Antioxidant effects of resveratrol in cardiovascular, cerebral and metabolic diseases

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1. Introduction

1.1. Structure and history of resveratrol

Resveratrol—a natural polyphenolic compound—was first discovered in the 1940s. Although initially used for cancer therapy, it has shown beneficial effects against most cardiovascular and cerebrovascular diseases. A large part of these effects are related to its antioxidant properties. Here we review: (a) the sources, the metabolism, and the bioavailability of resveratrol; (b) the ability of resveratrol to modulate redox signalling and to interact with multiple molecular targets of diverse intracellular pathways; (c) its protective effects against oxidative damage in cardio-cerebro-vascular districts and metabolic disorders such as diabetes; and (d) the evidence for its efficacy and toxicity in humans. The overall aim of this review is to discuss the frontiers in the field of resveratrol’s mechanisms, bioactivity, biology, and health-related use.

1.2. Sources of resveratrol

Resveratrol is produced by various plants as a defense against stress, injury, excessive sunlight, ultraviolet radiation, infection, and invading fungi (Singh et al., 2013). For example, the roots of the plant P. cuspidatum, much cultivated in Asia, provides a rich source of resveratrol from which commercially available trans-resveratrol (98% pure) is isolated by high-speed counter-current chromatography (Yang et al., 2001). Resveratrol is also considered a nutraceutical present in grapes, peanuts, pine trees, cassia and other plants, and many food products (Ramprasath et al., 2010;
Soleas et al., 1997). In wine, the concentration of resveratrol varies: red wines contain between 0.2 and 5.8 mg/L, depending upon the grape variety, whereas white wines contain ~0.68 mg/L (Romero-Pérez et al., 1999; Sato et al., 1997). This variation derives from the fact that red wine is extracted with the grape skin intact, whereas white wine is fermented after removal of the skin. Red wine contains more trans-resveratrol than white wine, whereas white has a higher concentration of cis-resveratrol (Feijóo et al., 2008). Concentrations of resveratrol in some natural foods are given in Table 1.

1.3. Metabolism of resveratrol

In rats and humans, resveratrol is a molecule involved in the enterohepatic cycle of metabolism. In particular, after resveratrol is taken up rapidly by enterocytes, it is metabolized to glucuronide- (3-O-glucuronide and 4’-O-glucuronoide) and sulfate-conjugates (3-O-sulfate), which are secreted back into the intestine where they may be deconjugated and reabsorbed or excreted in the feces (Walle et al., 2004; Marier et al., 2002). The enterohepatic cycle thus reduces the concentration of the free compound reaching target tissues. So, the low concentration of resveratrol found in blood is likely explained by this enterohepatic cycle and its rapid metabolism in the liver. Apart from dihydroresveratrol, the major metabolites formed are the glucuronide- and sulfate-conjugates, including glucuronides and mixed sulfate-glucuronides (Wang et al., 2005). Concentrations of these metabolites are reported to be higher than resveratrol post-absorption and to have longer half-lives (Goldberg et al., 2003). A study performed by Walle et al. using 14C-trans-resveratrol (25 mg orally) in humans showed that 70% of the resveratrol dose was absorbed by the body (Walle et al., 2004); a similar finding (~50%) was reported for rats (Marier et al., 2002). The glucuronide- and sulfate-conjugated metabolites of resveratrol peaked in plasma at 30–60 min post-administration, with a plasma half-life of 9.2 h. (Walle et al., 2004). In contrast, only small amounts of unmodified resveratrol (~5 ng/mL) were detected in plasma in a similar timeframe (Singh et al., 2013). In another study conducted on mice, rats, and humans, it was shown that within 24 h after administration of 0.03 mg/kg body weight (BW) resveratrol, nearly 50% of the resveratrol was excreted in the urine. However, because ~25% of the resveratrol was found in the urine with a dose of 1 mg/kg BW, these results suggest that resveratrol undergoes rapid gastrointestinal absorption in all the three species studied (Meng et al., 2004).

The amount of resveratrol ingested from dietary sources, such as red wine and juices, rarely exceeds 5 mg/L and often results in plasma levels that are either not detectable or several orders of magnitude below the micromolar concentrations that are employed in experimentation in vitro, i.e., ~32 nM to 100 μM (Smoliga et al., 2011). For example, administration of about 25 mg resveratrol resulted in plasma concentrations of the free form that ranged from 1 to 5 ng/mL (Almeida et al., 2009), and administration of higher doses (up to 5 g) increased the plasma resveratrol concentration to about 500 ng/mL (Boocock et al., 2007). The low doses of resveratrol observed in the plasma after ingestion are very low, as the concentrations used in vitro are not reached. However, due to its lipophilic character, tissue levels of resveratrol may be higher than those found in plasma (Timmers et al., 2012). Nonetheless, some of the biological effects of resveratrol are observed at very low concentrations (Waite et al., 2005; Pearce et al., 2008), bringing forward the idea that resveratrol exerts its major effects on intestinal tissue, affecting the rest of the body through secondary effects that are independent of the plasma levels reached by the compound (Baur et al., 2006). In rodent models, the doses employed normally range from as low as 0.1 mg/kg BW to up to 1000 mg/kg BW, with even higher or lower doses occasionally being used (Baur et al., 2006). Interestingly, studies show that the bioavailability of resveratrol can be

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**Table 1**

Resveratrol content in certain natural foods (Prasad, 2012).

| Food stuff               | Concentration range |
|--------------------------|---------------------|
| Grapes                   | 0.16–3.54 μg/g      |
| Dry grape skin           | ~24.06 μg/g         |
| Red grape juice          | ~0.5 mg/L           |
| White grape juice        | ~0.05 mg/L          |
| Red wine                 | 0.1–14.5 mg/L       |
| White wine               | 0.1–2.1 mg/L        |
| Peanuts                  | 0.02–1.92 μg/g      |
| Pistachios               | 0.09–1.67 μg/g      |

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**Fig. 1.** (a) Structure of resveratrol. (b) Structures of trans and cis isomers of resveratrol and piced.
enhanced by using more potent resveratrol analogs (i.e. SRT501) (Howells et al., 2011), by enhancing delivery methods, such as liposomal encapsulation (Narayanan et al., 2009), or by combining it with piperine, a natural product from black pepper (Piper spp.) (Johnson et al., 2011).

1.5. Aims of the review

Studies performed in vivo and in vitro have shown that resveratrol exerts pleiotropic effects and can prevent or slow the progression of several pathological conditions, including cardiovascular and metabolic disorders, such as diabetes, and reporting also the production of free radicals that lead to the oxidation of low density lipoprotein (LDL) (Kovanen and Pentikäinen, 2003; Puca et al., 2013). It is well known that oxidized LDL accumulates at the site of atherosclerotic lesions (Ramprashat and Jones, 2010), contributing to the formation of macrophage foam cells that induce endothelial dysfunction (Mietus-Snyder et al., 2000), a common marker of CVD. Because it prevents lipid peroxidation, inhibits uptake of oxidized LDL, and inhibits lipoygenase activity (Maccarrone et al., 1999; Kovanen and Pentikäinen, 2003), resveratrol is a good candidate for the fight against oxidative stress in atherosclerosis (Fremont et al., 1999; Leighton et al., 1999; Bhavnani et al., 2001; Olas and Wachowicz, 2002). Oxidation of LDL cholesterol is strongly associated with risk of CVD (Holvoet, 2004). In this regard, resveratrol was found in rat liver microsomes to inhibit iron-induced, as well as ultraviolet-irradiated, lipid peroxidation and to prevent LDL oxidation by copper (Fauconneau et al., 1997; Miura et al., 2000); moreover, Rocha et al. found a reduction in oxidized LDL in rats fed on a high fat diet when treated with resveratrol for 45 days at a dose of 1 mg/kg BW/day (Rocha et al., 2009).

