

## Resveratrol in cardiovascular disease: what is known from current research?

Hong Wang · Yue-Jin Yang · Hai-Yan Qian ·  
Qian Zhang · Hui Xu · Jian-Jun Li

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**Abstract** Resveratrol is a well-known antioxidant that exists in grape skin/seed, red wine, and the root of *Polygonum cuspidatum*, a traditional Chinese and Japanese medicinal material. Studies have found that resveratrol has many interesting properties, including anti-carcinogenic properties, anti-microbial and antiviral effects, the ability to reverse dyslipidemia and obesity, the ability to attenuate hyperglycemia and hyperinsulinemia, and the ability to protect endothelial function. Heart failure is the final consequence of the majority of cardiovascular diseases, and resveratrol has been shown to directly attenuate heart contraction. The cardiovascular protective capacities of resveratrol are associated with multiple molecular targets and may lead to the development of novel therapeutic strategies for atherosclerosis, ischemia/reperfusion, metabolic syndrome, and heart failure. This article will mainly review recently published basic researches about the protective cardiovascular effects of resveratrol because these results may lead to the development of new clinical therapeutics in patients.

**Keywords** Resveratrol · Antioxidant · Cardiovascular disease · Sirtuin type 1 · Adenosine monophosphate-activated protein kinase

### Introduction

Cardiovascular disease is one of the leading causes of death throughout the world. A common feature of cardiovascular risk factors, including hypertension, obesity, dyslipidemia, insulin resistance, and glucose intolerance, is the increase in oxidative stress [1, 2]. Many studies show that antioxidants such as tempol and apocynin significantly prevent organ damage induced by a variety of factors, including cuff injury, hypoxia, ischemia/reperfusion (I/R) injury, angiotensin II/high salt loading, and metabolic disorder [3–8]. However, the toxicity of tempol and apocynin limits their application in humans. Numerous clinical trials have evaluated the effects of vitamin C and vitamin E, effective antioxidants in animal experiments, on the prevention of coronary heart disease and stroke, but most of which have reached disappointing conclusions [2, 9]. Typically, HOPE and GISSI studies with antioxidative vitamin E supplement failed to improve the outcomes of cardiovascular disease patients [10–12]. The use of angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, calcium channel blockers, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and peroxisome-proliferator-activated receptor (PPAR)- $\gamma$  agonists has been reported to decrease oxidative stress in many clinical treatments [13–18], but there is not a specific, effective, and safe antioxidant that is currently used for the treatment of patients with cardiovascular disease.

On the other hand, it seems that a drug targeting multiple points may exhibit better therapeutic efficacy than that blocking or activating one target in complex conditions [19]. A possible reason is that common disorders such as cardiovascular diseases tend to result from multiple molecular abnormalities. One drug to one target and taking various tablets will cause higher cost, more interactions

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H. Wang · Y.-J. Yang (✉) · H.-Y. Qian (✉) · Q. Zhang ·  
H. Xu · J.-J. Li

Centre for Coronary Heart Disease, Department of Cardiology,  
Fuwai Hospital and Cardiovascular Institute, Chinese Academy  
of Medical Sciences and Peking Union Medical College,  
167 BeiLiShi Rd, 100037 Xicheng District, Beijing,  
People's Republic of China  
e-mail: yangyjfw@yahoo.com.cn

H.-Y. Qian  
e-mail: ahqhy712@yahoo.com.cn

between drugs and lower compliance. Resveratrol (3,5,4'-trihydroxystilbene), one of the main polyphenol extracts in grape skin/seed, red wine, and the root of *Polygonum cuspidatum*, is found to have protective potentials to multi-targets related to cardiovascular diseases [20, 21]. Especially, resveratrol is best known for its antioxidant properties in vivo, and several protective intracellular pathways of resveratrol are associated with oxidative stress.

