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Review

Resveratrol and Its Effects on the Vascular System

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Abstract: Resveratrol, the phenolic substance isolated initially from *Veratrum grandiflorum* and richly present in grapes, wine, peanuts, soy, and berries, has been attracting attention of scientists and medical doctors for many decades. Herein, we review its effects on the vascular system. Studies utilizing cell cultures and pre-clinical models showed that resveratrol alleviates oxidative stress and inflammation. Furthermore, resveratrol suppresses vascular smooth muscle cell proliferation, promotes autophagy, and has been investigated in the context of vascular senescence. Pre-clinical models unambiguously demonstrated numerous vasculoprotective effects of resveratrol. In clinical trials, resveratrol moderately diminished systolic blood pressure in hypertensive patients, as well as blood glucose in patients with diabetes mellitus. Yet, open questions remain, as exemplified by a recent report which states that the intake of resveratrol might blunt certain positive effects of exercise in older persons, and further research addressing the framework for long-term use of resveratrol as a food supplement, will stay in demand.

Keywords: resveratrol; clinical studies; cardiovascular disease; vasculoprotective effects

1. Introduction

Resveratrol, *3,4′,5-trihydroxystilbene*, was first isolated from Veratrum grandiflorum by Takaoka in 1939 [1]. This phenolic substance is present in grapes and wine, as well as in peanuts, soy, berries, and Itadori tea [2–4]. Resveratrol is known for its anti-oxidative properties as a scavenger of reactive oxygen species (ROS) such as hydroxyl-, superoxide-, and metal-induced radicals [5,6]. In addition, resveratrol is widely recognized for its anti-aging effects observed in lower organisms [7,8] as well as for its anti-cancer effects [9–17]. Lifespan expansion was observed e.g., in *Saccharomyces cerevisiae* [18], *Caenorhabditis elegans* [19], *Drosophila melanogaster* [19] as well as in honey bees [20], and in some short lived vertebrates treated with resveratrol [21]. In mice, resveratrol delayed age-related changes mimicking certain effects of dietary restriction, however, without increasing the life span [22,23]. Many of the anti-aging, as well as anti-cancer effects of resveratrol were assigned to increasing levels of the NAD-dependent deacetylase, designated as "silent mating type information regulation 2 homolog 1", SIRT1 [24,25].

Resveratrol is in general very well tolerated by human [26–28], and only high doses of orally taken resveratrol (2000 mg twice daily) were reported to instigate mild to moderate gastrointestinal symptoms in healthy volunteers [29]. Likewise, no adverse effects were seen for orally administrated resveratrol in experimental animals, at doses 200 mg/kg/day in rats, and 600 mg/kg/day in dogs for 90 days [30]. However, even though the absorption of resveratrol is high, studies in mice, rats, and rabbits demonstrated that resveratrol in the blood degrades relatively quickly, thus reducing its bioavailability [31–33]. In rabbits, for instance, its half-life in plasma is only 14 min [34].

Resveratrol's bioavailability can be partly enhanced by combining it with other phytochemicals e.g., piperine [35], or by using either controlled-release devices or nanotechnological formulations [31,36–38]. Resveratrol is, in humans, quickly converted to sulfate- and glucuronide conjugated forms, mainly to *resveratrol-3-O-sulfate*, *resveratrol-4′-O-glucuronide*, and *resveratrol-3-O-glucuronide* [26,39], and these metabolites may provide an intracellular reservoir for the generation of parent resveratrol [40]. Some oncological studies suggested that resveratrol may exhibit biphasic dose responses [41]. Similar concentration-dependent effects were described e.g., in an ischemic heart model, in which resveratrol was cardioprotective when rats were fed for 21 days with low doses (2.5 mg/kg and 25 mg/kg), while it was not protective when fed in high (100 mg/kg) doses [42].

The notion that resveratrol may be beneficial for the human vasculature arose from the epidemiological data and so-called "French paradox". According to those findings, the French population, in spite of a high intake of saturated fat, is at rather low risk of cardiovascular diseases, and the protective effects were assigned to relatively high wine consumption [43]. In later studies, resveratrol was designated as a substance partly accountable for such protective effects [44–48]. Studies showed that the vasculoprotective benefits of resveratrol are mediated by different mechanisms, including the lowering of oxidative stress and inflammation, enhancing metabolic capacity, increasing NO synthesis by endothelial cells, suppressing vascular smooth muscle cell (VSMC) proliferation and promoting autophagy. Furthermore, resveratrol was investigated for its ability to prevent cellular senescence, but accomplished works showed conflicting results. Below we discuss studies performed in cell-cultures, pre-clinical models, and human clinical trials, investigating in detail different aspects of resveratrol effects on the vasculature.

