Effect of Resveratrol on the Cardiovascular System

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RES (3,5,4-trihydroxystilbene), a natural phytoalexin found in a wide variety of plants (e.g., nuts, berries, and grapes) is produced in response to environmental stress. RES exists as two geometric isomers: cis-(Z) and trans-(E). Trans- and cis-resveratrol can be either free or bound to glucose.

resveratrol oxidative stress inflammation cardiovascular diseases heart failure

1. Introduction

RES is well-absorbed in the jejunum and ileum after oral administration; however, its bioavailability is poor. Pharmacokinetic trials with trans-resveratrol have shown very low serum levels of unmetabolized RES after oral administration, [1] but after absorption, RES undergoes rapid and extensive metabolism in the intestine and liver, which is responsible for the low plasma levels [2][3]. However, according to the literature, the conjugate metabolites (resveratrol glucuronides and sulphates) also have relevant biological activities; furthermore, RES accumulates in several tissues [4][5][6]. In 2017, Böhmdorfer et al. demonstrated that in mice, the concentration of unconjugated RES in heart tissue (3.698 ± 2.519 nmol/g) was significantly (approximately 30×) higher compared to the plasma (0.140 ± 0.012 nmol/mL) level 30 min after administration. In addition, the concentration of its conjugated metabolites (e.g., resveratrol-3-O-glucuronide; 2.155 ± 1.284 nmol/g) was also approximately 10× higher in heart tissue 30 min after administration compared to plasma levels (0.289 ± 0.102 nmol/mL) [7]. Moreover, according to Biasutto et al., although low serum RES levels were detected in numerous human studies, up to 76% of RES is not accounted for if only plasma is analyzed. If the whole blood evaluation was performed, also including the cellular fraction, the validity of the measurement would be more representative [8]. Regardless of doses, the plasma half-life of RES in humans is generally 4–8 h [9].

2. Preclinical and Clinical Studies with RES on Cardiovascular System

2.1. Atherosclerosis and Risk Factors of Cardiovascular Diseases

Atherosclerosis predominantly involves the intimal layer of the arterial vessel wall and is characterized by the deposition of lipids, the proliferation and migration of local smooth muscle cells, and chronic inflammation. It leads to luminal narrowing and/or thrombus formation, resulting in clinical events such as coronary artery disease, peripheral arterial disease, and stroke.

2.1.1. Preclinical Evidence

The cardiovascular protective effects of RES are mainly based on its capabilities of reducing oxidative stress, moderating inflammation, and favorably modifying CV risk factors.

Deng et al. found that RES can decrease vascular inflammatory injury and atherogenesis via downregulating NF-κB p65 and p38 MAPK expression and upregulating SIRT1 expression [10]. The role of abnormalities in the cholesterol and lipoprotein metabolism is well-known in the pathogenesis of atherosclerosis. LDL exposed to the macrophages of an atherosclerotic lesion become oxidized. The oxidized LDL particles (LDL-ox) are able to damage endothelial cells, contributing to the progression of atherosclerotic lesions. Some preclinical studies have shown that RES could modify this process, notably by decreasing plasma triglyceride and LDL-cholesterol levels and by increasing HDL-cholesterol. In in vitro studies, RES inhibits the LDL and HDL oxidation [11] and can reduce the plasma oxidized LDL cholesterol level [12].

According to several animal studies in recent decades, RES supplementation reduces the level of triglyceride, total cholesterol, and LDL-C [13][14][15][16][17][18] via increasing the synthesis and efflux of bile acids [19] and moderating oxidative stress and inflammation [20][21]. In a recent experimental study from 2020, RES (20 mg/kg for 10 weeks) beneficially influenced the cholesterol concentrations in diabetic rats [22].

The cytokine IL-8, as well as the adhesion molecules VCAM and ICAM, together with the passive lipid accumulation in the arterial walls, are known to play an important role in the initiation of atherosclerosis [23][24].

Diabetes mellitus is also a major risk factor of cardiovascular diseases. According to experimental studies, RES can regulate glucose homeostasis by improving insulin sensitivity [25][26]. RES improves diabetic complications and restores glucose homeostasis via modulating SIRT1/AMPK/NF-κB [27][28] and p38-MAPK/TGF-beta1 [29] signaling pathways, inhibiting Drp1-mediated mitochondrial fission, and preventing ER stress-associated NLRP3 inflammasome activation [30].