Resveratrol also prevents the oxidation of polyunsaturated fatty acids found in LDL (Miller and Rice-Evans, 1995), inhibits the oxidized LDL uptake in the vascular wall in a dose-dependent manner (Fremont, 2000), and prevents damage caused to lipids by peroxidation (Frankel and Waterhouse, 1993; Leighton et al., 1999). Its effect was found to be stronger than the well-known antioxidant α-tocopherol (Frankel and Waterhouse, 1993). The protective effect of resveratrol against lipid peroxidation was also found in the heart of rats exposed to low doses of doxorubicin, an antitumor drug that causes oxidative stress (Dudka et al., 2012), found in the heart of rats exposed to low doses of doxorubicin, an antitumor drug that causes oxidative stress (Dudka et al., 2012).

2. Antioxidant properties of resveratrol

2.1. Impact of resveratrol on cardiovascular diseases

2.1.1. Effects of resveratrol on lipid peroxidation

Oxidative stress is one of the risks of cardiovascular disease (CVD), such as atherosclerosis, and is characterized by the production of free radicals that lead to the oxidation of low density lipoprotein (LDL) (Kovanen and Pentikäinen, 2003; Puca et al., 2013).

| Antioxidant defense | Oxidant machinery |
|---------------------|------------------|
| Sirtuin 1           | NADPH-oxidase    |
| Peroxisome proliferator-activated receptor-γ coactivator-1α | Hypoxanthine/xanthine oxidase |
| GTP cyclohydrolase I | Myeloperoxidase |
| Tetrahydrobiopterin | eNOS uncoupling  |
| Superoxide dismutase |                   |
| Catalase            |                  |
| Glutathione peroxidase |              |
| Glutathione reductase |              |
| Glutathione-S-transferase |             |
| Heme oxygenase-1    |                  |
| Nuclear factor (erythroid-derived 2)-like 2 |                  |

2.1.2. Effects of resveratrol on antioxidant mechanisms protecting against oxidative cardiovascular pathophysiology

It has been recently demonstrated that resveratrol reduces endothelial dysfunction in vessel from dyslipidemic patients with hypertension; this antioxidant action of resveratrol was mediated by upregulation of manganese superoxide dismutase (Mn-SOD) via a mechanism dependent upon nuclear factor (erythroid-derived 2)-like 2 (NRF2) (Carrizzo et al., 2013). This finding in humans was in agreement with experimental models showing that resveratrol was able to increase Mn-SOD expression in the mouse myoblast line C2C12 via nuclear translocation and activation of sirtuin 1 (SIRT1), a NAD+-dependent class III histone deacetylase. In obese rats, Franco et al. found that the activity of both SOD and catalase (CAT) was increased in plasma by the administration of resveratrol, preventing oxidative stress and reducing the risk of hypertension (Franco et al., 2013). Similarly, hepatic expression of SIRT1 and
Mn-SOD genes was induced in wild-type rats by 0.02% resveratrol after 4 weeks of treatment (Nakata et al., 2012). The stimulation of Mn-SOD levels was also reported in cultured cardiomyocytes and in coronary artery endothelial cells (Movahed et al., 2012; Ungvari et al., 2009; Tanno et al., 2010). In human aortic smooth muscle cells, it increased the expression of heme oxygenase-1 (HO-1), which degrades pro-oxidant heme to biliverdin/bilirubin, iron, and carbon monoxide, consequently reducing ROS levels (Jiang et al., 2005). In vascular smooth muscle cell, resveratrol reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity induced by angiotensin II, and enhanced SOD activity, promoting a significant decrease in ROS generation (Zhang et al., 2013). Moreover, resveratrol inhibits the expression of NADPH oxidase in cardiovascular tissues and reduces O2 production from mitochondria (Li et al., 2013). Recently, it has been demonstrated that resveratrol-mediated upregulation of GCH-1 (GTP cyclohydrolase I) and BH4 (tetrahydrobiopterin) biosynthesis prevents endothelial nitric oxide synthase (eNOS) uncoupling and reduces ROS production in the vasculature (Carrizzo et al., 2013).

Xanthine oxidase has been shown to be an important source of oxidant production in vascular endothelium (Sabán et al., 2013) and also a contributing factor to oxidative stress during strenuous exercise. On this issue, has been demonstrated that resveratrol inhibits hypoxanthine/xanthine oxidase in mice, reducing ROS generation (Ryan et al., 2010). Moreover, it has been reported that resveratrol treatment decreases ROS levels in high-capacity runner rats especially in endurance racing; in particular, it increased the aerobic performance and upper-limb strength of these rats. This beneficial effect is mediated by enhanced mitochondrial biogenesis, with activation of the AMPK–SIRT1–PGC-1α pathway (Hart et al., 2013). Also, resveratrol inhibited oxidative stress in vivo by scavenging ROS and attenuating peroxyn radical, hydrogen peroxide (H2O2), and superoxide radical (O2•−) (Liu et al., 2003; Chen et al., 2004). In rat phaeochromocytoma (PC12) cells, which are characterized by a high level of catecholamines, 1–100 mmol/L resveratrol inhibited production of ROS (Jang and Surh, 2001).

Resveratrol has also been shown to inhibit O2•− and H2O2 production in murine macrophages stimulated by lipopolysaccharides (LPS) or phorbol esters (Martinez and Moreno, 2000). In embryonic rat cardiac cells, it prevented mitochondrial damage induced by H2O2 (He et al., 2012). Moreover, resveratrol activates an important survival signal pathway consisting in A1 and A3 adenosine receptors-mediated activation of the PI3K–AKT pathway and the AMP response element-binding protein (CREB), promoting upregulation of Bcl-2 and, hence, protecting cardiac tissue from cell death (Li et al., 2012).

In human platelets, resveratrol significantly lowers the levels of thiol proteins (Olas et al., 2004). It also hampers platelet aggregation and activation: phytoalexin seems to inhibit the interaction of platelets with collagen and thrombin in vitro in isolated platelets and in animal models. The mechanism remain unclear, but it seems that inhibition of prostaglandin H synthase 1 and cyclooxygenase-1 over COX2 represent possible mechanisms for the anti-platelet aggregation effect of resveratrol (Borriello et al., 2010).

In a wide variety of cells, such as myeloid, lymphoid, and epithelial cells, resveratrol has been shown to prevent the production of ROS induced by tumor necrosis factor (TNFα) (Manna et al., 2000). In aortic endothelial cells, resveratrol (100 nM) was found to prevent TNFα-induced oxidative stress through a reduction in NADPH oxidase activity and the production of H2O2 and O2•− (Vecchione et al., 2009a,b). Recently, Wang et al. demonstrated that resveratrol decreases apoptosis induced by oxidative stress in vascular adventitial fibroblasts of rats treated with TNF-α, acting by activating SIRT1 (Wang et al., 2013).

