Cardiovascular effects of resveratrol

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Introduction

Resveratrol, trans-3, 5, 4′-trihydroxy stilbene is a naturally occurring phytoalexin present in many different types of nutrients which we consume on daily basis. Resveratrol was first isolated from dried roots of Polygonum cuspidatum, as the principal active ingredient. Polygonum cuspidatum and its extract have been used in Japanese and Chinese traditional medicine for treatment of various skin inflammations, cardiovascular and liver diseases, and fungal infections 1, 2.

There are two isoforms of resveratrol: cis- and trans-resveratrol. Trans–resveratrol is biologically active isoform. The main source of resveratrol is grape skin. Also, resveratrol is present in fruits such as cranberry, lingonberry, bilberry, mulberry, deer berry, blueberry, sparkleberry, partridgeberry, jackfruit, and in a peanut orchid tree, scots pine, corn lily, white hellebore, eucalyptus, spruce etc. (Table 1) 3, 4. Resveratrol has anti-cancer and anti-inflammatory effects and beneficial cardiovascular effects 4. There were around 800 published articles about biological properties of resveratrol and its health benefits, from 1940 until 2005. From 2005 until nowadays, there are more than 4,000 new studies with resveratrol on cells, isolated animal organs, animals and humans.

It is well known that resveratrol has beneficial effects on the cardiovascular system. It plays the most important role in the epidemiological phenomenon called “French paradox” (existence of cardiovascular risk factors with low incidence/mortality rates which may attribute to moderate consumption of red wine) 5,10. The following will describe

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount of resveratrol found in natural food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilberries</td>
<td>~0.65 μg/g 5</td>
</tr>
<tr>
<td>Blueberries</td>
<td>~0.12 ng/g 6</td>
</tr>
<tr>
<td>Dry grape skin</td>
<td>~24.06 μg/g 7</td>
</tr>
<tr>
<td>Grapes</td>
<td>0.16–3.54 μg/g 11</td>
</tr>
<tr>
<td>Peanuts</td>
<td>0.02–1.92 μg/g 10</td>
</tr>
<tr>
<td>Pistachios</td>
<td>0.09–1.67 μg/g 9</td>
</tr>
<tr>
<td>Red wines</td>
<td>01–14.3 mg/L 11</td>
</tr>
</tbody>
</table>

The most important effects of resveratrol on the cardiovascular system.

Bioavailability of resveratrol

After oral administration, resveratrol absorbs rapidly (75%) by transepithelial diffusion. It is detected in a 15-min post-administration and reaches peak concentrations after 30 min. Values returned to baseline within 4 h 14. Previously, we showed that different bile acids micellar solutions improved resveratrol solubilization 15. The metabolism of resveratrol is extensive in the intestine and liver. Because of intense metabolism, an oral bioavailability of resveratrol is less than 1%. The major active metabolites of resveratrol are glucuronides (trans-resveratrol-3-O-glucuronide) and sulfates (trans-resveratrol-3-sulfate). Also, colonic bacterial metabolism plays an important role in resveratrol metabolism 16. Metabolites of resveratrol are eliminated by kidneys.
How much?

The best source of resveratrol is considered to be red wine and it is generally believed that resveratrol is responsible for cardioprotective effects related to red wine consumption. Approximately 300 mL of red wine for men and up to 200 mL for women is the average recommended dose (equate to a dose of 15 mg and 10 mg of resveratrol, respectively). It is well known that resveratrol produces beneficial effects to human health in a dose-dependent manner, by diverse mechanisms. Data about dose-dependency of resveratrol in the cardiovascular system are shown in Table 2.

Effects of different doses of resveratrol on the cardiovascular system

<table>
<thead>
<tr>
<th>Doses</th>
<th>Effects on cardiovascular system</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 nM</td>
<td>Induces eNOS activity and activates ERK</td>
</tr>
<tr>
<td>0.15/0.25 μM</td>
<td>Inhibits platelet activation</td>
</tr>
<tr>
<td>10 μM</td>
<td>Improves cardiac functions after ischemia/reperfusion injury</td>
</tr>
<tr>
<td>25 μM</td>
<td>Exerts lesser degree of cardioprotection</td>
</tr>
<tr>
<td>2.5 mg/kg bw</td>
<td>Alleviates cardiac dysfunction in streptozotocin-induced diabetes</td>
</tr>
<tr>
<td>2.5–5 mg/kg</td>
<td>Improves post ischemic cardiac functions</td>
</tr>
<tr>
<td>22.4 mg/kg</td>
<td>Extends the life span, in case of high-calorie diets induce mice, by overexpressing sirtuin 1 (SIRT1)</td>
</tr>
<tr>
<td>50–100 μM</td>
<td>Inhibition of metabolic activity and cell proliferation</td>
</tr>
<tr>
<td>1–100 μM</td>
<td>Vasodilatation</td>
</tr>
</tbody>
</table>

eNOS – endothelial nitric oxide synthase; ERK – extracellular signal regulated kinase.