2. In Vitro Studies and Studies in Pre-clinical Models on Resveratrol in the Context of Cardiovascular Diseases

2.1. Resveratrol Reduces Oxidative Stress, Alleviates Inflammation, and Increases NO Synthesis

Early studies showed that resveratrol suppresses oxidation of human low-density lipoprotein, (LDL) [49], as well as reduces lipid peroxidation [50]. Feeding with resveratrol decreased lethality in mice challenged by lipopolysaccharide (LPS) treatment [51]. Resveratrol food supplementation increased activities of the anti-oxidative enzymes superoxide dismutase and glutathione peroxidase in rat myocardium and aorta [52]. Such treatment also enhanced the expression of the protective nuclear factor erythroid 2-related factor 2 (Nrf2) and reduced the mortality of mice exposed to catecholamine administration [52]. Resveratrol furthermore reduces the oxidative load via suppressing NADPH oxidase-mediated production of ROS, and via enhancing the expression of various antioxidant enzymes [53]. In *Caenorhabditis elegans*, resveratrol diminished oxidative stress induced by radiation, in two different studies [54,55].

Anti-inflammatory effects of resveratrol include the inhibition of the pro-inflammatory enzyme cyclooxygenase-1 (COX-1), leading to the suppression of synthesis of proinflammatory eicosanoids [56,57]. The anti-inflammatory effects can be mediated by SIRT1 that, via deacetylation, suppresses the major inflammatory transcription factor nuclear factor-κB, NF-κB [58]. In mouse skin, resveratrol moderates the phorbol ester-induced pro-inflammatory NF-κB and AP-1 pathways, and suppresses expression of COX-2 [59,60]. Resveratrol also alleviates the induction of inflammation in mice fed with a high-fat diet [61].

Further vasculoprotective benefits of resveratrol enclose an increase in the formation of the vasculoprotective nitric oxide (NO). Such effect was observed in human umbilical vein endothelial cells (HUVECs) and HUVEC-derived EA.hy 926 cells, where resveratrol, similarly as an alcohol-free red wine polyphenol extract, induced the expression of endothelial nitric oxide synthase (eNOS) thus leading to an increased NO synthesis [62,63]. These effects of resveratrol in endothelial cells are fostered by the activation of estrogen receptor (ER)- and mitogen-activated protein kinase (MAPK) signaling [64], and additionally mediated by SIRT1, and the transcription factors FOXO1 and FOXO3a [65]. The enhancement of eNOS synthesis and NO production that was facilitated in

HUVECs by ER and peroxisome proliferator-activated receptor α (PPARα), became robust during repeated and long-term treatment with resveratrol [66]. Resveratrol also induced the expression of the vasculoprotective transcription factor Krüppel-like factor 2 (KLF2) via SIRT1 activation [67]. The protective effects of resveratrol mediated by increased NO synthesis were not only seen in cell culture, but also demonstrated in animal models. For example, the feeding of hypercholesterolemic rabbits with resveratrol, or the administration of red wine or dealcoholized red wine, improved the functionality of the endothelium, as detected by flow-mediated dilation measurements in the femoral artery [44]. These alterations were accompanied by diminished endothelin 1 (ET-1)- and enhanced NO levels in plasma [44]. The intake of resveratrol stimulated the expression of eNOS, of inducible NO synthase (iNOS) and of vascular endothelial growth factor (VEGF) in the heart of experimental rats [68].

2.2. Resveratrol Enhances Aerobic Capacity of Muscles and Alleviates Endothelial Dysfunction Induced by Diabetes and Obesity

The oral administration of resveratrol to mice fed with a high-fat diet enhanced their aerobic capacity, as demonstrated by prolonged running times and increased muscle oxygen consumption [69]. Such changes were associated with an increased expression of genes involved in oxidative phosphorylation and mitochondrial biogenesis (in the heart, muscles, and brown adipose tissue), and were linked to SIRT1 expression controlling energy and metabolic homeostasis [69]. Resveratrol also maintained the mitochondrial function and stimulated the mitochondrial biogenesis in regulatory T-cells in mice fed with a high-fat diet, pointing to the fact that the effects of resveratrol on oxidative metabolisms of mitochondria are not restricted to certain tissues [70].