Other mechanisms through which resveratrol has been suggested to exert CVD-preventing antioxidant effects are:

(a) competition with coenzyme Q, decreasing oxidative chain complex III, and increasing endogenous antioxidants and phase 2 enzymes in rat cardiomyocytes (Cao and Li, 2004);
(b) antioxidant effects against linoleic acid peroxidation in sodium dodecyl sulfate and cetyltrimethylammonium bromide micelles (Fang et al., 2002; Fang and Zhou, 2008);
(c) maintenance of glutathione levels in oxidatively stressed human peripheral blood mononuclear cells, and elevation of glutathione levels in human lymphocytes activated by H2O2 (Losu, 2003; Olas et al., 2004). A strong dose-dependent induction of antioxidant genes was demonstrated when rats were supplemented with 0.3, 1, and 3 g/kg BW/day resveratro for 28 days (Hebar et al., 2005);
(d) interaction with AMP-activated protein kinase (AMPK) in diabetic LDL-receptor-deficient mice (Zang et al., 2006), and PPARγ coactivator (PGC)-1α in mouse cardiac tissue (Lagouge et al., 2006);
(e) reduction in the rate of cytochrome C oxidation by hydroxyl radicals (Turrens et al., 1997). Jihan et al. reported that resveratrol significantly reduced cytochrome C protein levels in the heart tissue of rats subjected to trauma-hemorrhage; the authors suggest that resveratrol may be important for mitochondrial membrane integrity, leading to a reduction of ROS generation (Jian et al., 2012).

2.1.3. Effects of resveratrol on nitric oxide metabolism

Nitric oxide (NO) plays a critical role in maintaining cardiovascular homeostasis (Dudzinski et al., 2006; Dudzinski and Michel, 2007; Puca et al., 2012). In the vasculature, NO is constitutively synthesized by eNOS and acts by relaxing vascular smooth muscle cells and upregulating blood flow, and so prevents thrombogenic and atherogenic processes. It has been demonstrated both in vitro and in vivo that resveratrol is involved in NO metabolism. For example, 30 μM resveratrol inhibited the contractile response to phenylephrine in isolated rat aorta (Chen and Pace-Asciak, 1996). Similarly, 70 μM resveratrol caused relaxation of isolated human saphenous vein and internal mammary artery rings (Rakici et al., 2005), and relaxed porcine arterial rings pre-contracted with KCl (Li et al., 2006). In those studies, the inhibitory effect of resveratrol was reversed by removal of the endothelium or by inhibition of eNOS. Oral et al. reported that resveratrol (1–30 μM) relaxed the contractile response of rat aortic rings to phenylephrine and KCl in an NO-dependent manner (Orallo et al., 2002); however, it was suggested that resveratrol does not affect eNOS activity, but instead inhibits NADH/NADPH oxidase, with a decreased reduction in superoxide generation, leading to improved NO bioavailability. Resveratrol rapidly increased NO production in cultured endothelial EA.hy926 cells, although at a high concentration (10 μM) (Wallnerth et al., 2002). In bovine aortic endothelial cells, 100 nM resveratrol for 15 min was found to increase NO production through phosphorylation of AKT, extracellular signal-regulated kinase (ERK)1/2, and eNOS (Wang et al., 2011). Klinge et al. proposed that resveratrol increases NO production through membrane estrogen receptors (ERs) in bovine aortic cells, human umbilical vein cells, and human microvascular endothelial cells (Klinge et al., 2005, 2008) by rapid activation of Src and ERK1/2, leading to eNOS activation. However, as demonstrated by studies on isolated porcine coronary arteries (Li et al., 2006) and murine endothelial f-2 cells (Takahashi et al., 2009), ER antagonists do not inhibit resveratrol-stimulated NO production.

Wallnerth et al. reported that the treatment of cultured endothelial cells with resveratrol (10–100 μM) for 24–72 h upregulated eNOS mRNA and protein expression levels, resulting in increased
production of NO (Wallerath et al., 2002; Conti et al., 2012). Similarly, other studies confirmed that high concentrations of resveratrol significantly enhanced eNOS gene expression and enzyme activity, and hence NO production, in vitro assays (Räthel et al., 2007; Appeldoorn et al., 2009). In contrast, Nicholson et al. (Nicholson et al., 2010) reported that exposure of HUVECs to nanomolar concentrations of resveratrol for 24 h increased the eNOS mRNA level, although eNOS protein and NO production were not affected. In the same cell line, Takahashi et al. demonstrated that 50 nM resveratrol did not alter the eNOS protein level or NO production after 24 h of treatment, whereas daily treatment for 5 days significantly increased both eNOS protein and NO production without producing any cytoprotective effects (Takahashi and Nakashima, 2011). Resveratrol also increased the synthesis of NO in ischemic re-perfused rat tissue (Hattori et al., 2002) and preserved eNOS phosphorylation in diabetic type 2 (db/db) mice (Zhang et al., 2009).

3. Impact of resveratrol on cerebrovascular diseases

Many studies have reported that the central nervous system is targeted by resveratrol. This compound is in fact able to pass the blood-brain barrier (Baur et al., 2006). Regarding its radical-scavenging activity, structural studies demonstrated that the hydroxyl group at the 4′ position of resveratrol is much easier to subject to oxidation than other hydroxyl groups in the antioxidant reaction (Caruso et al., 2004). Intrapitoneal administration of resveratrol exerted neuroprotective effects, upregulating several endogenous antioxidant enzymes, such as SOD and CAT, in the brain of healthy rats (Mokni et al., 2007). Regarding the various isofoms of SOD, SOD2 plays a more important role against oxidant-induced mitochondrial oxidative stress and cytotoxicity in neuronal cells (Vincen et al., 2007). Fukui et al. demonstrated in HT22 neural cells that the neuroprotective effect of resveratrol after glutamate-induced cytotoxicity is largely independent of its direct antioxidant activity; rather, this effect was mediated by induction of SOD2 expression via activation of the PI3K–Akt–GSK-3β–β-catenin signaling pathway (Fukui et al., 2010). In rats, prolonged administration of resveratrol improved colchicine-induced cognitive impairment, reduced malondialdehyde—an indicator of lipid peroxidation and nitrite levels—and restored depleted glutathione (GSH), a ROS scavenger (Kumar et al., 2007).

It is interesting that resveratrol might be involved in the attenuation of neuroinflammatory responses because it is able to reduce the concentration of 8-iso-prostaglandin F2α, an indicator of free-radical generation in rat microglia (Candelario-Jalil et al., 2007). It has also been shown that resveratrol inhibits COX1, but does not affect the expression of COX2 (Davinielli et al., 2012). Since nuclear factor-κB (NF-κB) signaling activation also plays an important role in neurodegeneration, a link between Alzheimer’s Disease (AD) and the neuroprotective activity of resveratrol is its ability to reduce, in cultured rat astroglia C6 cells, the expression of genes modulated by NF-κB, such as inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2), as well as cathepsin and NO (Kim et al., 2006). Resveratrol also attenuates LPS-stimulated NF-κB activation in primary murine microglia and astrocytes, suggesting that the inflammatory responses induced by LPS could be limited by resveratrol (Lu et al., 2010).

In experimental models of stroke, Sinha et al. have shown a significant attenuation of malondialdehyde and reduced GSH in the rat middle-cerebral-artery occlusion model after 21 days of treatment with 20 mg/kg BW trans-resveratrol (Sinha et al., 2002). Moreover, resveratrol significantly decreased oxidative stress markers, including serum glycated albumin and urinary hydroxyguanosine, in stroke-prone spontaneously hypertensive rats (Mizutani et al., 2001). Also, studies performed on ischemia–reperfusion models have demonstrated that resveratrol inhibits peroxisome proliferator-activated receptors alpha (PPARα) (Inoue et al., 2003) and reduces NF-κB p65 expression (Wang et al., 2003).

