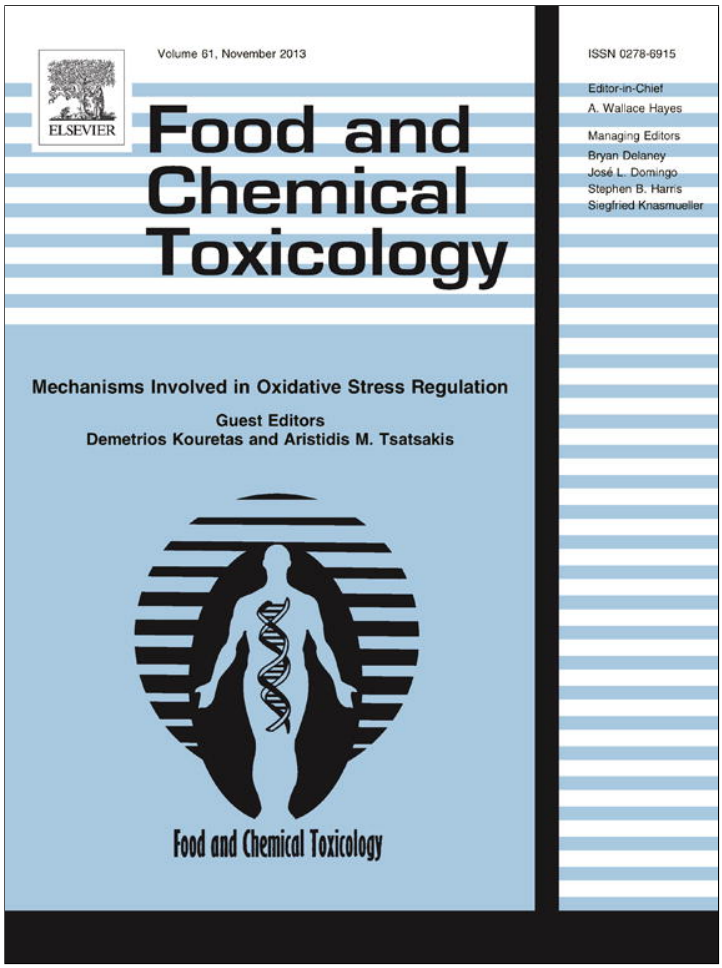

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Antioxidant effects of resveratrol in cardiovascular, cerebral and metabolic diseases

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ABSTRACT

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. Introduction

1.1. Structure and history of resveratrol

Resveratrol—3,4′,5-trihydroxy-*trans*-stilbene (MW: 228.2)—is a natural non-flavonoid polyphenol compound containing a stilbene structure similar to that of estrogen diethylstilbestrol (Fig. 1a). It is a fat-soluble compound existing in *cis*, *trans*-, and piceid isomeric forms (Fig. 1b). It was first isolated in 1940 from the roots of white hellebore (*Veratum grandiflorum O. Loes*) and later, in 1963, from the roots of *Polygonum cupsidatum*, a plant used in traditional Chinese and Japanese medicine (Nonomura et al., 1963). Resveratrol has been in use since ancient times as an Indian herbal preparation termed 'Darakchasava', which is derived from fermented grapes. Remarkably, the effects described for Darakchasava more than 4500 years ago (Singh et al., 2013) are the same described for resveratrol today. Today, Darakchasava is produced by several pharmaceutical companies and contains about 1.3–6.0 mg/L resveratrol (Paul et al., 1999). Despite its ancient discovery, the first real interest in resveratrol came in 1992 when it was postulated to explain some of the cardio-protective effects of red wine (Siemann and Creasy, 1992). It was suggested to be the solution to the "French Paradox", a term used to describe the observation that the French population had a very low incidence of cardiovascular disease despite a high consumption of wine and saturated fat (Liu et al., 2007). In 1997, Jang and colleagues reported that resveratrol acts as a chemo-preventive agent, due to its ability to inhibit carcinogenesis at multiple stages (Jang et al., 1997). More recently, anti-inflammatory and antioxidant properties have been reported also (Baur and Sinclair, 2006; Vang et al., 2011), so today it has become a highly important natural active ingredient with potential therapeutic effects and market prospects.