Resveratrol-induced vasorelaxation

Resveratrol relaxes isolated human internal mammary artery, rat aorta and mesenteric artery (Figure 1). Also, there are evidences that resveratrol relaxes mesenteric and uterine arteries of guinea pig and porcine coronary and retinal artery. Rakici et al. have described that resveratrol effects vascular tone and endothelial function of the human saphenous vein and internal mammary artery. In addition, resveratrol significantly improves vascular response in streptozotocin-induced diabetic rats.

Mechanism of vasodilatation by resveratrol is not well defined. Resveratrol induces endothelium-dependent and endothelium-independent vasorelaxation. Endothelium-dependent mechanisms of relaxation by resveratrol include stimulation of endothelial nitric oxide (NO) production by SIRT1-dependent endothelial NO synthase (eNOS) upregulation and SIRT1-dependent eNOS deacetylation. Estrogen receptor (Esr)-dependent, ERK1/2-mediated eNOS phosphorylation is stimulated by resveratrol. Resveratrol lowers superoxide-mediated NO inactivation by different mechanisms. It decreases expression and activity of vascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) and stimulates expression of superoxide dismutases (SOD), catalase and glutathione peroxidases. Thus, oral treatment with resveratrol results in endothelium-dependent relaxation.

The endothelium-independent relaxation is probably mediated by different ion channels in the membrane of vascular smooth muscle cells, including big Ca²⁺-activated K⁺ (BKca) channels or voltage-gated calcium channels. Also, there are evidences that margatoxin-sensitive smooth muscle voltage-sensitive K⁺ (Kv) channels play important role in va-
sorelaxation induced by resveratrol (Figure 2). All studies suggest tissue and species selectivity for resveratrol.

The effects of resveratrol on vascular inflammation

It is well-known that resveratrol has anti-inflammatory effect. The major molecular target for the anti-inflammatory effects of resveratrol in the vasculature is nuclear factor kappa-beta (NF-κB). Resveratrol inhibits NF-κB and there are several mechanisms which are involved in this inhibition. The inhibitory effect of resveratrol on NF-κB may be mediated by SIRT1. Also, resveratrol inhibits reactive oxygen species (ROS)-mediated NF-κB activation by reducing H₂O₂ levels. Resveratrol inhibits activation of κB kinases (IKK). IKK kinases are upstream kinases known to activate NF-κB. Those results were obtained in experimental study in skin tumor models. Also, the transcription of NF-κB is blocked by resveratrol.

Antiplatelet effects of resveratrol

Resveratrol has antiplatelet effects. This effect of resveratrol has been shown on isolated platelets from healthy subjects. There is experimental study which described that resveratrol has prophylactic effects on portal vein thrombosis in the rat. According to this study, foods containing resveratrol can be advised to minimize portal vein thrombosis, at least among patients undergoing liver transplantation and displaying certain cardiovascular disease risk factors. The mechanism of antiplatelet effect of resveratrol is not completely clear. Resveratrol enhances endothelial NO production, NO could diffuse into platelets and inhibits platelet aggregation by activation of guanylyl cyclase and production of cyclic guanosine monophosphate (cGMP). It was described in the isolated human platelets.

The level of cGMP was increased in endothelium-independent manner. There are assumptions that resveratrol enhanced platelet NO production and improved NO bioactivity due to the reduction of oxidative stress. Also, resveratrol is a potent inhibitor of cyclooxygenase 1 (COX-1). The inhibition of COX-1 is irreversible and non-competitive. On the other hand, Kundu et al. described that resveratrol inhibited both COX-1 and COX-2. There are some evidences that resveratrol inhibited thromboxane synthesis by inhibition of a pathway involving p38 mitogen-activated protein (MAP) kinase.

Resveratrol and atherosclerosis

In an experimental study, which included rabbits on the hypercholesterolemic diet, resveratrol had significant anti-atherogenetic effects. The effect of resveratrol supplements, with regard to the modulation of lipid profiles, cholesterol synthesis and anti-atherogenesis, were examined in apo E-deficient (apoE(−/−)) mice fed a normal diet. The concentration of total cholesterol (total C) and low-density lipoprotein cholesterol (LDL-C) in plasma was significantly lower in the resveratrol-supplemented groups compared to the control group of mice. The effect of resveratrol on intimal hyperplasia after endothelial denudation was examined in experimental rabbits. The results of this examination suggest that this polyphenol might have clinical potential in prevention and treatment of restenosis after angioplasty. Also, this compound may inhibit lipid peroxidation by scavenging free radicals. The mechanism which is, also, involved in anti-atherogenetic effect of resveratrol is inhibition of vascular inflammation (described above). Resveratrol inhibits proliferation and migration of the vascular smooth muscle cell. There is evidence that resveratrol blocks oxidized LDL-induced proliferation of smooth muscle cell. Actually, resveratrol inhibits the mammalian target of rapamycin (mTOR) mitogenic signaling pathway. According to this, it is obvious that all the described mechanisms might be involved in an anti-atherogenetic effect of resveratrol.

