Significance of wine and resveratrol in cardiovascular disease: French paradox revisited

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Many recent studies have reported promising health benefits from red wine consumption. The present article reviews some of the key studies, and the known mechanisms for these beneficial effects. Evidence from different experimental studies, including from the authors’ laboratories, have suggested that these beneficial effects are due to polyphenols found in red wine, especially resveratrol in grape skins. These benefits include a reduction in cardiovascular morbidity and mortality, lung cancer and prostate cancer by approximately 30% to 50%, 57% and 50%, respectively. Polyphenols possess antioxidant, superoxide-scavenging, ischemic-preconditioning and angiogenic properties. Some of these properties of polyphenols may explain their protective effects on the cardiovascular system, as well as other body organs. In fact, results from several epidemiological, case-control and prospective studies have prompted the United States Department of Health and Human Services to recommend moderate alcohol consumption in its national health promotion and disease prevention initiative, Healthy People 2010. Further studies are warranted to describe the precise molecular mechanisms for these potential beneficial effects of red wine on the general health of the population, particularly on cardiovascular morbidity and mortality.

Key Words: Antioxidant; Cytokines; Nitric oxide; Oxidized LDL

EPIDEMIOLOGICAL EVIDENCE

It has long been known that high dietary fat intake is associated with excessive mortality from cardiovascular risk factors. Data examining 40 dietary variables from 40 countries at various levels of economic development showed a significant positive correlation between mortality from coronary artery disease and a lipid score combining the intake levels of cholesterol and saturated fat (cholesterol-saturated fat index) (10). However, the French paradox, as described by St Leger et al (6), states that there is a strong inverse correlation between wine intake and coronary mortality, which is independent of fat intake or other dietary constituents. In countries such as France and Finland, some researchers have attributed this protective effect to an increased consumption of plant foods, as well as regular, moderate consumption of wine. There are many variables that affect the precise validity of these data because the conclusions may be affected by confounding factors (eg, lifestyle and socioeconomic status) that are difficult to control. On the other hand, case-control studies have been published that used matched controls to examine the association between alcohol and end points such as myocardial infarction (MI), atherosclerosis and sudden cardiac death (11,12). The Copenhagen Heart Study (13), a prospective follow-up of 13,000 individuals, showed an inverse correlation between the amount of alcohol consumed and coronary risk, but only for wine drinkers, and not for consumers of beer and spirits.
Although these studies have generally concluded that light to moderate alcohol intake significantly reduces cardiac mortality, participants may not have been representative of the general population, given the population's variability in lifestyle, and in the frequency and pattern of drinking. The prospective cohort studies have also shown that the relative risk of coronary death is reduced by 30% with moderate alcohol consumption, which is consistent between sexes, and across different races and high-risk groups such as those with insulin-dependent diabetes mellitus (14). Although it is impossible to confirm these data by conducting a multicentre randomized controlled study due to logistical and ethical reasons, the above studies provide compelling evidence that light to moderate consumption of alcohol is associated with reduced morbidity and mortality from cardiovascular diseases.

**BIOLOGICAL COMPOUNDS IN WINE**

Wines contain important substances that affect their taste, bitterness, color, preservation and oxidation when exposed to air. Wine phenolic compounds include flavonoids and non-flavonoids. Flavonoids are polyphenols consisting of anthocyanins. Nonflavonoids include hydroxyxynamic acid, benzoic acid, tannins and stilbenes. Both flavonol and non-flavonoids have been implicated in the so-called French paradox. Recently, there has been an increased focus on stilbene and resveratrol with respect to their cardioprotective effects, which are discussed later on. Procyanidin, another phenolic compound, has also been shown to possess endothelium-dependent relaxing activity in blood vessels in vitro (15).

The specific effects of these polyphenolic compounds found in red wine have been shown to decrease the risk of coronary artery disease by attenuating the oxidation of low density lipoprotein (LDL) (16). Oxidized LDL has been suggested to play a major role in the pathogenesis of atherosclerosis (17), and is also responsible for decreasing anti-inflammatory activity and improving impaired endothelial function. Phenolic antioxidants found in red wine inhibit the upregulation of nuclear factor-kappa B (NF-kB), which is a redox-sensitive nuclear transcription factor with a key role in immune and inflammatory responses in isolated monocytes (18). Resveratrol, a polyphenol, is discussed in detail later on.