In addition, resveratrol counteracted some harmful effects of diet-induced obesity and reduced insulin resistance in animal models. Its administration to middle-aged mice fed with a high-calorie diet improved the motor function and enlarged the number of mitochondria [71]. Such treatment also affected numerous signaling pathways and resulted in enhanced insulin sensitivity, decreased levels of insulin-like growth factor-1, and raises in peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and AMP-activated protein kinase (AMPK) activity [71]. The latter protein is known as an important nutrient and energy sensor maintaining energy homeostasis of the organism [72].

In the myocardium of rats with streptozotocin-induced diabetes, resveratrol stimulated GLUT-4 translocation to the cell membrane, and this alteration was mediated by the AMPK/Akt/eNOS pathway [73]. Resveratrol also delayed vascular aging in rats without prolonging their life span [74]. In rhesus monkeys fed with a high-fat/high-sugar diet, a two-year supplementation with resveratrol reduced the adipocyte size as well as the inflammatory response in the adipose tissues [75]. Such treatment also improved insulin signaling [75]. The protective effects of resveratrol-administration in rhesus monkeys fed with a high-fat/high-sugar diet also included the prevention of beta-cell dedifferentiation [76]. Resveratrol furthermore suppressed, in rhesus monkeys fed with high-fat/high-sucrose diet, inflammation and the stiffening of the arterial wall [77]. The feeding of rats with resveratrol also increased SIRT1 and adiponectin levels in their serum [78].

In cultured human coronary arterial endothelial cells, resveratrol-treatment alleviated mitochondrial oxidative stress induced by high-glucose [79]. These protective effects were boosted by overexpressing SIRT1, and diminished by its downregulation [79]. In human coronary arterial endothelial cells, resveratrol furthermore enhanced mitochondrial mass and mitochondrial DNA [80,81]. Such effects were dependent on the expression of SIRT1 [80] and of the antioxidant transcription factor Nrf2 [81]. The impact of these findings was further reinforced by the fact that prolonged resveratrol-treatment normalized mitochondrial biogenesis in the aortas of type 2 diabetic-(db/db) [80], as well as of wild-type mice fed with a high-fat diet [81]. Various studies also showed that resveratrol inhibits lipogenesis as well as differentiation of pre-adipocytes to mature adipocytes [82–84]. Resveratrol furthermore lessened consequences of experimentally-induced diabetic neuropathy in rats [85]. Specifically, a two-week treatment of rats with resveratrol that started six week after diabetes

induction by streptozotocin, significantly counteracted the reduction in motor nerve conduction velocity and in nerve blood flow, and diminished thermal hyperalgesia of rats [85]. Protective effects of resveratrol intake were also reported in db/db mice and included decrease in blood glucose, free fatty acid and triglycerides levels [86]. These effects were associated with the increased expression of GLUT4 protein in the skeletal muscle, and the activation of AMPK and its downstream targets [86].

2.3. *Resveratrol Promotes* Autophagy *and Might Protect Against Cellular* Senescence

Resveratrol stimulated autophagy, the process of removing and recycling damaged cellular components, such as organelles, membranes or proteins, in different cell-types [87], e.g., in endothelial cells exposed to tumor necrosis factor-α (TNF-α), where its effects were mediated via the cAMP signaling pathway [88]. As it is known that insufficiently operating autophagy promotes mitochondrial dysfunction and oxidative stress [89–91], the above studies provide further support for the vasculoprotective role of resveratrol.

Conflicting results were, however, reported on the role of resveratrol in mediating cellular senescence, the state in which cells have lost their capacity to divide but secrete inflammatory cytokines [92–95]. Such proinflammatory senescent cells, accumulating with age in the affected tissues, contribute to the loss of tissue homeostasis, and to the development of age-associated pathologies [93]. In an attempt to investigate the presumed beneficial effects of resveratrol, surprisingly, the continuous treatment of HUVECs with 10 μM resveratrol during extended cell-propagation, resulted in the premature replicative senescence of these cells. They were found arrested in the S phase of the cell cycle, caused, apparently, by elevated levels of ROS [96]. Such increased ROS production, detected in HUVECs treated with resveratrol, was mediated via the NADPH oxidases Nox1 and Nox4, and the blocking of these enzymes prevented the resveratrol-induced cellular senescence [96]. On the other hand, another group reported that resveratrol protects human endothelium against H_2O_2 induced senescence, specifically by reducing H_2O_2-induced oxidative stress via activating SIRT1 [97]. In line with the view of an overall protective effect of resveratrol are data obtained in vivo, in rats fed with a high-fat/high-sucrose diet and concomitantly treated with resveratrol [98]. In the aortas of these animals, resveratrol prevented the rise in senescent cells [98]. In addition, resveratrol lessened the induction of senescence in bovine aortic endothelial cells cultured in high-glucose medium [98]. The protective effects of resveratrol-treatment in this study were assigned to its ability to diminish an increase in NADPH oxidase subunit p47phox expression and counteract a decrease in SIRT1 expression caused by high-fat/high-sucrose treatment [98].