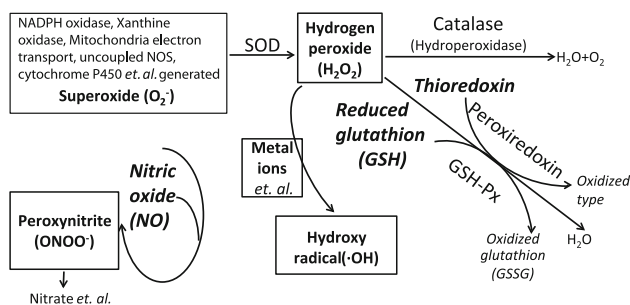
### Antioxidant properties of resveratrol

Resveratrol acts as a radical-scavenging antioxidant via the following reaction:  $\text{Res}-(\text{OH})_3 + \text{R}\cdot \rightarrow \text{Res}-(\text{OH})_2\text{O}\cdot + \text{RH}$ , in which  $\text{Res}-(\text{OH})_3$  represents resveratrol and  $\text{R}\cdot$  represents free radical [22]. The unpaired electron of  $\text{Res}-(\text{OH})_2\text{O}\cdot$  is expected to be delocalized over aromatic rings of resveratrol, resulting in poor reactivity or nocuity [22]. However, the direct antioxidant effects of resveratrol are weak. The protective effects of resveratrol against oxidative injury both in vivo and in vitro are likely to be attributed to the upregulation of endogenous cellular antioxidant systems rather than the direct scavenging activity of reactive oxygen species (ROS) [23].

The free radical reactions are shown in Fig. 1. Resveratrol has been shown to inhibit oxygen free radical formation by suppressing pro-oxidative genes (such as nicotinamide adenine dinucleotide phosphate oxidase and myeloperoxidase) [20, 23–25] and inducing antioxidative

enzymes or substrates of these enzymes including superoxide dismutase (SOD), catalase, thioredoxin, and glutathione peroxidase (GSH-Px) [23, 26–28]. Superoxide dismutase and GSH-Px are the major enzymes responsible for the inactivation of  $\text{O}_2^-$  and hydrogen peroxide, respectively, and they can restore the activity of other endogenous antioxidants. The major SOD regulated by resveratrol is manganese SOD. Manganese SOD locates mainly in mitochondria and counteracts ROS production from mitochondrial electron transport chain [27]. Studies have reported that resveratrol chelates transition metallic copper, which is able to generate free radicals and cause lipid peroxidation [29, 30]. Moreover, heme oxygenase-1 (HO-1) is a stress-response protein, which may play an important role in mediating protection against oxidative injury, and resveratrol can upregulate HO-1 [26, 28].

Resveratrol has been shown to enhance the expression of endothelial nitric oxide synthase (eNOS), modulate the deacetylation of eNOS, and increase plasma nitric oxide (NO) levels [31–34]. Nitric oxide [also catalyzed by inducible NO synthase (iNOS); see preconditioning] behaves as a potent antioxidant, which reacts with  $\text{O}_2^-$  and generates peroxynitrate radicals ( $\text{ONOO}^-$ ) in vivo [35, 36]. In physiological systems such as the heart where adequate amounts of thiol and ascorbate are present, the  $\text{ONOO}^-$  preferentially react with the  $-\text{SH}$  groups of thiol and ascorbate, thus losing nocuity [35]. Most importantly, the affinity of NO for  $\text{O}_2^-$  is far greater than the affinity of SOD for  $\text{O}_2^-$ , thus the resveratrol/NO pathway plays an important role in  $\text{O}_2^-$  elimination [35].



**Fig. 1** Main endogenous oxygen radical reactions. Oxidases convert oxygen to superoxide, which is then converted to hydrogen peroxide by SOD [1]. Hydrogen peroxide can either be converted to  $\text{H}_2\text{O}$  by catalase, peroxidoredoxin or GSH-Px, or to a hydroxyl radical after reacting with metal ions. The substrate of GSH-Px and the substrate of peroxidoredoxin are reduced glutathione and thioredoxin, which are endogenous antioxidants that play a central role in the antioxidant system of most aerobic cells. Resveratrol is also the direct scavenger of hydroxyl radical and superoxide. In addition, superoxide reacts rapidly with nitric oxide to form peroxynitrite. Peroxynitrite either is oxidized to the inactive nitrate or reacts with the  $-\text{SH}$  group of thiol and ascorbate [35, 36]. *NADPH* nicotinamide adenine dinucleotide phosphate, *SOD* superoxide dismutase, *GSH-Px* glutathione peroxidase

### Anti-inflammation and anti-coagulation activities

#### Resveratrol and inflammation

Atherosclerosis is now considered as an inflammatory disease. Inflammatory processes occur during atherogenesis, and the major events in the inflammatory process include the activated inflammatory cells with subsequent enhanced infiltration, the amplified release of chemoattractants/inflammatory cytokines, and the increased leukocyte–endothelial cell interactions. These processes can lead to a weakening of the fibrous cap that overlies the lipid core of plaque and promote the susceptibility of plaque to rupture and subsequent thrombosis. Reactive oxygen species play an important role in the development of inflammation and lead to development in metabolic dyslipidemia, impaired glucose metabolism and hypertension [37]. On the other hand, the upregulation of proinflammatory adipokines is observed to promote oxidative stress in obesity and inflammation situation. The interplay of oxidative

stress, inflammation, obesity, insulin resistance, and hypertension ultimately increases atherogenic risk [37, 38].