Endothelial dysfunction induces atheromatous plaque formation and it is considered to be an important factor in the development of cardiovascular diseases [31]. Several studies have shown the favorable effects of RES on endothelial function in recent years.

RES can also effectively improve cardiac and vascular autonomic function, protecting erythrocytes via interacting with hemoglobin and reducing heme-iron oxidation [32].

2.1.2. Human Clinical Trials

There are only a few human clinical trials with RES in CVD; however, RES appears to have a significant therapeutic potential against CVDs.

In a human clinical trial, 400 mg trans-resveratrol was administered to 44 healthy participants for 30 days. After the termination of treatment, the blood plasma of participants was incubated with cultured human coronary artery endothelial cells. According to the results, a significant reduction in the messenger RNA expression of IL-8, VCAM, and ICAM was found due to RES treatment compared to the baseline plasma, and an inverse relationship was observed between the concentration of plasma RES and the expression of IL-8, VCAM, and ICAM. This study firstly proved that RES may have protective effects against atherosclerosis in low-CV-risk individuals, thereby suggesting that RES should receive consideration as a primary preventive agent [24][33].

Multiple potential mechanisms of RES to normalize the lipid profile in humans have already been examined. These include a decrease in mRNA expression of hepatic HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase and activation of SIRT1 [34], which may potentially lead to reverse cholesterol transport [35] and favorable alteration in lipid profile [36].

In parallel to the aforementioned studies, Simental-Mendia et al. examined the effect of RES in patients with newly diagnosed dyslipidemia. In total, 71 patients were enrolled in this randomized double-blind, placebo-controlled trial and were randomly allocated to receive either 100 mg/day RES or placebo. RES supplementation after 2 months significantly reduced total cholesterol and triacylglycerol concentrations in individuals with dyslipidemia [37].

In 2012, Magyar et al. found that RES administration (10 mg/day for 3 months, n = 40) significantly decreased the LDL-cholesterol levels in patients with ischemic heart disease, but no significant effect was detected on other lipid parameters such as total cholesterol, HDL cholesterol, and triglyceride levels [38]. In addition, our workgroup demonstrated in 2020 that in patients with heart failure, higher-dose RES (100 mg/day) for 3 months significantly decreased both LDL-cholesterol and total cholesterol levels; however, the HDL-cholesterol level was also slightly lower in the RES group compared to the placebo group [39].

However, in 2016, Bo et al. found that RES administration (500 mg/day for 24 weeks; n = 120) significantly increased the total cholesterol level, but LDL-cholesterol, HDL-cholesterol, and triglyceride levels did not change significantly in the RES group [40].

A meta-analysis by Asgary et al. showed that although RES did not significantly affect the total cholesterol level, HDL cholesterol level could be increased by RES treatment [41].

2.2. Vascular Function and Hypertension

2.2.1. Preclinical Studies

RES administration could reduce blood pressure in several experimental models of hypertension, including angiotensin II- (146 mg/day for 4 weeks) [42], renal artery clipping (5, 10, or 20 mg/kg/day for 4 weeks) [43], hypoxia-induced hypertensive rats (10 mg/day for 4 weeks), and fructose-fed rats [44]. Several mechanisms are involved in the antihypertensive effect of RES, including AMPK phosphorylation, SIRT1 activation, increased NO levels, and decreased ROS production due to regulating NADPH oxidase, SOD-2, and glutathione reductase [42][43][44][45].

Franco et al. demonstrated that RES (30 mg/kg/day for 30 days) could mitigate oxidative stress (RES normalized the SOD level in treated group) and hypertension in adult obese rats [46]. According to another experimental model by Tain et al., RES can prevent high-fructose-intake-induced hypertension in adult rats via targeting oxidative stress, nutrient-sensing signals, and gut microbiota dysbiosis [47].