2.4. *Resveratrol Alleviates Oxidative Stress in Cardiac Cells and Macrophages*

Resveratrol also affected other cell-types. In the H9C2 cell line derived from embryonic rat heart ventricle, it stimulated the expression of cellular antioxidants, as well as phase 2 enzymes, and diminished intracellular ROS levels that had been induced by oxidative or electrophilic injury [99]. In LPS-stimulated macrophages resveratrol suppressed their transition to foam cells and alleviated oxidative stress, by suppressing Nox1 expression and ROS production [100]. Further changes mediated by resveratrol in LPS-stimulated macrophages, included a diminished expression of the chemoattractant monocyte chemotactic protein-1, MCP-1 [100].

2.5. *Resveratrol Suppresses VSMC Proliferation and Platelet Aggregation*

Dysregulated and excessive VSMC proliferation is known to contribute to the development of atherosclerosis, as well as restenosis after vascular surgery [101,102]. Several in vitro and in vivo studies demonstrated that resveratrol diminishes VSMC proliferation. The treatment of VSMCs, derived from spontaneously hypertensive rats, with resveratrol suppressed advanced glycation end-products (AGEs)-induced proliferation of VSMCs, as well as reduced collagen synthesis [103]. Resveratrol also inhibited the serum-induced proliferation of rat aortic-SMCs, and this effect was synergistically enhanced in the presence of other polyphenols present in red wine (quercetin,

(+)-catechin and ethyl gallate) [104]. Resveratrol furthermore suppressed oxidized low-density lipoprotein (ox-LDL)-induced proliferation of cultured bovine aortic SMCs [105]. Mechanistically, the inhibitory effects of resveratrol were associated with the suppression of MAPK ERK1/2 and the weakening oxLDL-induced ROS and H_2O_2 production [105]. In addition, resveratrol attenuated the proliferation of human coronary SMCs induced by ET-1, and these effects were associated with the activation of kinase-G and suppressing ERK1/2 activation [106]. The subcutaneous administration of resveratrol to neonatal rats placed into a hypobaric hypoxic chamber alleviated remodeling of the right ventricle and of the pulmonary artery [107], a hallmark of pulmonary hypertension [108]. In vitro, resveratrol diminished the hypoxia-induced proliferation of human pulmonary artery-SMCs via inhibiting arginase II, an enzyme known to be upregulated in patients with pulmonary hypertension, and these effects were mediated via affecting PI3K-Akt signaling [107]. Resveratrol furthermore attenuated the homocysteine-induced proliferation of VSMCs, by reducing hypermethylation of phosphatase and tensin homologue on chromosome 10, PTEN [109]. In addition, in rats subjected to a chronic myocardial ischemia model, resveratrol induced the expression of Krüppel-like factor 15 (KLF15), known to play a protective role in the ischemic myocardium [110].

Importantly, some vasculoprotective effects of resveratrol could be attributed to inhibiting platelet aggregation, as exacerbated platelet aggregation/activation is an important risk factor for atherosclerosis [111]. The treatment of human platelets with resveratrol significantly suppressed their aggregation induced by collagen, thrombin, or ADP [112,113]. The administration of resveratrol (4 mg/kg/day) to rabbits fed with a high-cholesterol diet diminished ADP-induced platelet aggregation ex vivo [112].

2.6. Resveratrol has Protective Effects in Heart-, Lung-, Brain-, and Skin Injury Models

Resveratrol also was protective in heart injury/infarction- and hemorrhagic lung-, brain-, and skin injury pre-clinical models, and these effects were mediated via suppressing oxidative stress and inflammation, increasing NO levels, mediating ion channel activation, and promoting autophagy.