**CARDIOVASCULAR EFFECTS OF WINE AND OTHER ALCOHOLIC BEVERAGES**

**Effect on serum lipids**

Wine drinkers have higher high density lipoprotein (HDL) levels than that of nonwine drinkers (19). High HDL levels are known to exert a protective effect against coronary vascular events due to atherosclerosis. Rimm et al (20) have shown that for every gram of alcohol consumed per day, the HDL level increases by 0.004 mmol/L. Regular alcohol consumption may be associated with an increase in the synthesis of lipoproteins, a reduction in the degradation of HDL-cholesterol and a higher hepatic metabolism of LDL-cholesterol (21). The ingestion of red wine is associated with an increase in the antioxidant activity in the serum, an increase in apolipoprotein A-1 and a decrease in the atherogenic agent lipoprotein(a), mainly due to the presence of flavonoids and stilbenes (22). It has been further suggested that this increase in antioxidant activity in patients regularly drinking red wine may be the primary factor inhibiting LDL oxidation, which, in turn, reduces atherosclerotic complications.

**Hemostasis**

The effects of red wine on homeostasis and platelet function have been extensively studied. Platelet aggregation is a fundamental phenomenon in the genesis of atherosclerotic plaques in coronary vessels. Several studies have documented that moderate wine consumption reduces platelet aggregation, thereby producing an antiatherosclerotic effect in the arteries. Polyphenols in wine may exert their effects by reducing prostaglandin synthesis from arachidonate. In addition, it has been suggested that polyphenols may reduce platelet activity mediated by nitric oxide (NO) (16). Moreover, polyphenols increase vitamin E levels while decreasing the oxidation of platelets exposed to oxidative stress. It has also been shown that wine drinkers have reduced fibrinogen levels and increased fibrinolytic activity, probably due to upregulation of tissue plasminogen activator in preformed plaques (17,20). Resveratrol and quercetin seem to play an important role in this antiplatelet aggregating effect, as discussed later on.

**Role of NO**

NO, produced by endothelial nitric oxide synthase (eNOS), is the key regulator of vascular homeostasis, including vascular tone and blood pressure. Decreased eNOS protein and reduced NO production is an early and persistent feature of vascular dysfunction in diabetes, hypertension and heart failure (18). It can also lead to vasoconstriction, platelet aggregation, smooth muscle cell proliferation and leukocyte adhesion. The red wine polyphenols have been shown to trigger NO-dependent signalling, which mediates a number of cardioprotective actions of NO, including a decrease in contractility, coronary resistance, myocardial oxygen demand and improvement of metabolic function (19). The increased bioavailability of NO plays an important role in polyphenol-dependent cardioprotective mechanisms through the regulation of antioxidant and NO-producing enzymes.

**Biological compounds in wine as antioxidants**

According to one hypothesis of atherosclerosis, LDL oxidation plays a major role in the early development and progression of atherogenesis (17). Oxidized LDL is more atherosclerotic than native LDL, because it contributes to the cellular accumulation of cholesterol and oxidized lipids, and to foam cell formation. Many studies have demonstrated the antioxidative properties of red wine (eg, against in vitro LDL oxidation), which are attributed mainly to the presence of phenolic compounds (21). This effect seems to be dependent on the concentration of polyphenols in the wine products. In vivo studies have also shown that the daily consumption of 400 mL of red wine for two weeks increases plasma and LDL-associated polyphenols, and protects LDL against copper ion-induced oxidation (22). Quercetin and catechin, which are present in red wine, have been shown to possess free radical-scavenging properties (23). Increased production of reactive oxygen species within a vessel is considered to be an important mechanism for endothelial dysfunction. Specifically, superoxide reacts rapidly with NO to form peroxynitrite, which is both an intracellular and extracellular metabolite, causing loss of NO bioavailability by oxidizing tetrahydrobiopterin, which is a crucial cofactor for NOS. Wine polyphenols have been shown to scavenge peroxynitrite, and exhibit antioxidant, anti-inflammatory and antiatherogenic effects (22).
Anti-inflammatory effects

Inflammation plays a significant role in the initiation and progression of atherosclerosis, which may predispose an individual to major cardiovascular adverse events. Recent studies have examined the anti-inflammatory effects of wines, with a particular focus on some of the polyphenolic compounds found in white wine, namely, tyrosol and caffeic acid. Bertelli et al (24,25) showed an inhibitory effect of tyrosol and caffeic acid on lipopolysaccharide-induced tumour necrosis factor-alpha, interleukin (IL)-1 beta and IL-6 production from the peripheral blood mononuclear cells of healthy volunteers.

