suppressed activation of p38 MAPK and NF-kB induced by TNF-α, blocked the expression of monocyte adhesion molecules and ICAM-1 [118].

8.9. Effects of resveratrol on vascular tone

The endothelium releases various vasoactive mediators to regulate platelet and vascular smooth muscle cell functions. Vasodilatory factors act as myorelaxants, exert cytostatic effects on smooth muscle cells and prevent platelet aggregation; these include prostacyclin (PGI2), nitric oxide (NO), endothelium-derived relaxing factor (EDRF) and hyperpolarizing factor (EDHF). Vasoconstrictive agents are thromboxane (TXA2), O^{2-} and endothelin-1 (ET-1) [183]. Upregulation of ET-1, as a potent vasoconstrictor, has been associated with development of atherosclerosis [184]. The protective effects of RSV on endothelial function and blood pressure have been previously linked with increased production of NO and decreased ET-1 synthesis, respectively [185]. RSV-treated rabbits have shown reduced levels of ET-1 synthesis in both endothelial and smooth muscle cells [186]. Zhang et al., found that RSV has an antioxidant-like inhibitory effect on smooth muscle cell proliferation and angiotensin II (AII) induced ET-1 gene expression. Similarly, RSV also suppressed extracellular signal-regulated kinase (ERK) pathway which in turn reduced cell proliferation by angiotensin II and attenuated the expression of ET-1 [187]. It is assumed that there are numerous redox-sensitive phases in AII-activated signaling pathway. RSV treatment has modified cellular redox balance through its antioxidant potential. In brief, RSV prevents AII-induced ROS production, ET-1 gene expression, ERK phosphorylation, and vascular SMC proliferation

[187,188]. In a study on H_2O_2-treated vascular SMCs, ET-1 expression was elevated. RSV blocked the activation of oxidative stress-stimulated cytosolic phospho-lipase A2 which is an indicator of ET-1 activity [189]. Notably, multiple red wine-derived compounds have significantly reduced ET-1 synthesis in bovine aortic endothelial cells due to their polyphenol constituents [190]. It is documented that RSV can reduce TXA2 by acting on COX −1 and COX-2 enzymes [191]. A study by Dutra et al. showed that RSV-furoxan compound can exhibit vasodilatory effects by enhancing NO release [192]. Another study on aged Wistar rats showed that RSV increased NO through inhibition of methylglyoxal level. Moreover, studies have demonstrated that RSV reduced endothelin receptors on endothelium via $ERK^{1/2}$/NF-κB and stir1 pathways [193]. It also has inhibitory effects and activates NO synthase in TNF-α induced endothelin-1 [156].

9. Conclusions and perspectives

Endothelial dysfunction is an important contributor to many types of disorders, including atherosclerosis, hypertension, diabetes and many others [236]. Despite inconsistencies [70,71], numerous studies have shown the cardiovascular benefits and molecular targets of RSV. RSV is a multi-target therapeutic agent that protects against endothelial dysfunction and cardiometabolic disorders due to its pleiotropic properties similar to lipid-lowering statins. Future direction of the pharmacological research of RSV is as follows: (1) Determinining whether the pharmacological effects of RSV are dependent on SIRT1 using endothelial cell-specific SIRT1-knockout mice; (2) Application of RSV as a drug candidate, which leads to developing derivatives with higher vasoprotective effects and nanoparticulate drug delivery systems to increase its oral bioavailability; (3) Determining the bioactive metabolites of RSV in vivo and assess whether microbiota modulation is involved in RSV-mediated endothelial protective effects; (4) more comprehensive randomized clinical trials with larger sample sizes are warrented to address the appropriate dose range of RSV and to assess its therapeutic effects in patients with cardiovascular diseases.

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Conflict of interest

The authors declare that they have no competing interests.

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