The beneficial effects of resveratrol on cardiomyocytes seen in an ischemia-reperfusion model included the suppression of superoxide levels, the activation of potassium channels, as well as an increase in endothelium-dependent vasodilatation [114]. In rats fed with a hypercholesterolemic diet, and subjected to experimentally induced myocardial infarction, the oral intake of resveratrol amended certain cardiologic parameters such as ejection fraction and fractional shortening and fostered neovascularization in the injured myocardium [115]. These benefits were associated with increased expressions of hemeoxygenase-1 (HO-1), eNOS and VEGF in resveratrol-treated animals [115]. Furthermore, a three week feeding of rats with resveratrol was protective against ischemia/reperfusion injury, and normalized an altered microRNA pattern [116]. Resveratrol enhanced survival, hemodynamics and energetics in rats, in a model of hypertension leading to heart failure [117]. Specifically, Dahl salt-sensitive rats had been fed with a high-salt diet, and resveratrol was administrated for eight weeks after inducing hypertension and cardiac hypertrophy. Such treatment increased the rats' survival, by counteracting cardiac dysfunction [117]. Observed changes also included the preservation of mitochondrial mass, and an increase in PPARα-expression [117].

The intraperitoneal administration of resveratrol to newborn rats subjected to hyperoxia-induced lung injury significantly diminished TNF-α levels and increased the expression of crucial antioxidants glutathione- and superoxide dismutase (SOD) [118]. Resveratrol also suppressed inflammation and fibrosis in the lungs of neonatal rats exposed to hyperoxia-induced oxidative stress, and these effects were accompanied by inhibition of Wnt/beta-catenin signaling [119]. The intraperitoneal administration of resveratrol prevented the expression of inflammatory markers in an acute lung injury model in rats [120].

The prolonged administration of resveratrol in rats was also neuroprotective, as such treatment partially prevented tissue damage in the olfactory cortex and the hippocampus, caused by systemic injection of the excitotoxin kainic acid [121]. Resveratrol was also found neuroprotective in a

rat stroke model where its benefits were assigned to suppressing of phosphodiesterases and influencing the cAMP/AMPK/SIRT1 pathway [122]. Treatment of rats with resveratrol immediately after subarachnoid hemorrhagic injury, reduced mortality and brain edema [123]. In this model, the protective effects of resveratrol were mediated by the Akt/mTOR pathway [123].

Finally, the prolonged local treatment of skin wounds of rats with resveratrol caused accelerated wound healing due to enhanced vascularization [124]. These effects were mediated via stimulation of the AMPK pathway [124].

3. Clinical Studies on Resveratrol in the Context of Cardiovascular Diseases

Many clinical studies investigated the effects of resveratrol intake in the context of cardiovascular diseases [125]. These studies differ widely in the used amounts of resveratrol (ca. 5 to 5000 mg/day), and in treatment periods (ranging from s couple of days to months). Results of some of these works are highlighted in Table 1.

Table 1. Outcome of clinical studies involving intake of resveratrol.

Type of the Study/Number of Probands	Clinical Outcome	References
Healthy volunteers (N = 20) tested before and after 15 days of controlled wine consumption (300 mL/day)	Increase in resveratrol concentration in plasma after wine consumption. Enhancement of platelet NO synthase (NOS) activity, decrease in phosphorylation of p38 MAPK and reduction in NADPH oxidase activity after treatment of platelets with resveratrol *in vitro*	[126]
Healthy volunteers (N = 22) who received orally placebo and two doses of resveratrol (250 and 500 mg) on separate days	Enhancement in cerebral blood-flow after resveratrol intake (cognitive functions stayed not affected)	[127]
Patients with mild-to-moderate Alzheimer's disease (N = 119) randomized to placebo or resveratrol group and treated for 52 weeks (the latter group was receiving orally 500 mg of resveratrol once daily with dose escalation until a final dose of 1000 mg twice daily)	Presence of low nanomolar concentration of resveratrol in the cerebrospinal fluid of resveratrol-treated group; a 50% decrease of MMP-9 level and increase in activation of microglia/macrophages; reduced plasma levels of proinflammatory interleukin (IL)-1R4, IL-12p40, IL-12p70, and TNF; weight loss in resveratrol-treated group	[128]
Healthy obese men (N = 11) treated with placebo and subsequently with 150 mg/day resveratrol for 30 days	Significant reduction in sleeping- and resting metabolic rates due to resveratrol-treatment. Activation of AMPK, enhancement of SIRT1 and PGC-1α protein levels in muscle, and decrease in plasma glucose, triglycerides levels and inflammation markers	[129]
Pooled analysis of 21 clinical studies that included overweight and obese human	Resveratrol-treatment significantly decreased total cholesterol, systolic blood pressure and fasting glucose, effects more pronounced in individuals ingesting more than 300 mg of resveratrol per day	[130]
Meta-analysis of 28 randomized controlled trials	Significant reduction in body weight, BMI and waist circumference; effects of resveratrol most prominent in obese patients and in trials longer than three months	[131]
Meta-analysis of 36 randomized controlled trials	Significant reduction in body weight, BMI, fat mass and waist circumference; no significant effect of resveratrol intake on leptin and adiponectin levels	[132]
Meta-analysis of 17 randomized controlled trials	Intake of resveratrol did not significantly affect systolic, diastolic or mean blood pressure. However, significant blood pressure lowering effects were found in individuals treated with resveratrol daily at dosage $\geq$ 300 mg per day and in diabetic patients	[133]