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;

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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-glucuronide) 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 disulfates 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 (Andres-Lacueva et al., 2009; Polycarpou et al., 2013). In fact, the majority of orally dosed resveratrol is found in urine as sulfate- or glucuronic acid-conjugates (Singh et al., 2013). In particular, the proportion of glucuronide- and sulfate-metabolites are reported to change depending on the tissue and species considered (Juan et al., 2010; Azorín-Ortuño et al., 2011): glucuronide

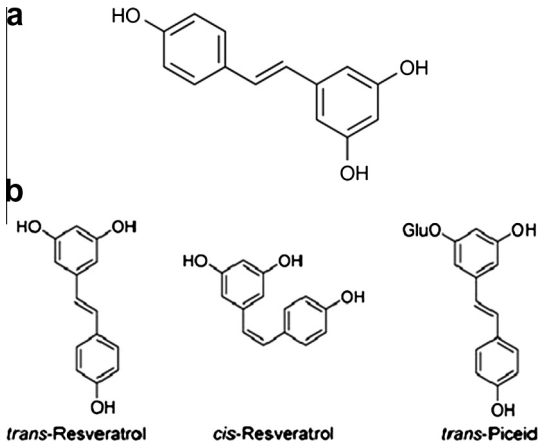

Fig. 1. (a) Structure of resveratrol. (b) Structures of *trans* and *cis* isomers of resveratrol and piceid.

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

conjugates are reported to be the main metabolites in rodents, whereas primarily sulfates are found in humans (Walle, 2011); moreover, the quantity of glucuronides is higher than sulfates in rat testes and liver, but not in lung (Juan et al., 2010). As a result, many authors are beginning to investigate the effects of resveratrol metabolites on *in vitro* and *in vivo* models: for example, resveratrol 3-*O*-D-sulfate, as well as resveratrol 3-*O*-D-glucuronide and resveratrol 4-*O*-D-glucuronide, was found to inhibit cycloxygenase (COX1 and COX2) (Calamini et al., 2010), whereas 3-*O*-D-sulfate and resveratrol 4-*O*-D-glucuronide were reported to reduce triacylglycerol content in 3T3-L1 adipocytes (Lasa et al., 2012). Recently, Polycarpou et al. demonstrated that resveratrol glucoronides are able to arrest the growth of different human colon cancer cells (Polycarpou et al., 2013). Thus, many of the effects reported for resveratrol may be due to the action of resveratrol's metabolites.

1.4. Bioavailability of resveratrol and plasma levels

Many studies have shown that resveratrol, like other polyphenols, has very low bioavailability (Goldberg et al., 2003). The bioavailability and pharmacokinetics of resveratrol have been studied in humans and in animal models. In humans, resveratrol is rapidly taken up after oral consumption of a low dose, with the plasma resveratrol concentration peaking about 30 min after consumption (Goldberg et al., 2003); in rats, the plasma half-life of resveratrol was reported to be 12–15 min after oral administration (Gescher and Steward, 2003). A study performed by Walle et al. using ^{14}C-*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

Table 2
Antioxidant activity of resveratrol. The antioxidant molecules and enzymes stimulated by resveratrol are given on the left of the table; enzymes down-regulated by resveratrol are given on the right.

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

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 diseases, ischemic brain injuries, and cancer (Jang et al., 1997; Inoue et al., 2003), as well as extend lifespan in different organisms and enhance stress resistance (Yang et al., 2013). The aim of the present review is to highlight the antioxidant effects of resveratrol, focusing our attention on cardiovascular, cerebral, and metabolic disorders, such as diabetes, and reporting also the results of the main clinical trials.