Regular, moderate consumption of red wine increases the plasma concentration of IL-6, which has anti-inflammatory activity that may limit the production of the proinflammatory cytokines IL-1 and tumour necrosis factor-alpha (26). In their open, prospective, randomized, crossover, single-blind trial, Estruch et al (27) showed that the consumption of 30 g of ethanol once daily (as red wine) significantly reduced mean plasma fibrinogen, high-sensitivity C-reactive protein and IL-1. They also found that circulating endothelial cell adhesion molecules, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which may be early markers of atherosclerosis, were significantly reduced (27).

Cellular effects

Polyphenols, present in wine, exhibit many important cellular effects, which may contribute to beneficial effects on health (Figures 1 and 2). In a recent study by Blanco-Colio et al (18), NF-kB production in peripheral mononuclear cells was significantly decreased by red wine consumption in human volunteers. In cultured smooth muscle cells, the inhibition of platelet-derived growth factor receptor by catechins in red wine flavonoids was observed.

Because all these effects play an important role in the initiation, progression and organization of atherosclerotic plaques, their blockade may represent an additional mechanism of vascular protection by red wine polyphenols. It is likely that cardioprotection by red wine is mediated by its polyphenolic components, resveratrol and proanthocyanidin. Studies from our laboratory have shown that the red wine extracts proanthocyanidin and resveratrol are not only potent scavengers of peroxyl radicals, but they also reduce the extent of lipid peroxidation in the ischemic-reperfused myocardium. Wine, as opposed to other sources of polyphenols and antioxidants, is unique in that it is the richest source of natural polyphenol antioxidants, especially resveratrol.

Preconditioning effects

In addition to reducing vascular risk factors for ischemic heart disease, wines can directly protect the heart from ischemia-reperfusion injury by a preconditioning effect. The preconditioning phenomenon of the heart was originally reported by Murry et al (28), who showed that cyclic episodes of a brief period of ischemia and reperfusion rendered the heart tolerant to subsequent longer exposures to ischemia-reperfusion injury. Ischemic preconditioning cannot be used in humans for ethical reasons; therefore, pharmacological preconditioning has emerged as an ideal alternative to ischemic preconditioning. Thus far, many pharmacological agents have been found to produce similar preconditioning effects, and these effects are critically mediated by NO (29). Polyphenols, especially resveratrol, found in grapes play a significant role in this preconditioning effect, thus highlighting a potential therapeutic role for red wine. Various molecular mechanisms behind this pharmacological preconditioning have been elucidated by our laboratory, and are described in Figure 3.

RESVERATROL

Effect of resveratrol on the cardiovascular system

Myocardial angiogenesis: Therapeutic angiogenesis has emerged as a promising strategy for the treatment of patients with ischemic limb and heart disease. Therapeutic angiogenesis improves blood flow to ischemic tissue through the induction of neovascularization by angiogenic agents administered either as a recombinant protein or by gene therapy. In the past 10 years, alternative revascularization and angiogenesis strategies have progressed from bench to bedside, focusing on capillary sprouting and/or growth of new vessels to replace the old ones. However, most of the strategies involve the delivery of growth factors. Thus far, very little success with these strategies has been demonstrated for various reasons.