Another characteristic of resveratrol is anti-inflammation. Resveratrol not only modulates biochemical responses of polymorphonuclear leukocytes by interfering with the release of inflammatory mediators (e.g., platelet endothelial cell adhesion molecule-1) [24, 39], but also suppresses the activity of T cells, B cells, and macrophages, which was shown by significant inhibition of their proliferation, antibody production, and lymphokine secretion [40].

Resveratrol has also been shown to mediate anti-inflammatory processes by inhibiting cyclooxygenase (COX), which catalyzes the conversion of arachidonic acid into prostanoids and thromboxane A<sub>2</sub> (TxA<sub>2</sub>). There are two distinct membrane-anchored isoenzymes of COX: COX-1 and COX-2. Resveratrol may act similarly to aspirin, which is an effective cardioprotective agent that targets platelet-specific COX-1; however, the inhibitory efficacy of resveratrol on COX-1 may be weaker than that of other polyphenols in red wine [39, 41, 42]. Cyclooxygenase-2 is induced by proinflammatory mediators during inflammation. Resveratrol suppresses the expression and activity of COX-2 and the downstream signals like prostaglandin [43–45]. Proinflammatory mediator, particularly interleukin-1 $\beta$ , stimulates the production of leukotriene B<sub>4</sub> (LTB<sub>4</sub>), which is a risk factor of atherosclerosis and produced through the lipoxidase pathway of arachidonic acid metabolism. Resveratrol has been shown to decrease LTB<sub>4</sub>. At the same time, resveratrol reduces the production of matrix metalloproteinases (MMPs) [45]. Matrix metalloproteinases not only accelerate formation and progression of plaque, but also facilitate to weaken fibrous cap. Therefore, resveratrol is a hopeful medication for plaque stabilization.

Resveratrol has also been shown to elevate proteoglycan synthesis and may be involved in the prevention and treatment of autoimmune inflammation [45]. Moreover, resveratrol inhibits nuclear factor- $\kappa$ B (NF- $\kappa$ B) and modulates the plasma concentration of NF- $\kappa$ B-related inflammatory and autoimmune markers in the subjects with increased risks of cardiovascular disease [46–48].

#### Resveratrol and platelet

As described above, resveratrol inhibits TxA<sub>2</sub> formation via blocking COX [39, 49]. In addition, resveratrol prevents platelet activation through reducing intracellular calcium concentration ( $[Ca^{2+}]_i$ ) of platelet, which plays a key role in platelet aggregation. The mechanisms are involved in the inhibition of the p38 mitogen-activated protein kinase–cytosolic phospholipase A<sub>2</sub>–arachidonic acid–TxA<sub>2</sub>– $[Ca^{2+}]_i$  cascade and activation of NO/cyclic GMP, thus resulting in the inhibition of phospholipase C/protein kinase C and decrease in  $[Ca^{2+}]_i$  level [49, 50].

Resveratrol has also been shown to induce platelet apoptosis. Resveratrol stimulates mitochondrial membrane potential dissipation, caspase-9, caspase-3, and caspase-8 activation, human BH3 interacting domain death agonist cleavage, cytochrome C release, and phosphatidylserine exposure in washed human platelets, which promote platelet destruction and prevent pathological clotting [51].

There has been report that resveratrol prevents cigarette-smoking-induced eNOS acetylation and endothelial dysfunction via sirtuin type 1 (SIRT1), which is one of seven mammalian homologs of silent information regulator 2 (Sir2, sirtuin family of proteins in yeast), and catalyzes nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent protein deacetylation [34, 52]. Sirtuin type 1 is highly expressed in vascular endothelial cells. The normalization of injured endothelium will improve vascular tone, blood flow, cell adhesion, and leukocyte–endothelial cell interactions [31, 32, 53–56], which are very important contributors to platelet aggregation [57].