2. Antioxidant properties of resveratrol

A well-documented method for reducing oxidative stress is to reduce caloric intake by selecting appropriate foods (Nisoli et al., 2005). It is well known that nutrients, whether water soluble or lipid soluble, comprise an important aspect of the antioxidant defense system. Beyond their normal occurrence in cells and tissues of living organisms, free radicals and reactive species are present in the unhealthy foods that people consume every day, inducing undesirable reactions like oxidation of lipids, proteins, nucleic acids, and carbohydrates. An impaired ability to scavenge free radicals and reactive species, as a consequence of decreased levels of antioxidant cellular defense systems or excessive free-radical production, is common in cerebral and cardiovascular diseases in humans and animals (Alissa and Ferns, 2012).

Resveratrol plays a prominent role among the foods exerting an antioxidant activity. The main antioxidant activities of resveratrol are summarized in Table 2 (Rocha et al., 2009; Li et al., 2006; Juan et al., 2005; Kohnen et al., 2007). The data suggest that resveratrol exerts its action in different ways: it scavenges reactive oxygen species (ROS), increasing the activity of enzymes that metabolize ROS, such as superoxide dismutase (SOD), or decreases the activity of enzymes that play a role in ROS production.

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 Pentikaïnen, 2003; Puca et al., 2013). It is well known that oxidized LDL accumulates at the site of atherosclerotic lesions (Ramprasath 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 lipoxygenase activity (Maccarrone et al., 1999; Kovanen and Pentikaïnen, 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), and in the post-ischemic, re-perfused myocardium of rats (Ray et al., 1999).

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 (Juan 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 O_2^- 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 peroxyl radicals, hydrogen peroxide (H_2O_2), and superoxide radical ($^{-*}O_2$) (Liu et al., 2003; Chen et al., 2004). In rat pheochromocytoma (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 $^{-*}O_2$ and H_2O_2 produced 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 H_2O_2 (He et al., 2012). Moreover, resveratrol activates an important survival signal pathway consisting in A_1 and A_3 adenosine receptor-mediated activation of the PI3K–AKT pathway and the cAMP 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 H_2O_2 and $^{-*}O_2$ (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 H_2O_2 (Losa, 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 resveratrol for 28 days (Hebbar 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). Jiian 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. Orallo 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) (Wallerath 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.

Wallerath 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 *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 cytotoxic 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). Intraperitoneal 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 isoforms of SOD, SOD2 plays a more important role against oxidant-induced mitochondrial oxidative stress and cytotoxicity in neuronal cells (Vincent 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 be shown that resveratrol inhibits COX1, but does not affect the expression of COX2 (Davinelli et al., 2012). Since nuclear factor-kβ (NF-kβ) 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 astroglioma C6 cells, the expression of genes modulated by NF-kβ, 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-kβ 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 malondialdhehyde 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-kβ p65 expression (Wang et al., 2003).

3.1. Resveratrol and SIRT1

Several studies have attributed resveratrol the capacity to stimulate the activity of SIRT1 (Alcaín 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 (Rivière 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-associating protein 1 (KEAP1), which facilitates its polyubiquitylation 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 (Davinelli 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 $^{-*}O_2$ derived from NAD(P)H oxidase can be dismutased to produce H_2O_2 (Papa and Skulachev, 1997) or can be the cause of nitrative stress: in fact, the interaction of $^{-*}O_2$ 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 microvasculature 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 $^{-*}O_2$ 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-kβ, 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-kβ 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-kβ 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 glycate 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 neuropathy (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 28 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. reinforced 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

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

References	Sample population	Resveratrol dose	Duration	Molecular-level effects	
Ghanim et al. (2010)	20 healthy adults	40 mg	6 weeks	↓ ROS ↓ P47(phox) ↓ NFκB ↓ JNK-1, ↓ PTP-1B	↑ TNF-α ↑ IL-6 ↑ CRP ↑ SOCS-3
Ghanim et al. (2011)	4 healthy men and 6 women	100 mg + 75 mg grapeskin polyphenols	1 week	↓ ROS ↓ TLR-4 ↓ CD14 ↓ IL-1β ↓ SOCS-3	↑ Nrf-2 ↑ NQO-1 ↑ GST-P1
Brasnyo et al. (2011)	19 diabetic men	5 mg twice daily	4 weeks,	↓ ROS	↑ pAk
Timmers et al. (2011)	11 healthy obese men	150 mg twice daily	30 days	↓ glucose ↓ insulin ↓ ROS	↑ AMPK ↑ SIRT1 ↑ PGC1α
Bo et al. (2013)	50 healthy adult smokers	500 mg	30 days	↓ ROS ↓ CRP ↓TG	