In this regard, our data show increased capillary density in the resveratrol-pretreated infarcted heart, along with increased concentrations of the proangiogenic protein vascular endothelial growth factor (VEGF) and its receptor Flk-1. Most notably,

Figure 1) Molecular mechanisms of cardioprotection by wine extracts. CoX Cyclooxygenase; eNOS Endothelial nitric oxide synthase; ICAM Intercellular adhesion molecule; iNOS Inducible nitric oxide synthase; NO Nitric oxide; VCAM Vascular cell adhesion molecules

Figure 2) Mechanisms of resveratrol-induced anti-inflammatory activity in cardioprotection.
we found increased DNA-binding activity of NF-κB and specificity protein 1 in the myocardium pretreated with resveratrol. In a previous study, Sassli et al. (30) documented hypoxia/reoxygenation-mediated myocardial angiogenesis via an NF-κB-dependent mechanism in a chronic MI rat model. In this study, inhibition of angiogenesis by the administration of pyrrolidine dithiocarbamate, an NF-κB inhibitor, was successful in demonstrating the essential role of NF-κB in myocardial angiogenesis. Therefore, NF-κB activation by resveratrol may be of critical importance for the initiation of an angiogenic response in the rat MI model. Thus, resveratrol appears to differentially regulate NF-κB activity depending on the types of tissues and cells. The direct free radical-scavenging action of resveratrol inhibits LDL oxidation in the vascular wall and upregulation of NF-κB in inflammatory cells, leading to inhibition of atherosclerosis; moreover, the resveratrol-induced enhanced DNA-binding activity of NF-κB improves coronary circulation by increasing the generation of NO, and promotes angiogenesis by increasing the generation of angiogenic cytokines in the ischemic heart. Of note, the induction of eNOS and inducible iNOS (iNOS) by resveratrol in the myocardium provides evidence supporting the hypothesis that resveratrol regulates endothelial cell growth; this is also supported by the presence of increased perfused capillaries. eNOS is constitutively expressed and can be stimulated by interventions; on the other hand, iNOS is a cytokine-induced isoenzyme (31). The eNOS isoform has been reported to play an important role in circulatory function during heart failure, whereas the iNOS isoform may have an important role in hemodynamics early after MI (32). iNOS modulates arterial hemodynamics in large conduit arteries, whereas eNOS regulates resistance of the peripheral vessels (33).

Numerous experimental studies have shown that very low concentrations of NO, produced from eNOS, or pharmacological concentrations of exogenous NO, produced by NO donors, reduce apoptotic cell death (34,35). Previously, we found that besides eNOS induction, iNOS was also significantly induced in all resveratrol-treated groups. Recent studies have shown that eNOS-generated NO plays an important role in many VEGF-induced actions. VEGF has been shown to induce the production of NO in rabbit, pig, bovine and human vascular endothelial cells (36). The inhibition of NO production by eNOS inhibitors significantly reduces VEGF-induced mitogenic and angiogenic effects (37). eNOS-generated NO has been implicated as one of the important mediators for VEGF-induced hemodynamic changes and microvascular permeability.

Although eNOS was originally described as a constitutive enzyme, recent studies indicate that a variety of stimuli, including hypoxia, shear stress, inflammatory cytokines, high glucose levels and injury, can modulate eNOS expression and activity (38,39). In vitro experiments have shown that the activation of Flk-1/kinase insert domain receptor (KDR) induces proliferation and migration of endothelial cells, as well as expression of eNOS and iNOS (40,41). NO is a pleiotropic molecule that affects a wide variety of biochemical and physiological functions, including the regulation of vascular tone and vascular remodelling (42). A potential therapeutic target for NO is angiogenesis (43). Incubation of human vascular smooth muscle cells with NO donors enhances VEGF synthesis, and inhibition of NO abolishes VEGF production (44).

Inhibitors of eNOS have been shown to block VEGF-induced endothelial cell migration, proliferation and tube formation in vitro, as well as VEGF-induced angiogenesis in vivo. In the absence of eNOS inhibition, VEGF stimulates phosphatidylinositol-3 kinase and Akt-dependent phosphorylation of eNOS, resulting in the activation of eNOS and increased NO production. The Flk-1/KDR receptor of VEGF is predominantly involved in eNOS phosphorylation. Although both the tyrosine kinase receptors VEGF receptor-1 (Flt-1) and VEGF receptor-2 (Flk-1/KDR) are necessary for VEGF signalization, there is a basic difference between the two receptors (45). While stimulation of Flt-1 is linked to cell migration, Flk-1/KDR activation is associated with both cell migration and proliferation, which, of note, occurs by the mitogen-activated protein kinase cascade (46). Interestingly, while the induction of VEGF and Flt-1 expression occurs within a very short time, the induction of KDR expression does not occur until days later (47). Flk-1/KDR is believed to be involved in eNOS expression, because a Flk-1/KDR-selective mutant, and not a Flt-1 receptor-selective mutant, can increase eNOS expression.