#### Anti-aging characteristics

Aging is a risk factor of cardiovascular diseases. To slower the speed of aging and prevent the occurrence of age-associated chronic diseases is a key issue in modern society. Resveratrol can activate anti-aging genes and facilitate extending lifespan in lower organisms like yeasts and worms [20, 58]. Resveratrol also increase survival of the high-calorie-diet-fed mice. However, adding resveratrol to mice fed with a normal diet did not affect the overall survival or maximum lifespan, suggesting that resveratrol might be counteracting the negative consequences of obesity and insulin resistance, thus slowing aging [58, 59]. The positive effects of resveratrol on several age-related disorders are mediated by sirtuins [21, 52, 59]. Sirtuin proteins are essential for NF- $\kappa$ B, p53, eNOS, and peroxisome-proliferator-activated receptor co-activator (PGC-1 $\alpha$ ) deacetylation [60–62], which shortens NF- $\kappa$ B response and inhibits p53 activity. A part of the response caused by resveratrol may be related to the suppression of p53, which is expressed in response to various types of stress involving DNA damage and leads to cell apoptosis. A delay in apoptosis gives the cells additional time to repair damage and prevent unnecessary cell death [60, 61]. On the other hand, the anti-proliferative effect of resveratrol on cancer cells has been extensively documented and supported by the downregulation of cell cycle proteins and an induction of apoptosis in tumorigenic cells [63].

Resveratrol activates SIRT1 and PGC-1 $\alpha$  and contributes to mitochondrial function [59, 64], which can influence whole body metabolism. Resveratrol has also been shown to activate adenosine monophosphate-activated

protein kinase (AMPK) and the phosphorylation of its downstream indicator, acetyl-CoA carboxylase. AMPK activation can downregulate fatty acid synthase and prevent organ (liver, pancreas, heart, and aorta) damage in mice fed with high-calorie diets [59]. The changes in SIRT1, AMPK, and PGC-1 $\alpha$  were similar to changes observed in cellular starvation, which plays an important role in the induction of a number of genes involved in anti-oxidation and cell survival.

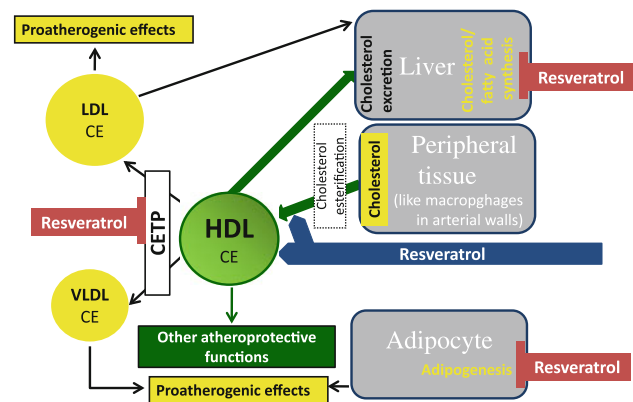
### Roles on lipid metabolism

Besides inhibiting the synthesis of fatty acid, resveratrol prevents the proliferation and differentiation of preadipocytes, promotes fat mobilization in white adipocytes, triggers lipolysis/loss of fat in differentiated fat cells, and protects mice against diet-induced-obesity by activating SIRT1 [52, 65, 66].

Resveratrol can also cause SIRT1-independent TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)-mediated apoptosis in fat cells [67]. In vivo studies indicate that resveratrol lowers serum triglyceride, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) cholesterol [68]. These effects, along with the reduction in LDL oxidation [69], the prevention of smooth muscle cells (SMCs) proliferation (this will be discussed in the following section) [70], the inhibition of inflammatory pathways in macrophages, and the promotion of endothelial function, contribute to the anti-atherosclerotic effect of resveratrol.

In addition, a recent study demonstrated that resveratrol exerted statin-like effects by downregulating HMG-CoA reductase in a hyperlipidemia model and increased the ratio of apolipoprotein (Apo) A1 to Apo B, which is negatively related to metabolic syndrome and cardiovascular risks [71]. High-density lipoprotein (HDL) is a continuously inverse cardiovascular risk factor and the major mechanism by which HDL protects against atherosclerosis is due to reverse cholesterol transport (RCT). Reverse cholesterol transport is the process through which excess cellular cholesterol is exported from peripheral tissues and returned to the liver for excretion in the bile. Cholesteryl ester transfer protein (CETP) is a crucial enzyme of RCT. Raised CETP activity induces high LDL level, thus contributing to atherosclerosis [72, 73]. Decreased CETP activity, elevated HDL level, and a promotion in the capacity of HDL to mediate cholesterol efflux have been observed with resveratrol treatment recently [29, 71, 73, 74]. These suggest that resveratrol can reduce the transfer of cholesteryl esters from HDL to VLDL/LDL and enhance RCT (Fig. 2).