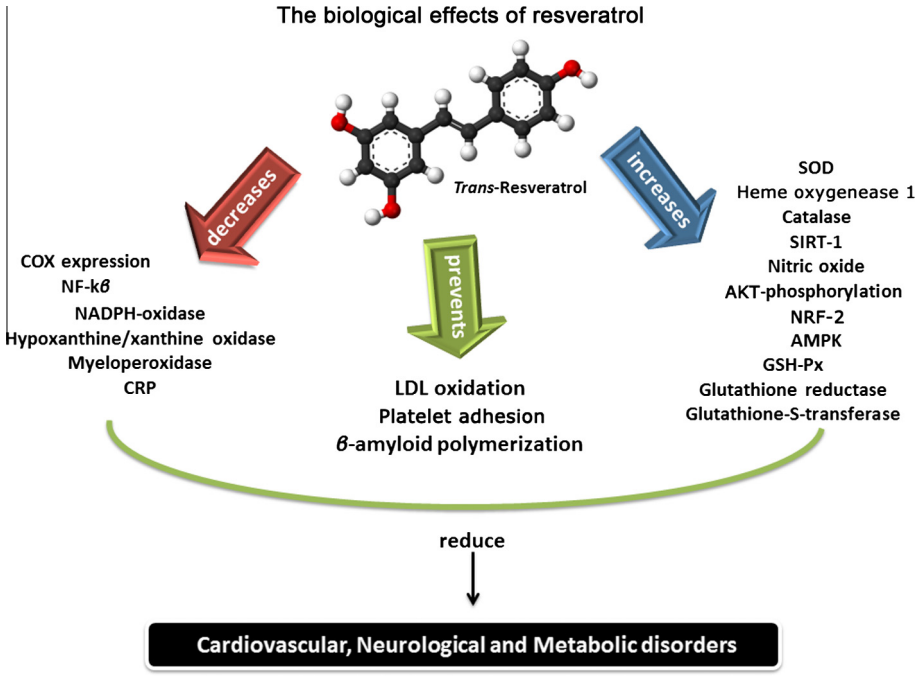

Fig. 2. Representative scheme of the biological effects recruited by resveratrol and their involvement in cardiovascular, metabolic and cerebrovascular diseases.

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, TNFα, and IL-6, and suppressed NF-kβ 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

decreasing plasma endotoxin. These data suggest strong antioxidant 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 inflammation markers.

Finally, Bo et al. evaluated the effects of resveratrol on healthy smokers: they found that 500 mg resveratrol for 30 days significantly increased total antioxidant status values (Bo et al., 2013). The authors suggested that resveratrol may reduce the risk of cardiovascular 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 neutralization of free radicals prevents the activation of redox-sensitive 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 resveratrol's mechanism of action, its safety, and its toxicology. In the light of existing data, it is clear that grapes—and wine—should be considered an 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

$^{-*}O_2$	Superoxide anion
8-OHdG	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	Cycloxigenase
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 I
GSH	Reduced glutathione
GSK-3β	Glycogen kinase 3 beta
GSS	Glutathione synthetase
GST	Glutathione S-transferase
GST-p1	Glutathione S-transferase p1
H_2O_2	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-SOD	Manganese superoxide dismutase
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NF-kβ	Nuclear factor-kβ
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 coactivator α
PGE2	Prostaglandin E2
PI3K	Phosphatidylinositide 3-kinases
PKC	Protein kinase C
PPAR	Peroxisome proliferator-activated receptors
ROS	Reactive oxygen species
SIRT-1	Sirtuin-1 NAD^+-dependent class III histone deacetylases
SOD	Superoxide dismutase
TAS	Total antioxidant status
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor alpha

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