Table 1. *Cont.*

Type of the Study/Number of Probands	Clinical Outcome	References
Meta-analysis of 21 randomized clinical trials	Resveratrol could not significantly change total cholesterol, LDL and HDL cholesterol levels, but it might decrease blood triglycerides levels	[134]
Meta-analysis of 10 randomized clinical trials	No changes in C-reactive protein (CRP) blood levels. In addition, no alterations in total cholesterol, LDL cholesterol and triglycerides plasma levels upon resveratrol treatment	[135]
A randomized placebo-controlled clinical trial including middle-aged men (N = 74) with metabolic syndrome receiving daily 1000 mg, 150 mg of resveratrol, or placebo for 16 weeks	No lowering of CRP, interleukin 6, or soluble urokinase plasminogen activator receptor plasma levels. No change in analyzed inflammatory gene expression in adipose and muscle tissues. No effect on blood pressure. A striking increase in total cholesterol and LDL cholesterol plasma levels in resveratrol-treated compared to placebo-treated men	[136]
Meta-analysis of 15 randomized clinical trials (N = 658)	Resveratrol decreased serum CRP levels; no significant change in serum IL-6 and TNF-α levels	[137]
Meta-analysis of 17 randomized clinical trials (N = 736)	Significant reduction in CRP- and TNF-α levels; no significant change in IL-6 in serum upon resveratrol treatment	[138]
Type 2 diabetes mellitus and hypertensive patients consuming daily resveratrol's enriched (8 mg) grape extract	Reduced expression of pro-inflammatory cytokines CCL3, IL-1β and TNF-α; modified pattern of inflammatory-related microRNAs in peripheral blood mononuclear cells due to resveratrol enriched grape extract consumption	[139]
Obese human subjects (N = 10) treated with resveratrol for 30 days	Decrease in postprandial glucagon levels due to resveratrol's intake, no changes in fasting plasma glucagon levels	[140]
A randomized clinical trial including a three month treatment of type 2 diabetic patients (N = 62) with 250 mg per day of resveratrol or placebo	Reduction in systolic blood pressure and total cholesterol levels, no change in body weight and LDL and HDL cholesterol levels in comparison with placebo group	[141]
Type 2 diabetic patients taking resveratrol orally (1 gram per day for 45 days) in the presence of standard antidiabetic treatment (N = 34 resveratrol, N = 32 placebo)	Reduction in systolic blood pressure, fasting blood glucose and HbA1c levels and improvement in insulin resistance in the resveratrol group	[142]
Meta-analyses of six randomized controlled clinical trials of type 2 diabetes mellitus patients (N=104 resveratrol, N = 92 placebo)	Reduction in systolic blood pressure, HbA1c, and creatinine levels in the resveratrol group. No change in other clinical parameters (fasting glucose, insulin resistance, triglycerides, LDL and HDL cholesterol)	[143]
Meta-analysis of 10 randomized clinical trials including patients with type 2 diabetes mellitus (N = 363)	Prolonged treatment of diabetic patients ($\geq$ 6 months) with resveratrol reduced triglyceride levels	[144]
Meta-analysis of nine randomized clinical trials including patients with type 2 diabetes mellitus (N = 283)	Significant improvement of the fasting plasma glucose and insulin levels (especially at a dose of resveratrol $\geq$ 100 mg per day) as well as reduction of blood pressure. No significant changes in HbA1c, LDL and HDL cholesterol	[145]
Meta-analysis of six studies involving patients treated with resveratrol (N = 247)	No significant reduction in systolic blood pressure in the whole resveratrol group. Reduction in systolic blood pressure in a subgroup treated at a high dose of resveratrol ($\geq$ 150 mg per day). No changes in diastolic blood pressure	[146]