Peroxisome-proliferator-activated receptors are able to provide protection against cardiovascular diseases by



**Fig. 2** Resveratrol and cholesterol metabolism. Resveratrol reduces cholesterol synthesis by downregulating HMG-CoA reductase. Resveratrol also enhances reverse cholesterol transport/cholesterol excretion through increasing HDL levels and the capacity of HDL to mediate cholesterol efflux from macrophages in arterial walls. CETP is a plasma glycoprotein that facilitates the transfer of cholesteryl esters from the atheroprotective HDL to the proatherogenic LDL and VLDL [72] and resveratrol has been shown to inhibit the activity of CETP. Furthermore, adipocytes store cholesterol and have proatherogenic effects. Resveratrol can prevent adipogenesis and plays a role in dyslipidemia and obesity. *LDL* low-density lipoprotein, *CE* cholesteryl ester, *CETP* cholesteryl ester transfer protein, *HDL* high-density lipoprotein, *VLDL* very-low-density lipoprotein

modifying lipid metabolism and inflammation. Resveratrol has a dual effect on PPAR $\alpha$  activity in diethylmaleate (a glutathione-depleting agent)-treated RH7777 hepatoma cells [75]. After diethylmaleate administration, an increased PPAR $\alpha$  activity at earlier time points and a depressed PPAR $\alpha$  activity at later time points were observed. Resveratrol-induced SIRT1 activation may repress PPAR- $\gamma$  and suppress adipogenesis or white adipocyte differentiation [65], whereas resveratrol prevented the cholesterol accumulation caused by advanced glycosylation end products (important pathogenetic mediators of almost all diabetes complications) in macrophages via PPAR- $\gamma$  but not PPAR $\alpha$  activation [76]. The relationships between resveratrol and various PPAR isoforms are still unclear. Current reports imply the difference in tissues/cells and the time course may affect the targets of resveratrol.

### Values on glucose metabolism and insulin sensitivity

Insulin regulates glucose homeostasis by reducing hepatic glucose production and increasing glucose transport into the skeletal muscle. Insulin resistance happens in most of the type 2 diabetic patients. Insulin resistance is always accompanied with increased levels of the injury-inducible molecules, such as insulin-like growth factors (IGFs). People with higher blood glucose, impaired glucose



tolerance, and insulin resistance are susceptible to cardiovascular disorders [59].

Resveratrol is observed to improve the changes in glucose, insulin, and IGFs through AMPK, which modulates gluconeogenesis, glucose transport, and insulin sensitivity [59, 77]. Resveratrol is first identified as an activator of SIRT1 from cell-free assays, in which AMPK was not present. Recently, chronic treatments with resveratrol have suggested that SIRT1 and AMPK are related to each other. On one hand, SIRT1 may be the upstream of AMPK. This hypothesis is supported by the findings that SIRT1 gain of function increases AMPK activity, an effect which may be mediated by deacetylation/activation of the AMPK upstream kinase, serine/threonine protein kinase 11 (STK11; also known as LKB1) [78]. On the other hand, AMPK may be the upstream of SIRT1 because AMPK activation increases NAD<sup>+</sup>/NADH ratio and SIRT1 is NAD<sup>+</sup>-dependent [79]. In AMPK $\alpha$ -null mice, resveratrol failed to increase the NAD<sup>+</sup>/NADH ratio or to reduce PGC1 $\alpha$  acetylation in skeletal muscle [78].

Insulin resistance has been reported to be associated with mitochondrial dysfunction. Decrease in the expression of PGC-1 $\alpha$ , which is post-translationally modulated by AMPK (phosphorylation) [80] and by SIRT1 (deacetylation) [62], and in mitochondrial DNA content was observed in type 2 diabetic patients [64] and individuals with an increased risk of developing diabetes [79, 81]. Resveratrol may attenuate the alterations of AMPK, SIRT1, PGC-1 $\alpha$ , and mitochondrial dysfunction under insulin resistance [59].

In addition, estrogen receptor (ER) activation, which attenuates insulin resistance, impaired glucose tolerance and adipocyte hyperplasia in both male and female rodents, mediates resveratrol-stimulated glucose uptake in skeletal muscle [82–86]. The increased glucose uptake/metabolism normalizes serum glucose and the secondary hypertension or other histopathological changes in diabetes.