In a recent remarkable study by Prysyazhna et al., RES also decreased the blood pressure in hypertensive mice; however, a paradoxical mechanism of action of RES has been described. According to this new paradigm, RES can surprisingly induce direct protein oxidation, thereby activating cGMP-dependent PKG1α (protein kinase 1α), which can lead to vasorelaxation. This paradoxical, pro-oxidative property of RES is likely due to ROS formation upon electron transfer from RES to oxygen, especially during times of oxidative stress (diseased tissues), thus mediating beneficial signaling at the site of injury [48].

2.2.2. Human Clinical Trials

Many clinical trials have reported that RES decreases blood pressure in patients with obesity [49], type 2 diabetes mellitus [50][51], or fatty liver disease [52]. Moreover, several meta-analyses indicate that RES intake reduces systolic and diastolic blood pressure at doses higher than 150 mg/day [53][54]. However, other meta-analyses of human clinical trials showed no significant effect of RES treatment on systolic and/or diastolic blood pressure [55]. In summary, beneficial effects of RES on blood pressure can only be observed when the effect is analyzed in obesity or in diabetes.

RES is known to improve endothelial function in animals; however, clinical trials are limited. Flow-mediated dilation (FMD) of the brachial artery is an important marker of endothelial function, and it can be used as an indicator of structural and functional endothelium changes. Wong et al. found in a pilot study that administration of RES (270 mg/day for 4 weeks) significantly increased FMD in overweight, hypertensive participants [56].

In 2012, Magyar et al. examined vascular function after 10 mg per day RES administration for 3 months in patients with stable coronary artery disease. Endothelial function was measured by FMD, and a significant improvement was found with regard to vasorelaxation in the RES-treated group compared to placebo [38].

In 2018, Marques et al. examined the effect of a single dose of trans-resveratrol (300 mg) on endothelial dysfunction in hypertensive patients. They proved that acute supplementation of trans-resveratrol caused an improvement in endothelial function measured by FMD; however, brachial blood pressure and aortic systolic blood pressure did not change significantly [57].

Red blood cell (RBC) aggregation and deformability significantly influences blood flow in coronary microcirculation. In 2020, Gal et al. demonstrated in a human clinical trial that RES (100 mg pro day for 3 months)-induced improvement of red blood cell aggregation may positively influence microcirculation, tissue perfusion, and oxygen supply, and hence can cause improvement in coronary and peripheral blood flow [58].

2.3. Heart Failure

Heart failure (HF) is a complex multifactorial condition caused by structural and/or functional cardiac abnormalities, resulting in a reduced cardiac output or elevated intracardiac pressure [59].

2.3.1. The Effect of RES in Heart Failure—Preclinical Trials

There is a large amount of evidence that oxidative stress and the consequent chronic inflammation play an important role in the development of heart failure [60][61]. Oxidative stress activates different intracellular signaling pathways regulating cardiac remodeling, hypertrophy, survival of myocytes, apoptosis, and necrosis [62].

The antioxidant and anti-inflammatory properties of RES were intensively investigated in recent decades in various heart failure models in rodents. According to the literature, RES can improve the diastolic and systolic function of the heart, it can reduce atrial and left ventricular remodeling, and it can improve cardiac energetics, which may contribute to the cardioprotective effects of RES in heart failure.

Ahmet et al. published a long-term (10 months) study in 2017 and found that RES supplementation (5 mg/kg/day) can significantly improve LV systolic function in a postinfarction (surgical ligation of left coronary artery) heart failure rat model [63]. In 2017, Riba et al. also investigated the effects of RES in a postinfarction heart failure rat model, where isoproterenol was used to induce myocardial infarction and postinfarction remodeling. According to the results, systolic left ventricular function was significantly increased, whereas plasma BNP levels, left ventricular wall thickness and dimensions were decreased after 8 weeks RES treatment (15 mg/kg/day). Moreover, RES moderated oxidative stress and favorably modified the activity of several intracellular signaling pathways (Akt-1/GSK-3β, p38-MAPK, ERK1/2, MKP-1, COX-2, and iNOS uncoupling). In summary, RES was capable of preserving LV function and moderated the severity of heart failure already after 2 months [64].