3.1. Resveratrol and SIRT1

Several studies have attributed resveratrol the capacity to stimulate the activity of SIRT1 (Alcain and Villalba, 2009). Consequently, resveratrol administration appears to mimic caloric restriction (Baur et al., 2006). A calorie-restricted diet has been demonstrated to attenuate AD pathogenesis through an increase in SIRT1 activity in a mouse model of AD (Saiko et al., 2008), and also to reduce β-amyloid (Aβ) deposition and Aβ-associated neuropathology in different animal models (Wang et al., 2005; Patel et al., 2005; Gentile et al., 2009). Kim et al. showed in a transgenic AD mouse model that resveratrol reduced neurodegeneration through a decrease in the acetylation of known SIRT1 substrates, for example peroxisome-proliferator-activated receptor gamma coactivator alpha (PGC-1α) and p53 (Kim et al., 2006). Resveratrol-activated SIRT1 also reduced amyloid neuropathology in the brains of Tg2576 mice and protected cells against Aβ-induced ROS production (Kelsey et al., 2010). Taking into account that resveratrol can be considered a neuroprotective compound in the context of AD, it can be speculated that the ability to counteract Aβ toxicity is due to its antioxidant properties, but also due to SIRT1 activation.

The anti-amyloidogenic activity of resveratrol has been reported in several studies: for example, Riviere et al. showed that more than other stilbenes, resveratrol inhibits β-amyloid peptide polymerization in vitro, even though its anti-amyloidogenic mechanism remained unknown (Riviere et al., 2007). As illustrated by Marambaud and colleagues, resveratrol promotes clearance of intracellular Aβ by activating proteasomal degradation (Marambaud et al., 2005). Moreover, SIRT1 overexpression reduces Aβ pathology in APP-expressing neuronal cultures by delaying Aβ synthesis (Marambaud et al., 2005; Tang and Chua, 2008). Feng et al. demonstrated that resveratrol disrupts Aβ hydrogen binding, preventing fibril formation by destabilizing preformed fibrils without affecting oligomerization (Feng et al., 2009). Furthermore, studies have shown that the protective effects of resveratrol on β-amyloid-induced toxicity are related to activation of PKC or AMPK (Han et al., 2004; Karuppagounder et al., 2009).

3.2. Resveratrol and Nrf2

Nrf2 is a key regulator of cellular antioxidant responses and appears to be a good candidate for neuroprotection in AD. In fact, Nrf2 regulates the expression of genes encoding antioxidant and detoxifying proteins, such as glutathione S-transferase (GST), glutathione synthetase (GSS), HO-1, and NAD(P)H-quinone oxidoreductase (Scapagnini et al., 2011). Under basal conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1), which facilitates its polyubiquitilation and proteasome-mediated degradation. KEAP1 functions as a sensor of stress signals. Exposure to oxidants disrupts the KEAP1–Nrf2 complex, stabilizing Nrf2 and allowing it to accumulate in the nucleus. Nrf2 activates the transcription of its target genes via antioxidant response elements (AREs) in their promoter regions, binding as a heterodimer with members of the Maf and Jun families (Davinielli et al., 2012). To date, only few studies have shown that the activation of Nrf2 and of its antioxidant genes by resveratrol treatment is sufficient to protect against AD. However, Chen et al. reported that resveratrol is able to increase the expression of HO-1 and GSH, protecting PC12 cells from oxidative stress via activation of the Nrf2–ARE signaling pathway (Chen et al., 2005), which does
suggest a potential for the treatment of AD. Similarly, resveratrol was able to induce HO-1 in primary neuronal cultures, presumably through the activation of NRF2 (Zhuang et al., 2003). The neuroprotective actions of HO-1 are attributable to the formation of biliverdin and bilirubin during heme degradation, both of which can serve as ROS scavengers (Otterbein and Choi, 2000; Stocker et al., 2000). In conclusion, NRF2 is an attractive target for the discovery of natural neuroprotective agents, such as resveratrol.

4. Impact of resveratrol on diabetes

It has been proposed that oxidative stress caused especially by a sedentary lifestyle and an unhealthy diet is an important risk factor for the development of diabetes. Some studies have proposed resveratrol as a possible candidate for diabetes prevention.

4.1. Resveratrol and NAD(P)H oxidase

Activation of NAD(P)H oxidase contributes to vascular oxidative stress in experimental diabetes (Vecchione et al., 2006). In particular, TNFα-mediated activation of NAD(P)H oxidase is mainly responsible for the generation of the oxidative stress encountered in the coronary microcirculation in type 2 diabetes (Gao et al., 2007; Vecchione et al., 2007). The $\cdot O_2^-$ derived from NAD(P)H oxidase can be dismutated to produce $H_2O_2$ (Papa and Skulachev, 1997) or can be the cause of nitrative stress: in fact, the interaction of $\cdot O_2^-$ with NO produces peroxynitrite, which leads to protein tyrosine nitration generating nitrotyrosine, an index of reactive nitrogen species; it also reduces NO bioavailability, causing endothelial dysfunction (Shah and Channon, 2004). Increased nitrotyrosine stress and peroxynitrite formation are associated with diabetes development, as demonstrated in various studies (Pacher et al., 2007; Frustaci et al., 2000; Pacher and Szabo, 2006). For example, nitrotyrosine content was found to be high in microvascular endothelial cells of diabetic patients (Ceriello et al., 2002). In the aorta of diabetic mice, resveratrol was found to downregulate NAD(P)H oxidase expression, and thus contributed to a reduction in $\cdot O_2^-$ production (Zhang et al., 2009). Aortic nitrotyrosine protein and $H_2O_2$ levels also attenuate after treatment with resveratrol (Zhang et al., 2009). In type 2 diabetic mice, Kitada et al. demonstrated that resveratrol normalized Mn-SOD activity, through a reduction in tyrosine-nitrate modifications and decreased urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG), a marker of oxidative stress, and $O_2^-$ levels (Kitada et al., 2011).

4.2. Resveratrol and nuclear factor-kB

Hyperglycemia—the hallmark of diabetes—can also induce oxidative stress via several pathways that converge on NF-kB, the activation of which in turn contributes to a further enhancement of pro-inflammatory cytokines, oxidative stress, and apoptosis (Kern, 2007; Singh et al., 2011). In this context, resveratrol was demonstrated to produce several anti-diabetic effects, such as reduction of circulatory pro-inflammatory cytokines, inhibition of apoptosis, and concomitant enhancement of antioxidant defenses (Lee et al., 2011; Palsamy and Subramanian, 2010; Sharma et al., 2009, 2011; Zhang et al., 2010). It has been documented that short-term treatment of diabetic subjects with resveratrol inhibited the activation of NF-kB at transcriptional or post-transcriptional levels (Lee et al., 2009; Zhang et al., 2010). Resveratrol may attenuate the inflammatory process through a reduction of oxidative damage and NF-kB activity (Kubota et al., 2009).