## Effects on endothelial protection

### Estrogenic activities

In addition to the effects on glucose metabolism and insulin sensitivity through ER, resveratrol also inhibits lipopolysaccharide-stimulated induction of iNOS in macrophages and improves endothelial function, which is similar to estradiol [34, 87]. Moreover, resveratrol enhances the interaction between ER, caveolin-1 (Cav-1), and c-Src (a tyrosine kinase), increases the phosphorylation of Cav-1, c-Src, extracellular signal-regulated kinase 1/2, and eNOS

through non-genomic effect of ER, and stimulates NO production [88]. These effects are important in vasodilation and endothelial protection.

### Effects on endothelial progenitor cells

The integrity of the endothelium is very important to keep the normal function of the blood vessel and to avoid platelet aggregation. Circulating or resident endothelial progenitor cells (EPCs), which can differentiate into endothelial cells, exert an important impact as endogenously reparative mechanism to maintain the integrity of the blood vessel. Increasing evidence suggests that post-natal neovascularization relies not exclusively on resident cells but also involves the contribution of circulating EPCs [89, 90].

Bone marrow-derived mononuclear cells (BMMCs) are one of the sources of circulating stem cells. The consumption of resveratrol is associated with a significant increase in the number of bone marrow EPCs, which enter into circulating blood after hindlimb ischemia in hypercholesterolemic Apo E knockout mice [91]. In addition, resveratrol is able to enhance the EPCs migration and capillary-like tube formation through the angiogenic Akt (a serine/threonine protein kinase)/eNOS/NO/vascular endothelial growth factor (VEGF) pathway in endothelial cells exposed to oxidized LDL [90]. Similarly, the neovascularization capacity of BMMCs from diabetic mice is improved with resveratrol, resulting in a reduction in oxidative stress and an induction of angiogenic factors [91]. Resveratrol consistently augments the activation of telomerase through the phosphatidylinositol-3 kinase/Akt signaling pathway and attenuates EPCs reduction or senescence [92]. In general, resveratrol is important to the functions of EPCs, including proliferation, adhesion, migration, and tube formation [90, 92–95].

### Effects on atherosusceptible sites of the endothelium

Atherosclerosis primarily occurs at a specific site where endothelial shear stress created by high-speed rotating blood flow contributes to the focal geometric progression of atherogenesis [96]. Resveratrol activates Kruppel-like factor (KLF) 2, KLF4, and nuclear factor erythroid 2-related factor 2 (Nrf2), which protect endothelial cells from oxidant injury and shear stress. Furthermore, Kruppel-like factors have been reported to be critical regulators of endothelial homeostasis [53–55, 97, 98]. Therefore, the targeting to KLFs or Nrf2 by resveratrol may be a promising therapeutic for an impaired endothelium at atherosusceptible sites.

## Influence on preconditioning

Preconditioning has previously been shown to attenuate I/R-induced injuries due to the reduction in oxidative stress. Resveratrol-stimulated NO is able to protect against oxidative damage produced by oxoferryl-myoglobin, which is a potent oxidant found in I/R injury [35]. Although eNOS plays a role in the effects of resveratrol, iNOS, which is usually related to tissue injury, also mediates preconditioning because resveratrol fails to precondition hearts in iNOS knockout mice [35, 99, 100]. Controversial research showed that resveratrol was efficient and promising to prevent cardiac dysfunction after I/R injury, but the beneficial effect of resveratrol was not mediated by NO [101]. Besides the different experiment conditions, SIRT1 and PPARs may be involved in the preconditioning, since SIRT1 and PPAR $\alpha$  have been shown to participate in brain protection achieved by resveratrol administration [102, 103].

In addition, autophagy is a process that cells “eat/digest” autologous macromolecules or organelles, which are damaged under starvation, I/R injury, and other kinds of stress. Autophagy may be a homeostatic mechanism or a catabolic energy source by which apoptosis is inhibited and the deleterious effects of ischemia are limited. Resveratrol treatment induces autophagy both in vivo and in vitro via mammalian target of rapamycin (mTOR) pathway [104, 105]. This helps cardiomyocytes to live and reduces the secondary impairment of cardiac function after I/R.