In another postinfarction heart failure rat model, Matsumura et al. in 2018 used cardiotoxic hydroxyeicosatetraenoic acid (HETE) to induce myocardial infarction and heart failure. The results showed that RES treatment (5.82 mg/kg/day) significantly improved the ejection fraction in rats and reduced postinfarction left ventricular and atrial remodeling. Interestingly, the mechanism by which low dose RES exerts its cardioprotective effects was independent of the classical SIRT1 and antioxidant pathways, suggesting another additional pathway [65].

Sung et al. investigated the effects of RES on cardiac structure and function in a pressure-overload–induced heart failure mice model. At the end of the study, RES improved diastolic function and reduced the LV diameters and volumes. RES treatment (150 mg/kg/day) also reduced cardiac fibrosis, hypertrophy, and remodeling via its antifibrotic and anti-inflammatory effects. However, systolic function did not change after a 2-week-long RES supplementation [66].

This result is in accordance with other preclinical trials. Wojciechowski et al. found that low dose RES supplementation (2.5 mg/kg/day for 28 days) regressed the pressure-overload-induced cardiac hypertrophy and remodeling in rats. RES also significantly reduced oxidative stress in cardiac tissue [67].

Ma et al. demonstrated that RES (25 mg/kg/day) reduces the development of myocardial hypertrophy and fibrosis via SIRT1 activation in mice with heart failure. The enhanced SIRT1 improved mitochondrial function through the deacetylation (activation) of PGC-1α and thereby the regulation of downstream proteins such as Nrf-1 and Nrf-2 [68]. Similar results were published by Bagul et al. In this study, RES (10 mg/kg/day for 8 weeks) decreased the cardiac hypertrophy in diabetic rats via its SIRT1-mediated antioxidant effects [69].

Not only heart function and remodeling but also exercise capacity showed significant improvement in several preclinical studies. Sung et al. demonstrated that RES supplementation (450 mg/kg/day for 2 weeks) may effectively improve fatigue and exercise intolerance in pressure-overload-induced heart failure mice, associated with favorably changed gut microbiota composition and increased whole-body glucose utilization [70]. According to a study by Hart et al., RES supplementation (100 mg/kg/day) for 12 weeks significantly enhances the exercise capacity of rats. This beneficial effect is mediated by enhanced mitochondrial biogenesis with the activation of the AMPK-SIRT1-PGC-1α pathway [71].

In addition to the aforementioned, the cardioprotective effects of RES in heart failure have also been evaluated in many other preclinical studies in recent years, including pressure overload [67][72], hypertension [73], diabetes [74], chemotherapy [75][76], and myocarditis-induced [77] as well as genetic models of heart failure [78].

2.3.2. Human Clinical Trials with RES in Heart Failure

Despite the large number of preclinical studies that have reported the beneficial effects of RES in heart failure, the number of human clinical studies investigating these effects are very limited.

In a previous study Magyar et al. examined the possible cardioprotective effects of RES in patients after myocardial infarction with preserved ejection fraction (54.77 ± 1.64% at the baseline in the treated group) and found that the diastolic function was significantly improved after 10 mg/day RES administration for 3 months. However, the systolic function did not change significantly [38].

In 2013, Militaru et al. demonstrated that 20 mg RES per day administered for 2 months resulted in a significant decrease in NT-proBNP level (biomarker of heart failure) in patients with angina pectoris, but without proven heart failure [79]. These aforementioned studies were not designed specifically for heart failure.

In 2020, It is proved that RES beneficially influences heart failure in a randomized double-blind human clinical trial (RCT). A total of 60 outpatients with systolic heart failure in NYHA class II-III were enrolled in this clinical trial and randomized into two groups: receiving either daily 100 mg RES or placebo for three months. The RES treatment improved several parameters of heart function, including systolic and diastolic function, as well as global longitudinal strain. In parallel, the level of cardiac biomarkers of heart failure and remodeling (NT-proBNP and galectin-3) decreased significantly, and exercise tolerance as well as quality of life improved in the treated group. Moreover, RES exerted an anti-inflammatory effect measured by the decrease in levels of inflammatory cytokines (IL-1 and IL-6). According to the results, the decreased activity of leukocytes can be an important mechanism of RES, and it can contribute to its cardioprotective effect in heart failure [39].

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