4.3. Resveratrol and oxidative markers

Oxidation of glucose is another mechanism occurring in diabetes (Maritim et al., 2003). Proteins such as hemoglobin and antioxidant enzymes can be glycated in the presence of a high concentration of oxidated glucose. This leads to a reduction in detoxification of ROS, resulting in lipid-, protein-, and DNA-peroxidation, and, finally, apoptosis (Rains and Jain, 2011). Glycated hemoglobin (HbA1c) is a good marker for diagnosis and prognosis of complications in diabetes, such as retinopathy, nephropathy, and neuroopathy (Howlett and Ashwell, 2008). For example, it was shown that reduction of HbA1c by only 1 unit (8–7%) can reduce the risk of retinopathy by over 30% (Kowluru and Chan, 2007). Four months of resveratrol supplementation was found to reduce HbA1c levels in diabetic rats (Soufi et al., 2012).

Another good marker of oxidative and antioxidant homeostasis is 8-isoprostane (8-iso-prostaglandin F2α), a product of the oxidation of arachidonic acid present in phospholipids (Morrow et al., 1995). It was reported that plasma levels of 8-isoprostane increased with diabetes-induced lipid peroxidation and oxidative stress (Ndisang et al., 2010; Salim et al., 2010). Moreover, retinal 8-isoprostane increased during hypoxia-induced retinopathy (Kimura et al., 2007), and resveratrol reduced 8-isoprostane levels in blood and retinal tissue of normal and diabetic rats, demonstrating that resveratrol has a strong antioxidant effect and attenuates oxidative stress (Soufi et al., 2012).

In diabetes, the attenuation of oxidative stress reduces the level of activated caspases and, thus, reduces apoptosis. In fact, resveratrol was found to modulate embryonic oxidative stress and apoptosis in diabetic pregnancy: in particular, it reduced oxidative stress by restoring the level of reduced glutathione, total thiol, lipid peroxidation, and 4-hydroxy-2-non-enal (HNE) in diabetic dams (Singh et al., 2013).

5. Toxicity of resveratrol

Many studies have investigated the toxic effect of resveratrol. Most of the data available, both in human and in animal models, suggest that resveratrol does not have a significant toxic effect in the wide range of concentrations tested (Ramprasath and Jones, 2010). For example, no toxic effects were found in rats after oral administration of 20 mg/kg BW/day for 29 days, a dose higher than that produced by one glass of red wine per day (Juan et al., 2002). Moreover, no toxic effects were observed in rats given a supplementation of 300 mg resveratrol/day for 4 weeks. In humans, Boocock et al. found no toxicity after administration of a single dose of up to 5 g resveratrol (Boocock et al., 2007). In addition, clinical, biochemical, and hematological indices revealed no serious toxic effects in 44 healthy volunteers (10–12 per group) administered resveratrol for 29 days at a daily dose of 0.5, 1.0, 2.5, or 5.0 g (Brown et al., 2010). However, adverse effects found in 28 participants were considered possibly due to resveratrol: common symptoms were gastrointestinal in nature, particularly diarrhea, nausea, and abdominal pain, at a dose of 1 g. Typically, gastrointestinal symptoms occurred ~1 h after administration, and improved during the course of the day. However, all the events were graded as mild, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Ramprasath and Jones, 2010). Based on the these findings, the authors suggested that daily doses of resveratrol for subsequent clinical evaluation should not exceed 1 g (Brown et al., 2010). Chow et al. enforced those findings and demonstrated that 1 g resveratrol taken once daily for 4 week was generally well tolerated in healthy participants (Chow et al., 2010): all the reported adverse events were CTC grade 1 or 2, with many being mild and transient. The frequency of the side
effects experienced was consistent with that observed in a trial described by Brown et al. (Brown et al., 2010) and in shorter-term studies involving fractionated daily doses (la Porte et al., 2010; Almeida et al., 2009; Nunes et al., 2009).

Finally, it is important to underline that resveratrol can exhibit pro-oxidant activities in the presence of transition metal ions, such as copper, leading to oxidative breakage of cellular DNA (de la Lastra and Villegas, 2007).

6. Clinical trials on the antioxidant effects of resveratrol

To date, only a small number of clinical trials on the antioxidant effects of resveratrol have been reported. The most significant clinical trials are summarized in Table 3. Ghanim et al. (2010) investigated the effects of resveratrol on different markers of inflammation and oxidative stress in a randomized placebo-controlled trial: the study was performed on 20 healthy adults receiving a 200 mg *P. cuspidatum* extract supplement containing 40 mg of resveratrol, for 6 weeks. Resveratrol did not alter fasting plasma concentrations of cholesterol (total, LDL, and HDL), triglycerides, or leptin compared with placebo. However, the treatment reduced ROS levels, TNF-α, and IL-6, and suppressed NF-κB in mononuclear cells. Additionally, C-reactive protein (CRP)—another important marker of inflammation—was significantly reduced.

Ghanim et al. also conducted a separate crossover placebo-controlled trial on 10 healthy humans fed with a high-fat, high-carbohydrate meal (Ghanim et al., 2011). The 100 mg resveratrol supplementation used significantly increased NRF2-binding activity following the meal, and significantly increased mRNA expression of important antioxidant enzymes, such as the NAD(P)H dehydrogenase [quinone] 1 (NQO-1) and glutathione S-transferase P1 (GST-P1). Resveratrol also attenuated the postprandial rise in cluster of differentiation 14 (CD14), IL-1β mRNA, and toll-like receptor 4 (TLR4) protein in mononuclear cells, while also

Table 3
Summary of clinical trials on antioxidant effects of resveratrol. ↓, downregulation; ↑, upregulation.

| References          | Sample population          | Resveratrol dose | Duration | Molecular-level effects                  |
|---------------------|----------------------------|------------------|----------|------------------------------------------|
| Ghanim et al. (2010) | 20 healthy adults          | 40 mg            | 6 weeks  | ↓ROS<br>↑TNF-α<br>↓P47(phox)<br>↓NFκB<br>↓JNK-1<br>↑CRP<br>↑PTP-1B<br>↑SOCS-3 |
| Ghanim et al. (2011) | 4 healthy men and 6 women  | 100 mg + 75 mg grapeskin polyphenols | 1 week   | ↓ROS<br>↑Nrf-2<br>↑TLR-4<br>↑CD14<br>↓IL-1β<br>↑SOCS-3 |
| Brasnyo et al. (2011)| 19 diabetic men            | 5 mg twice daily | 4 weeks  | ↓ROS<br>↑pAk |
| Timmers et al. (2011)| 11 healthy obese men       | 150 mg twice daily | 30 days  | ↓glucose<br>↑AMPK<br>↑insulin<br>↑SIRT1<br>↑ROS<br>↑PGC1α |
| Bo et al. (2013)     | 50 healthy adult smokers   | 500 mg           | 30 days  | ↓ROS<br>↑CRP<br>↑TG |

Fig. 2. Representative scheme of the biological effects recruited by resveratrol and their involvement in cardiovascular, metabolic and cerebrovascular diseases.
decreasing plasma endotoxin. These data suggest strong antioxid-
ant and anti-inflammatory effects of resveratrol in response to
the high-fat, high-carbohydrate meal and a potential use in
reducing the risk of atherosclerosis and diabetes.

Interestingly, in a randomized double-blind placebo-controlled
crossover study, 5 mg trans-resveratrol supplementation, given
twice daily for 4 weeks improved insulin sensitivity and lowered
blood glucose levels, delaying its peak (Brasnyo et al., 2011).
Among the mechanisms suggested to exert these beneficial effects,
the authors indicated decreased oxidative stress and increased AKT
phosphorylation.