## Resveratrol in cardiovascular remodeling and heart failure

### To cardiac hypertrophy

Resveratrol did not lower high blood pressure directly in the spontaneously hypertensive rat, but it attenuated compliance and remodeling of small artery [106, 107]. Regression of pressure overload-induced cardiac hypertrophy and dysfunction has been reported in resveratrol-treated abdominal aortic-banded rats [108]. One of the determined anti-hypertrophic mechanisms of resveratrol is the upregulation of eNOS/NO [108].

Another anti-hypertrophic mechanism of resveratrol is via LKB1, which is an upstream signal of AMPK. Resveratrol prevents the inhibitory effect of oxidative stress on LKB1 and favors the activation of AMPK. Activation of AMPK and subsequent inactivation of mTOR/70-kDa ribosomal protein S6 kinase signaling pathway inhibit unnecessary protein synthesis and prevent remodeling in the heart [25, 109–111].

### To heart failure

In failing heart, decompensation and cardiomyocyte deficiency turned to be the predominant problem. Under such a condition, an active DNA repair process instead of an inhibited protein synthesis process was potentiated by resveratrol, which preserved the genomic stability of cardiomyocytes [108]. Activation of SIRT1 limits premature cellular senescence, prolongs the life of myocytes from failing hearts, and decreases cardiac fibrosis [27, 112, 113].

Because catecholamines re-uptake is reduced, noradrenaline concentration increases in left ventricle of objects with chronic heart failure, resulting in a reduced sensitivity of myocardium to catecholamine [114]. Resveratrol administration normalizes  $\beta$ -adrenoceptors density, restores the sensitivity of myocardium to catecholamine, reduces infarct size, and improves heart function after myocardial infarction [115]. Moreover, resveratrol can improve sympathetic neural remodeling, thus causing less ventricular arrhythmias [116]. Significant reduction in norepinephrine is detected in resveratrol-loaded rats with myocardial infarction. In the hearts of these rats, a significant reduction in nerve sprouting and sympathetic hyperinnervation are observed [116], thus contributing to less secondary effects of renin-angiotensin system, better cardiac compliance and cardiac output. After receiving resveratrol treatment, the level of atrial natriuretic factor (ANF) is also attenuated in rats with myocardial infarction [115].

Cardiac sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase 2 (SERCA2) is a direct regulator for cardiac systolic and diastolic functions through controlling sarcoplasmic reticulum Ca<sup>2+</sup> uptake [117]. Sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase 2 levels are decreased in mice with diabetic cardiomyopathy and rats with myocardial infarction, but they turned to be similar to normal control after resveratrol treatment, respectively [116, 118]. Intriguingly, overexpression of SIRT1 is sufficient to activate the SERCA2 promoter in cardiomyocytes [118], which means resveratrol may regulate SERCA2 level and subsequently improve heart function via activating SIRT1. All of these studies suggest that resveratrol not only delays the process of cardiac remodeling, but also directly improves cardiac function of failing heart.

### To cardiomyocytes regeneration

Transplantation of stem cells into injured or failing heart is a hopeful procedure for cardiomyocytes regeneration. Endogenous ROS functions as signaling molecules for myogenic differentiation [119–121]. A recent report showed that resveratrol maintained a reduced cardiac environment by overexpressing Nrf2 and redox effector

factor-1 in rats, resulting in an enhancement of the regeneration of the adult cardiac stem cells and leading to the improvement in cardiac function [122]. Cardiac stem cells pretreated with resveratrol were also showed better survival, proliferation, and differentiation toward cardiomyocyte in vivo. Transplantation of these resveratrol-modified cardiac stem cells improved cardiac function even at the end of 4 months [123].

To vascular remodeling

Resveratrol treatment can improve the morphology of the aortic elastic lamina via SIRT1 and AMPK in mice fed with a high-calorie diet [59]. Resveratrol also effectively inhibited proliferation and migration of aortic vascular SMCs by increasing ER-dependent NO production or decreasing the cross-talk between interleukin-18 and an inducer of MMPs [124, 125]. Vascular SMCs proliferation and migration, as well as excess deposition of extracellular matrix, are major factors contributing to vascular remodeling and luminal narrowing. The anti-proliferative properties of resveratrol have also been attributed to its inhibition of DNA synthesis and induction of p53 in SMCs [126, 127]. Moreover, resveratrol inhibits proliferation of cultured pulmonary arterial SMCs, which arrested the cell cycle in the S phase and prevented pulmonary hypertension [33].