Table 1. *Cont.*

Type of the Study/Number of Probands	Clinical Outcome	References
Healthy physically inactive 65 years old men subjected to eight week exercise training and additionally taking 250 mg per day of trans-resveratrol (N = 14) or placebo (N = 13)	In the trained placebo group: a ~45% higher increase in maximal oxygen uptake when compared to the trained resveratrol group. Reduction in the mean arterial pressure detected only in the trained placebo group. Lower interstitial levels of vasodilator prostacyclin and higher levels of muscle thromboxane synthase in the trained resveratrol group than in trained placebo group. Reduction in LDL, total cholesterol/HDL ratio and triglyceride concentrations in the blood detected only in the trained placebo group (not in the trained resveratrol group)	[147]
Healthy physically inactive 65 years old men subjected to eight week intense exercise training and additionally taking 250 mg per day of trans-resveratrol (N = 14) or placebo (N = 13). Non trained group received 250 mg per day of trans-resveratrol (N = 9) or placebo (N = 7)	In the trained placebo group: a ~20% increase in the ratio of capillary to muscle fibers as well as increase in levels of VEGF, VEGF receptor-2, and tissue inhibitor of matrix metalloproteinase (TIMP-1). In the trained resveratrol group: no increase in the ratio of capillary to muscle fibers as well as no increase in VEGF levels	[148]
60 sedentary persons aged > 65 years will be exercising three times weekly during three months. Participants are being/will be assigned to three groups: consuming 1) placebo, 2) 250 mg/day resveratrol, or 3) 1000 mg/day resveratrol.	This running clinical trial should provide an important information on the skeletal muscle mitochondrial function induced by a combined use of resveratrol and exercise in older sedentary persons	[149]

The controlled drinking of wine (300 mL/day) for 15 days by test persons led to an increase of plasma resveratrol concentration [126]. In addition, the treatment of platelets with resveratrol in vitro enhanced the activity of platelet NO synthase (NOS) and caused a decrease in phosphorylation of the proinflammatory p38 MAPK, and reduction in the NADPH oxidase activity [126].

The acute treatment of healthy volunteers with resveratrol enhanced cerebral blood flow [127]. Prolonged treatment of Alzheimer disease patients with orally administrated resveratrol (500 mg once daily with dose escalation until a final dose of 1000 mg twice daily) caused a decrease in matrix metalloproteinase 9 (MMP-9) levels, as well as improved responsiveness of microglia/macrophages in the cerebrospinal fluid [128]. In addition, in these subjects, reduced plasma levels of the proinflammatory factors, interleukin (IL)-1R4, IL-12p40, IL-12p70, and TNF-α were found [128].

Clinical trials investigated the effects of resveratrol in obese patients with metabolic syndrome and focused mainly on the investigation of metabolic changes and parameters, such as body mass, body mass index (BMI), blood pressure, lipid profile, glucose, and inflammation status. For example, a 30 day resveratrol intake, by obese humans, prompted metabolic changes in muscles such as the activation of AMPK, and increase in SIRT1- and PGC-1α protein levels [129]. In addition, plasma glucose, triglycerides, and inflammation markers, became reduced after resveratrol-treatment, and, the metabolic changes observed in this study mimicked the effects of calorie restriction [129]. Pooled analysis of 21 clinical studies that recruited overweight and obese study participants, showed that resveratrol-treatment significantly decreased total cholesterol, systolic blood pressure, and fasting glucose [130]. These effects were more prominent in individuals ingesting more than 300 mg of resveratrol per day [130]. A more recent study evaluating 28 randomized clinical trials accomplished until April 2018 revealed the significant impact of resveratrol intake on a decrease in body weight, BMI, and waist circumference [131]. These effects were more prominent in studies that lasted longer than three months and were performed on obese people [131]. Similar conclusions were drawn in a meta-analysis that encompassed 36 randomized clinical trials accomplished until July 2018. Here, resveratrol intake significantly decreased body weight, BMI, fat mass, and waist circumference [132], demonstrating altogether the positive effects of resveratrol supplementation on weight loss. Although