The metabolic effects of resveratrol have also been studied in
obese men (Timmers et al., 2011): supplementation with 75 mg
resveratrol for 30 days reduced sleeping- and resting-metabolic
rate in the absence of body weight changes; moreover, resveratrol
increased SIRT1 protein levels in muscle and reduced blood inflam-
mation markers.

Finally, Bo et al. evaluated the effects of resveratrol on healthy
smokers: they found that 500 mg resveratrol for 30 days signifi-
cantly increased total antioxidant status values (Bo et al., 2013).
The authors suggested that resveratrol may reduce the risk of car-
diovascular diseases in smokers.

7. Conclusion and recommendations

In this review, we have focused our attention on the antioxidant
effects of resveratrol and on its molecular mechanisms. The neu-
ralization of free radicals prevents the activation of redox-sensi-
tive molecules involved in the modulation of biological process,
such as cell cycle and mitochondrial biogenesis, and of a wide
range of chronic diseases, including cardiovascular, neurological,
and metabolic disorders (Fig. 2). It is necessary to underline that
all antioxidant substances must be used at the proper dose, since
high concentrations may induce undesirable effects, such as
non-specific reactions with proteins, and decrease antioxidant
properties. Although a beneficial “in vitro” antioxidant effect of
resveratrol on vessels from patients showing vascular dysfunction
is well defined, further clinical trials need to determine resvera-
trol’s mechanism of action, its safety, and its toxicity. In the light
of existing data, it is clear that grapes—and wine—should be con-
sidered as integral component of fruit- and vegetable-enriched
diets that are recommended by health authorities and widely
accepted as beneficial for human health and disease prevention.

8. Conflict of interest

The authors declare that there are no conflicts of interest.

List of abbreviations

- O₂⁻ Superoxide anion
8- OHDГ
8- 8-hydroxy-2’-deoxyguanosine
AMPK 5’ adenosine monophosphate-activated protein
kinase
AREs Antioxidant response elements
Aβ Beta amyloid
BBB Blood-brain barrier
Bcl-2 B-cell lymphoma 2
BH4 Tetrahydrobiopterin
BW Body weight
CAT Catalase
CD14 Cluster of differentiation 14
COX Cyclooxygenase
CREB cAMP response element-binding protein
CRP C-reactive protein
CTCAE Common Terminology Criteria for Adverse Events
CVD Cardiovascular diseases
eNOS Endothelial nitric oxide synthase
ER Estrogen receptors
ERK Extracellular signal-regulated kinase
GCH-1 GTP cyclohydrolase 1
GSH Reduced glutathione
GSK-3β Glycogen kinase 3 beta
GS Glutathione synthetase
GST Glutathione S-transferase
GST-p1 Glutathione S-transferase p1
H₂O₂ Hydrogen peroxide
HbA1c Glycated hemoglobin
HCR High capacity runner
HDL High density lipoprotein
HNE 4-hydroxy-2-non-enal
HO-1 Heme oxygenase-1
IL-6 Interleukin 6
iNOS Inducible nitric oxide synthase
Keap1 Kelch-like ECH-associating protein 1
LDL Low density lipoprotein
LPS Lipopolysaccharides
Mn- Manganese superoxide dismutase
NADPH Reduced nicotinamide adenine dinucleotide phosphate
NF-κβ Nuclear factor-κβ
NO Nitric oxide
NQO-1 NAD(P)H dehydrogenase [quinone] 1
NRF-2 Nuclear factor (erythroid-derived 2)-like 2
PGC-1α Peroxisome-proliferator-activated receptor gamma
PK coactivator 1α
PGE2 Prostaglandin E2
PI3K Phosphatidylinositol 3-kinases
PKC Protein kinase C
PPAR Peroxisome proliferator-activated receptors
ROS Reactive oxygen species
SIRT-1 Sirtuin-1 NAD+-dependent class III histone
decaylases
SOD Superoxide dismutase
TAS Total antioxidant status
TLR4 Toll-like receptor 4
TNF-α Tumor necrosis factor alpha

References

Alcain, F.J., Villalba, J.M., 2009. Sirtuin activators. Expert Opin. Ther. Pat. 19 (4), 403–
414.
Alissa, E.M., Ferns, G.A., 2012. Functional foods and nutraceuticals in the primary
prevention of cardiovascular diseases. J. Nutr. Metab. 2012, 569486.
Almeida, L., Vaz-da-Silva, M., Falcao, A., Soares, E., Costa, R., Loureiro, A.I.,
Fernandes-Lopes, C., Rocha, J.F., Nunes, T., Wright, L., Soares-da-Silva, P., 2009.
Pharmacokinetic and safety profile of transresveratrol in a rising multiple-dose
study in healthy volunteers. Mol. Nutr. Food. 53 (1), S7–S15.
Andres-Lacueva, C., Urpi-Sarda, M., Zamora-Ros, R., Lamuela-Raventos, R.M., 2009.
In: Fraga, C.G. (Ed.), Plant Phenolics and Human Health: Biochemistry, Nutrition
and, Pharmacology. pp. 265–299.
Appeldoorn, M.M., Venema, D.P., Peters, T.H., Koenen, M.E., Arts, I.C.W., Vincken, J.P.,
Gruppen, H., Renier, J., Hoffmann, P.C., 2009. Some phenolic compounds increase
the nitric oxide level in endothelial cells in vitro. J. Agric. Food Chem. 57, 7093–
7099.
Azorín-Ortuño, M., Yáñez-Gascón, M.J., Vallejo, P., Pallarés, F.J., Larroso, M., Lucas, R.,
Morales, J.C., Tomás-Barberán, F.A., García-Conesa, M.T., Espín, J.C., 2011.
Metabolites and tissue distribution of resveratrol in the pig. Mol. Nutr. Food
Res. 55 (8), 1154–1168.
Baur, J.A., Sinclair, D.A., 2006. Therapeutic potential of resveratrol: the in vivo
evidence. Nat. Rev. Drug Discov. 5, 493–506.
Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Calva, A., Prabhbu, V.V., Amrane, P., Resnick, M.S., Lewis, K., Kiezun, A., Sblattero, D., Schine, K.C., Resch, G., Ornin, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.C., Lakatta, E.G., Le Couteur, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., Sinclair, D.A., 2006. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444, 337–342.

Bhavnani, B.R., Cecutti, A., Gerulath, A., Woolever, A.C., Berco, M., 2001. Comparison of the antioxidant effects of euglenin, eugenol, and trans-resveratrol against human low density lipoprotein oxidation in postmenopausal women. Menopause 8, 408–419.

Bo, S., Ciccone, C., Castiglione, A., Gambino, R., De Michieli, F., Villoni, P., Durazzo, M., Cavallo-Perin, P., Cassader, M., 2013. Anti-inflammatory and antioxidant effects of resveratrol in healthy smokers a randomized, double-blind, placebo-controlled, cross-over trial. Curr. Med. Chem. 20 (10), 1323–1331.

Boocock, D.J., Patil, K.K., Faust, G.E., Normolle, D.P., Marczylo, T.H., Crowell, J.A., Brenner, D.E., Booth, T.D., Gescher, A., Steward, W.P., 2007. Quantitation of trans-resveratrol and detection of its metabolites in human plasma and urine by high performance liquid chromatography. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 854, 270–277.

Borriello, A.,ucciola, V., Della Ragione, F., Galli, P., 2010. Dietary polyphenols: focus on resveratrol, a promising agent in the prevention of cardiovascular disease and control of glucose homeostasis. Nutr. Metab. Cardiovasc. Dis. 20 (8), 618–625.