Resveratrol and diabetes

In animal studies, resveratrol decreases blood glucose and protects pancreatic β cells from oxidative damage. It binds to sulfonylurea receptor and block pancreatic adenosine-5’-triphosphate (ATP)-sensitive K+ channels. Also, resveratrol displaced binding of glibenclamide, the drug which blocks ATP-sensitive K+ channels in β cells. Resveratrol stimulated secretion of insulin in β cell insulinoma lines. In the presence of resveratrol, the amplifying pathway of insulin secretion, independent of the closure of ATP-sensitive K+ channels in β cells, was reported.

In development of type 2 diabetes, the most critical factor is insulin resistance. It is well known that SIRT1 has involved in the processes of glucose metabolism and insulin secretion. Increased expression of SIRT1 improves insulin sensitivity. Resveratrol is potent activator of SIRT1.
attenuates high fat diet-induced insulin resistance in vivo, in dose of 2.5 mg/kg/day.\textsuperscript{51}

The effect of resveratrol on energy metabolism and metabolic profile was investigated in randomized double-blind, crossover study which included 11 healthy, obese men treated with placebo or with resveratrol 150 mg/day for 30 days. The conclusion of this study was that resveratrol induced metabolic changes in the obese humans, mimicking the effects of calorie restriction. Resveratrol decreases intra-hepatic lipid content, circulating glucose, triglycerides and inflammation markers.\textsuperscript{52}

**Resveratrol and oxidative stress**

The direct antioxidant effect of resveratrol is not prominent. Well established antioxidants, such as ascorbate and cysteine are more potent than resveratrol.\textsuperscript{53} Resveratrol has been shown to be a scavenger of hydroxyl, superoxide, metal-induced radicals and H\textsubscript{2}O\textsubscript{2}. In cardiovascular tissues, resveratrol induces antioxidant enzymes. The molecular mechanisms of induction of antioxidant enzymes by resveratrol are not completely understood. Studies have demonstrated that SIRT1 and the nuclear factor E2-related factor-2 (Nrf2) play crucial roles in this process. Resveratrol induced SOD2 upregulation in cultured human coronary arterial endothelial cells. Such upregulation can be blocked by small interfering RNA (siRNA)-mediated knockdown of SIRT1. An overexpression of SIRT1 leads to SOD2 upregulation. Nrf2 is transcription factor involved in the regulation of a number of ROS detoxifying enzymes. In Nrf2-dependent manner, in cultured endothelial cell, resveratrol induced NAD(P)H: quinone oxidoreductases (NQO1), heme oxygenase-1 (HO-1) and c-glutamylcysteine synthetase (GCLC). The listed enzymes are rate-limited for glutathione synthesis. Also, resveratrol inhibits ROS production\textsuperscript{54}. Treatment with resveratrol reduces the expression of NOS in the heart of hypercholesterolemic mouse, as well as mono-nitrogen oxides in the aorta of trauma hemorrhagic rats.\textsuperscript{55,56} The activity of the NADPH oxidase enzyme complex is reduced by resveratrol.\textsuperscript{57}

**Resveratrol and heart**

According to numerous animal studies, proposed anti-ischemic mechanisms of resveratrol include: coronary vasodilation, inhibition of atheroma formation, metabolic protection and less ischemic-reperfusion injury. In addition, resveratrol (5 μM/L) inhibited growth of cardiac fibroblasts stimulated by angiotensin II, epidermal growth factor and transforming growth factor β, which are essential in cardiac fibrosis and heart failure.\textsuperscript{57} Zheng et al. demonstrated anti-arrhythmic effect of resveratrol. In the papillary muscles of guinea pig heart, resveratrol shortened duration of action potential and decreased velocity of phase 0 depolarization. Also, it inhibited delayed after depolarization and triggered activity. These effects were due to a decrease of calcium influx and intracellular calcium concentration.

**Conclusion**

Cardioprotection includes all the described effects of resveratrol. The most important evidence for cardioprotection rendered by resveratrol comes from in vivo studies carried out on animal models of chronic heart disease that resulted in heart dysfunction. Those include hypertension, obesity, metabolic syndrome, type I diabetes, type II diabetes, viral cardiomiopathy, toxin cardiomiopathy and aging.

According to the presented results, the cardioprotective effect of resveratrol is obvious. It is complex and not well defined. It is necessary to emphasize that all positive effects of resveratrol were demonstrated mainly in in vitro studies and in studies with experimental animals, while quality clinical studies are lacking.

Further clinical studies are necessary in order to define pharmacokinetics, efficacy, adequate therapeutic doses, tolerability and possible interactions of resveratrol with other drugs.

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