data of how resveratrol affects blood pressure are rather heterogeneous and partly controversial, positive blood pressure-lowering effects were concluded in a recent analysis of 17 randomized controlled clinical trials, in either individuals receiving more than 300 mg per day of resveratrol, or in diabetic patients [133]. Meta-analyses of randomized clinical trials furthermore concluded that the intake of resveratrol does not influence total cholesterol-, low-density lipoprotein (LDL)-, and high density lipoprotein (HDL) cholesterol levels, but it may decrease triglycerides [134]. However, no beneficial effects of resveratrol intake on lowering the inflammatory marker C-reactive protein (CRP) were found, neither in a meta-analysis of randomized controlled trial [135] nor in a later accomplished randomized placebo-controlled clinical trial [136]. These data are, however, in contrast with two more recent meta-analyses concluding the CRP-lowering effects of resveratrol use [137,138].

Treatment with resveratrol alleviated some clinical parameters of diabetes mellitus in several studies. For example, the daily consumption of a resveratrol-enriched grape extract for one year reduced the expression of pro-inflammatory cytokines CCL3, IL-1β, and TNF-α, and modified the pattern of inflammatory-related microRNAs in peripheral blood mononuclear cells of type 2 diabetes patients and hypertensive patients with coronary artery disease [139]. In another study, a 30 day resveratrol administration to obese human subjects, suppressed postprandial glucagon levels [140]. A three month intake of resveratrol (250 mg per day) by type 2 diabetic patients, reduced systolic blood pressure, as well as total cholesterol levels, even though it did not change body weight and LDL and HDL cholesterol levels in comparison with a placebo group [141]. Treatment of type 2 diabetic patients with resveratrol (one gram per day for 45 days) reduced fasting blood glucose levels as well as HbA1c and improved insulin resistance [142]. Meta-analyses of randomized placebo controlled clinical trials found positive effects of prolonged resveratrol intake in type 2 diabetes mellitus-patients on lowering systolic blood pressure [143], triglyceride levels [144] as well as HbA1c and creatinine levels [143]. No effects of resveratrol intake on fasting glucose, diastolic blood pressure, insulin, LDL, and HDL cholesterol levels were found here [143], contrary to other meta-analyses that reported glucose lowering effects of resveratrol administration [145]. The meta-analysis of six studies involving patients treated with resveratrol did not find blood pressure lowering effects of resveratrol [146]. Yet, reduction in systolic blood pressure was seen in a subgroup treated with a high dose of resveratrol ($\geq$150 mg per day) [146].

Contrary to exercise training, resveratrol intake surprisingly did not improve the metabolic or inflammatory status in skeletal muscles of elderly persons, and the authors furthermore concluded that the use of resveratrol may not be beneficial for the cardiovascular system in aged man [147,148,150]. These studies stimulated intense discussions in the scientific and medical community [151–157]. The effects of resveratrol intake and exercise are currently being investigated in a clinical trial involving 60 sedentary persons aged >65 years [149].

Beyond the conditions described above, future clinical studies might also focus on investigating the effects of resveratrol in ischemic heart disease and/or atrial fibrillation [158–161]. In addition, future studies might also be needed to determine in more detail the effects of resveratrol on chronic obstructive pulmonary disease [162], representing a serious clinical problem [108].

Additional reviews highlighting different aspects of resveratrol on the vasculature are e.g., References [163–174].

4. Conclusions

Numerous in vitro studies and studies in preclinical models demonstrated vasculoprotective effects of resveratrol. Resveratrol is well tolerated, both in experimental animals and in humans, and positive effects of resveratrol observed in pre-clinical models included e.g., alleviation of oxidative stress and inflammation, enhancement of metabolic capacity, increased NO synthesis, suppression of VSMC proliferation, and elevation of autophagy. Human clinical studies markedly differ in the doses of administrated resveratrol as well as in duration of the treatment. Overall, the most pronounced effects of resveratrol included reduction in body weight in obese patients and partly diminishing

systolic blood pressure as well as fasting blood glucose and HbA1c levels in patients with diabetes mellitus in some clinical trials. Currently intensively studied topics include e.g., the evaluation of the effects of a combined use of resveratrol and exercise in older sedentary persons, as well as the optimization of the dose- and time frame of resveratrol use.

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