### Resveratrol behaving as a hormetin

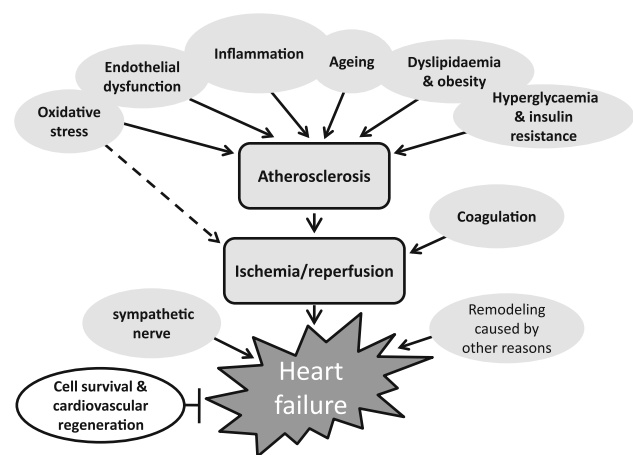
Resveratrol, termed as hormetin, can bring about biologically/physiologically beneficial effects by activating pathways of stress response. Resveratrol interrupts different stress-induced hormesis, leading to a significant improvement of the living system [128]. Resveratrol possesses both angiogenic and anti-angiogenic properties. Resveratrol can both prevent cardiac remodeling and enhance cardiac regeneration. However, it is still elusive why resveratrol could be a bidirectional modulator. Numerous researches provided another possible interpretation that resveratrol enhanced proliferation and survival of cardiomyocytes at lower dose and depressed cardiac function as well as inhibited proliferation at higher dose [25, 90, 92, 104, 111, 127, 129], like a J-curve. Higher dose of resveratrol not only inhibits endothelial cell growth and VEGF, but also hinders the synthesis of RNA, DNA, and protein, thus preventing tumor growth [63, 129–131].

### Clinical implications

Resveratrol is a food supplement for eliminating free radical and keeping healthy, but it is not into a clinical stage

yet currently. Resveratrol has a short initial half-life ( $\sim 8$ –14 min for the primary molecule) and is extensively metabolized in the body. Blocking the metabolism of resveratrol, developing analogs with improved bioavailability, or searching for new and more potent compounds that mimic its effects will become increasingly important [20]. Fortunately, research on the structure of resveratrol is ongoing [52]. Screening the effective elements of resveratrol in vivo and determining the differences between in vivo and in vitro results are challenge for researchers [20]. Moreover, the effective dose in animals cannot be extrapolated to a human equivalent dose by a simple conversion based on body weight [132].

To investigate the dose, effect, and safety of resveratrol, numerous clinical trials are on going (see ClinicalTrials.gov), and some results are being published. In one phase I study, resveratrol intake for 4 weeks by healthy volunteers caused a small but significant decrease in circulating IGF-1 and IGF-binding protein 3 compared with pre-dosing values [133]. Reduction in ROS and tumor necrosis factor- $\alpha$  as well as inflammation markers interleukin-6 and C-reactive protein is achieved in participants who received resveratrol [134]. Serious side-effects are not observed [133–136] in the known human experiments. In phase I dose escalation pharmacokinetic study in healthy volunteers, the increase in blood bilirubin and alanine aminotransferase is observed, which are potentially related to resveratrol administration [135]. In a rising multiple-dose



**Fig. 3** Multiple targets of resveratrol in cardiovascular disease. Resveratrol plays an import role in maintaining stationarity of the cardiovascular system. The risk factors colored gray make coronary atherosclerosis, myocardial ischemia, and end-stage heart failure happen. Resveratrol, by interrupting these factors and events, may be possible to prevent or slow the development of cardiovascular disease. In addition, resveratrol at lower dose prolongs cardiomyocytes survival in failing hearts, enhances angiogenesis under post-ischemic conditions, and improves cardiac stem cells homing, proliferation, and differentiation [122, 123], thus may be possible to reverse heart dysfunction

study in healthy volunteers, adverse events including frontal headache, myalgia, epididymitis, dizziness, and occipital headache are found. However, these symptoms are mild in severity and similar between groups of different doses. Repeated administration is also well tolerated [137].

Through correction of oxidative stress, inflammation, hypercoagulable state, dyslipidemia, obesity, hyperglycemia, hyperinsulinemia, I/R injury, sympathetic tone, unnecessary cell loss/proliferation, and endothelial/cardiac dysfunction, resveratrol shows a surprising potential to treat atherosclerosis and heart failure (Fig. 3). We hope that we will be able to use resveratrol to prevent and treat cardiovascular disease in the future.

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