Brasnyo, P., Molnar, G.A., Mohas, M., Marko, L., Laczky, B., Cohj, E., Mikolas, E., Szijarto, I.A., Merei, A., Halmai, R., Meszaros, L.G., Sumegi, B., Wittmann, L., 2011. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br. J. Nutr., 1–7.

Brown, V., Patil, K., Viskaduraki, M., Crowell, J.A., Perloff, M., Booth, T.D., Vasilin, B., Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., 2007. Pharmacology of endothelial nitric oxide synthase. Annu. Rev. Pharmacol. Toxicol. 47, 91–116.

Conti, V., Corbi, G., Russomanno, G., Simeon, V., Ferrara, N., Filippelli, W., Limongelli, Brown, V., Patel, K.R., Faust, G.E., Normolle, D.P., Marczylo, T.H., Crowell, J.A., Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., 2007. Antioxidant effects of resveratrol and its analogues against the free-radical-induced peroxidation of linoleic acid in micelles. Chemistry 8, 4191–4198.

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Lee, S.M., Yang, H., Tartar, D.M., Gao, B., Luo, X., Ye, S.Q., Zaghouani, H., Fang, D.,
Lasa, A., Churruca, I., Eseberri, I., Andrés-Lacueva, C., Portillo, M.P., 2012.
Klinge, C.M., Wickramasinghe, N.S., Ivanova, M.M., Dougherty, S.M., 2008.
Kitada, M., Kume, S., Imaizumi, N., Koya, D., 2011. Resveratrol improves oxidative
Kimura, T., Takagi, H., Suzuma, K., Kita, M., Watanabe, D., Yoshimura, N., 2007.
Kim, Y.A., Lim, S.K., Rhee, S.H., Park, K.Y., Kim, C.H., Choi, B.T., Lee, S.J., Park, Y.M.,
Kern, T.S., 2007. Contributions of inflammatory processes to the development of the
Kelsey, N.A., Wilkins, H.M., Linseman, D.A., 2010. Nutraceutical antioxidants as
Karuppagounder, S.S., Pinto, J.T., Xu, H., Chen, H.L., Beal, M.F., Gibson, G.E., 2009.
Juan, M.E., Maijo, M., Planas, J.M., 2010. Quantification of transresveratrol and its metabolites in rat plasma and tissues by HPLC. J. Pharm. Biomed. Anal. 51, 391–
Karuppagounder, S.S., Pinto, J.T., Xu, H., Chen, H.L., Beal, M.F., Gibson, G.E., 2009.
Juan, S.H., Cheng, T.H., Lin, H.C., Chu, Y.L., Lee, W.S., 2005. Mechanism of oxidative DNA damage and endothelial function in a diet and wine intervention study in humans. Drug Exp. Clin. Res. 25, 133–141.
KISA). Yakugaku Zasshi 83, 988–990.
Klingspor, W.E., Oates, J.A., Roberts 2nd, L.J., 1995. Increase in circulating products of lipid peroxidation in FST-1 knockout mice. Int. J. Cancer 125, 1–8.
Klotz, T., Vasterling, J.R., Morgan, J., Smith, A., 2002. The effects of dietary polyphenols regulate vascular endothelial cell expression of genes and proteins. Curr. Pharm. Des. 8, 1869–1878.
Klein, P.T., Pentikainen, M.O., 2003. Circulating lipoproteins as proinflammatory and anti-inflammatory particles in atherogenesis. Curr. Opin. Lipidol. 14, 411–
Klinge, C.M., Blankenship, K.A., Risinger, K.E., Bhatnagar, S., Noisín, E.L., Sunanasekera, W.K., Zhao, L., Brey, D.M., Keynton, R.S., 2005. Resveratrol and resveratrol diesters rapidly activate MAPK signaling through estrogen receptors α and β in endothelial cells. Biol. Chem. 386, 740–747.
Klinge, C.M., Wickamkuti, N.S., Ivanova, M.M., Dougerty, S.M., 2008. Resveratrol stimulates nitric oxide production by increasing estrogen receptor α-Src-caveolin-1 interaction and phosphorylation in human umbilical vein endothelial cells. Faseb J. 22 (7), 2185–2197.
Kohnen, S., Franck, T., van Antwerpen, P., Bouideltia, K.Z., Mouly-Mickalad, A., Deby, C., Moguilevsky, N., Deby-Dupont, G., Lamy, M., Serteyn, D., 2007. Resveratrol inhibits the activity of equine neutrophil myeloperoxidase by a direct interaction with the enzyme. J. Agric. Food Chem. 55 (20), 8080–8087.
Kovanen, P.T., Pentikainen, M.O. 2003. Circulating lipoproteins as proinflammatory and anti-inflammatory particles in atherogenesis. Curr. Opin. Lipidol. 14, 411–
Kowluru, R.A., Chan, P.S., 2007. Oxidative stress and diabetic retinopathy. Exp. Diabetol. Res. 2007, 95103.
Kobata, K., Kurisawa, T., Kishikawa, H., Satohika, S., Noda, K., Ozawa, O., Oyke, Y., Ishida, S., Tsubota, K., 2009. Prevention of ocular inflammation in endotoxin-induced uveitis with resveratrol by inhibiting oxidative damage and nuclear factor-kappaB activation. Invest. Ophthalmol. Vis. Sci. 50, 3512–3519.
Kumar, A., Nadu, P.S., Seghal, N., Padi, S.S.V., 2007. Neuroprotective effects of resveratrol against intracerebroventricular colchicine-induced cognitive impairment and oxidative stress in rats. Pharmacol. Ther. 75 (1), 17–28.
La Porte, C., Voduc, N., Zhang, G., Seguin, I., Tardif, D., Singhal, N., Cameron, D.W., 2010. Steady-state pharmacokinetics and tolerability of trans-resveratrol 2000 mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects. Clin. Pharmacokinet. 49, 449–464.
Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Leirin, C., Daussin, F., Messadeq, N., Milne, J., Lambert, P., Elliott, A., Roberts 2nd, L.J., 1995. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. N. Engl. J. Med. 332, 1198–1203.
Mouhabed, A., Xu, L., Thandapilly, S.J., Louis, X.L., Netland, T., 2012. Resveratrol protects adult cardiomyocytes against oxidative stress mediated cell injury. Arch. Biochem. Biophys. 527, 74–80.
Nakata, R., Takahashi, S., Inoue, H., 2012. Recent advances in the study of resveratrol. Biol. Pharm. Bull. 35, 274–279.
Narayanan, N.K., Nargi, D., Randolph, C., Narayanan, B.A., 2009. Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer cells’ resistance to PTEN knockout mice. Int. J. Cancer 125, 1–8.
Nisland, J.F., Lane, N., Syed, N., Jadhav, A. 2010. Up-regulating the heme oxygenase system with hemin improves insulin sensitivity and glucose metabolism in adult spontaneously hypertensive rats. Endocrinology 151, 549–560.
Nicholson, S.K., Tucker, G.A., Brameld, J.M., 2010. Physiological concentrations of dietary polyphenols regulate vascular endothelial cell expression of genes important in cardiovascular health. Br. J. Nutr. 103, 1388–1403.
Nisoli, E., Tonelli, C., Cardile, G., Forzi, V., Brade, R., Tedesco, L., Falcone, S., Valerio, A., Cantoni, O., Clementi, E., Moncada, S., Carruba, M.O., 2005. Calorie restriction delays the development of Alzheimer disease in transgenic mice. Proc. Natl. Acad. Sci. U. S. A. 102, 1361–1366.
Nonomura, S., Kanagawa, H., Makimoto, A., 1963. Chemical constituents of polygonaceous plants. I. Studies on the components of Ko-jokon (Polygonum cuspidatum Sieb. et Zucc.). Yakugaku Zasshi 83, 988–990.
Nunes, T., Almeida, L., Rocha, J.F., Falcão, A., Fernandes-Lopes, C., Loureiro, A., Wright, L., Vaz-da-Silva, M., Soares-da-Silva, P., 2009. Pharmacokinetics of trans-resveratrol following repeated administration in healthy elderly and young subjects. Clin. Pharmacol. 47, 1477–1482.
Olás, B., Wachowicz, B., 2002. Resveratrol and vitamin C as antioxidants in blood platelets. Thromb. Haemost. 88, 90–95.
Saiko, P., Szakmary, A., Jaeger, W., Szekeres, T., 2008. Resveratrol and its analogs: a review. Phytother. Res. 22, 1362–1367.