In a recent study, Das et al. (48) showed that resveratrol induces the expression of iNOS, eNOS, VEGF and Flk-1/KDR in a coordinated fashion in the order listed. Immunohistochemistry detected increased expression of iNOS, eNOS, VEGF and Flk-1/KDR in the hearts of resveratrol-fed rats subjected to 30 min of ischemia and 2 h of reperfusion compared with hearts of nonresveratrol-fed rats. A growing body of evidence indicates that resveratrol can pharmacologically precondition a heart in an NO-dependent manner (49). A number of other studies have also shown a direct role of NO in resveratrol-mediated cardioprotection (15,50-59). Several studies have reported that resveratrol can induce eNOS and iNOS expression. For example, resveratrol induced the expression of eNOS in human umbilical vein endothelial cells (60). In addition to its long-term effects on eNOS expression, resveratrol also enhances the production of bioactive NO in the short term (within 2 min), suggesting a role for iNOS. Our results support...
these previous observations, because we also observed iNOS expression within 24 h, whereas eNOS expression did not become apparent until after three days. In another study, resveratrol induced the expression of iNOS in cultured bovine pulmonary artery endothelial cells (61).

**Neovascularization in the infarcted rat myocardium:** A modern experimental strategy for treating myocardial ischemia is to induce neovascularization of the heart through the use of 'angiogens' (ie, by angiogenesis). Recent studies have shown that coronary collateral vessels protect the ischemic myocardium after coronary obstruction. Various interventions are being tested with the aim to improve arterial blood supply through the formation of coronary collateral vessels (angiogenesis) to the ischemic myocardium. Factors such as fibroblast growth factor and VEGF, which stimulate collateral growth, are expected to exert a protective effect against MI. Indeed, VEGF is a major regulator of angiogenesis and vasculogenesis (62). A strong temporal and spatial correlation exists between VEGF expression and angiogenesis in both animals and humans (63,64). The biological functions of VEGF, triggered by external stimuli, are initiated through the activation of intracellular signal transduction cascades involving specific kinases (65). In this respect, VEGF behaves as a classic stress-induced gene.

Conventional therapeutic approaches to restore flow to a localized segment are thrombolysis, angioplasty and bypass surgery. Tissue hypoxia/ischemia, as well as pharmacological agents such as resveratrol (polyphenol), have been identified as being very important for the induction of new vessel growth. Progressive, chronic coronary artery occlusion has been shown to induce the development of collateral arteries, re-establishing and maintaining blood flow to the at-risk myocardium via the growth of new capillary vessels (angiogenesis). Studies from our laboratory, as well as from others, have already confirmed the protective role of collaterals against myocardial ischemia and cell death (66-69). In adult rat myocardium (left ventricular), we have successfully shown that resveratrol significantly upregulates the protein expression profiles of VEGF and its tyrosine kinase receptors (Flk-1/KDR and Flt-1), as well as other angiogenic factors such as angiopoietin 1 and 2 and their receptor Tie-2 (70). We were also able to show increased capillary/arteriolar density, and improved left ventricular function and blood flow by resveratrol preconditioning in a rat model of chronic MI (71).