Olas, B., Wachowicz, B., Bald, E., Glowacki, R., 2004. The protective effects of resveratrol against changes in blood platelet function in aged rats. J. Cell. Physiol. 204, 820–827.

Sinha, K., Chaudhary, G., Gupta, Y.K., 2002. Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. Life Sci. 71, 655–665.

Smoliga, J.M., Vang, O., Baur, J.A., 2011. Challenges of translating basic research into therapeutics: resveratrol as an example. J. Gerontol. B Biol. Sci. Med. Sci. 67, 157–167.

Malliaras, D., Kioumourtzoglou, M.A., O’Donnell, C.J., 2011. Resveratrol: an emerging intervention in cardiovascular disease. Heart 97, 156–167.

Turrens, J.F., Lariccia, J., Nair, M.G., 1997. Resveratrol has no effect on lipoprotein profile and does not prevent peroxidation of serum lipids in normal rats. Free Radic. Res. 27, 557–562.

Nguyen, S.V., Lainskyy, N., Mukhopadhyay, P., Pinto, J.T., Bagi, Z., Ballabh, P., Zhang, C., Pacher, P., Csiszar, A., 2009. Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. Am. J. Physiol. Heart Circ. Physiol. 297, H1876–H1881.

Sinha, K., Chaudhary, G., Gupta, Y.K., 2002. Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. Life Sci. 71, 655–665.

Smoliga, J.M., Vang, O., Baur, J.A., 2011. Challenges of translating basic research into therapeutics: resveratrol as an example. J. Gerontol. B Biol. Sci. Med. Sci. 67, 157–167.

Malliaras, D., Kioumourtzoglou, M.A., O’Donnell, C.J., 2011. Resveratrol: an emerging intervention in cardiovascular disease. Heart 97, 156–167.

Turrens, J.F., Lariccia, J., Nair, M.G., 1997. Resveratrol has no effect on lipoprotein profile and does not prevent peroxidation of serum lipids in normal rats. Free Radic. Res. 27, 557–562.

Nguyen, S.V., Lainskyy, N., Mukhopadhyay, P., Pinto, J.T., Bagi, Z., Ballabh, P., Zhang, C., Pacher, P., Csiszar, A., 2009. Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. Am. J. Physiol. Heart Circ. Physiol. 297, H1876–H1881.

Sinha, K., Chaudhary, G., Gupta, Y.K., 2002. Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. Life Sci. 71, 655–665.

Smoliga, J.M., Vang, O., Baur, J.A., 2011. Challenges of translating basic research into therapeutics: resveratrol as an example. J. Gerontol. B Biol. Sci. Med. Sci. 67, 157–167.

Malliaras, D., Kioumourtzoglou, M.A., O’Donnell, C.J., 2011. Resveratrol: an emerging intervention in cardiovascular disease. Heart 97, 156–167.

Turrens, J.F., Lariccia, J., Nair, M.G., 1997. Resveratrol has no effect on lipoprotein profile and does not prevent peroxidation of serum lipids in normal rats. Free Radic. Res. 27, 557–562.
Wallerath, T., Deckert, G., Ternes, T., Anderson, H., Li, H., Witte, K., Förstermann, U., 2002. Resveratrol, a polyphenolic phytoalexin present in red wine, enhances expression and activity of endothelial nitric oxide synthase. Circulation 106, 1652–1658.

Wang, Y.I., He, F., Li, X.L., 2003. The neuroprotection of resveratrol in the experimental cerebral ischemia. Zhonghua Yi Xue Za Zhi. 83 (7), 534–536.

Wang, D., Hang, T., Wu, C., Liu, W., 2005. Identification of the major metabolites of resveratrol in rat urine by HPLC-MS/MS. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 829, 97–106.

Wang, N., Ko, S.H., Chai, W., Li, C., Barrett, E.J., Tao, L., Cao, W., Liu, Z., 2011. Resveratrol recruits rat muscle microvasculature via a nitric oxide-dependent mechanism that is blocked by TNFα. Am. J. Physiol. Endocrinol. Metab. 300, E195–E201.

Wang, W., Yan, C., Zhang, J., Lin, R., Lin, Q., Yang, L., Ren, F., Zhang, J., Ji, M., Li, Y., 2013. SIRT1 inhibits TNF-α-induced apoptosis of vascular adventitial fibroblasts partly through the deacetylation of FoxO1. Apoptosis 18 (6), 689–701.

Yang, F., Zhang, T., Ito, Y., 2001. Large-scale separation of resveratrol, anthraglycoside A and anthraglycoside B from Polygonum cuspidatum Sieb. et Zucc by high-speed counter-current chromatography. J. Chromatogr. A 919, 443–448.

Yang, J., Dong, S., Jiang, Q., Kuang, T., Huang, W., Yang, J., 2013. Changes in expression of manganese superoxide dismutase, copper and zinc superoxide dismutase and catalase in Brachionus calyciflorus during the aging process. PLoS One 8, e57186.

Zang, M., Xu, S., Maitland-Toolan, K.A., Zuccollo, A., Hou, X., Jiang, B., Wierzbicki, M., Verbeuren, T.J., Cohen, R.A., 2006. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherosclerosis in diabetic LDL receptor-deficient mice. Diabetes 55, 2180–2191.

Zhang, H., Zhang, J., Ungvari, Z., Zhang, C., 2009. Resveratrol improves endothelial function—role of TNFα and vascular oxidative stress. Arterioscler. Thromb. Vasc. Biol. 29, 1164–1171.

Zhang, H., Morgan, B., Potter, B.J., Ma, L., Dellsperger, K.C., Ungvari, Z., Zhang, C., 2010. Resveratrol improves left ventricular diastolic relaxation in type 2 diabetes by inhibiting oxidative/nitrative stress: in vivo demonstration with magnetic resonance imaging. Am. J. Physiol. Heart. Circ. Physiol. 299, H985–H994.

Zhang, J., Chen, J., Yang, J., Xu, C.W., Pu, P., Ding, J.W., Jiang, H., 2013. Resveratrol attenuates oxidative stress induced by balloon injury in the rat carotid artery through actions on the ERK1/2 and NF-kappa B pathway. Cell. Physiol. Biochem. 31 (2–3), 230–241.

Zhuang, H., Kim, Y.S., Koehler, R.C., Doré, S., 2003. Potential mechanism by which resveratrol, a red wine constituent, protects neurons Ann. N. Y. Acad. Sci. 993, 276–288.