We have recently demonstrated resveratrol-mediated induction of thioredoxin-1 (Trx-1) in the heart; Trx-1 is an intracellular redox regulator that is important in the regulation of transcription factors (72-74). Trx is generally located in the cytosol but translocates into the nucleus in response to various stimuli, such as oxidative stress. Several stress studies have reported the induction and translocation of Trx along with heme oxygenase-1 (HO-1). Recent reports suggest that the Trx system contributes to the upregulation of HO-1 protein levels, as well as HO-1 promoter activity, under conditions associated with inflammation and increased oxidative stress (75,76). Turoczi et al (77) found that transgenic mouse heart over-expressing Trx-1 are resistant to ischemia-reperfusion injury, as evidenced by improved postischemic ventricular function recovery and reduced myocardial infarct size compared with the corresponding wild-type mouse hearts. HO-1 is a cytoprotective enzyme that plays an important role in host defense against oxidative stress (78). Recently, Juan et al (79) reported that resveratrol-mediated HO-1 induction is modulated at both the transcription and translation levels in human aortic smooth muscle cells in vitro. We have previously shown a sequential activation of Trx and HO-1, as well as the pro-angiogenic factor and cardioprotective molecule VEGF in human coronary artery endothelial cells, and in rat neonatal cardiomyocytes and rat aortic smooth muscle cells in vitro. We have also shown that adjunctive treatment with tin-protoporphyrin significantly inhibits resveratrol-induced angiogenic activities in vitro and in vivo, as indicated by decreased tubulogenesis and capillary density. This in agreement with an earlier report showing that the overexpression of HO-1 augments the angiogenic effect of endothelial cells (80), and that the activation and overexpression of HO-1 leads to the upregulation of VEGF synthesis.

Resveratrol-mediated expression of Trx-1, HO-1 and VEGF has been found to reduce infarct size in a rat MI in vivo model. The cardioprotective effect is significantly attenuated by tin-protoporphyrin, which may be explained by a decrease in VEGF expression. It has been reported previously that the redox protein Trx-1 increases hypoxia inducible factor-1-alpha protein expression under both normoxic and hypoxic conditions. This is found to be associated with augmented VEGF formation and increased tumour angiogenesis in vivo (81). The hypoxia inducible factor-1 complex influences the expression of many genes, including VEGF (82). Thus, VEGF is implicated as a major angiogenic factor leading to the development of new vessels from pre-existing capillaries (83,84). Transfection of cells with human Trx-1 has been found to increase the overall production of VEGF in MCF-7 breast cancer, HT-29 colon cancer and WEHI7.2 lymphoma cells (85). The beneficial effects of resveratrol may have a multifactorial basis, because resveratrol is also found to augment NO production in endothelial cells (86), and in the kidney (58) and heart (87). Giovannini et al (58) and Naderali et al (88) have indicated that the upregulation of NO is a principal factor in the anti-ischemic function of resveratrol. We have also shown that the anti-ischemic effects of resveratrol are blocked by NG-nitro-L-arginine methyl ester, an inhibitor of NO synthesis, thus indicating that NO is a mediator of resveratrol preconditioning of the heart (87). Another study has indicated a strong reciprocal relationship between VEGF and NO in a rat model of chronic NO blockade (89). It is well accepted that VEGF-induced neovascularization strongly depends on the generation of NO, because NO inhibitors are found to reduce the angiogenic potential of endothelial cells (90). Therefore, resveratrol-mediated pharmacological preconditioning for cardioprotection is a complicated molecular mechanism. A simplified diagram explaining the above mechanisms is depicted in Figure 1. Future studies are warranted to determine whether regular wine drinking promotes long-lasting cardioprotection through activation of iNOS and downstream cardioprotective signalling.

**A phytoestrogen effect**

Based on its structural similarities to diethylstilbestrol, resveratrol is recognized to be a phytoestrogen. Resveratrol can bind to the estrogen receptors (ERs), thereby activating transcription of estrogen-responsive reporter genes in transfected cells (91,92). Resveratrol has been shown to function as a super-agonist when combined with estradiol (E2), and can induce the expression of estrogen-regulated genes (93); however, several other studies show conflicting results. In another study
using the same cell line, resveratrol showed antiestrogen activity; specifically, it suppressed progesterone receptor expression induced by E2. Both isomers of resveratrol have been shown to possess very good estrogenic activity at only moderate concentrations (greater than 10 µM), whereas at lower concentrations (less than 1 µM), antiestrogenic effects prevail (94). Most in vivo studies have failed to confirm the estrogenic potential of resveratrol. At physiological concentrations, resveratrol did not induce any changes in uterine weight, uterine epithelial cell height or serum cholesterol (95). Only at a very high concentration did resveratrol modulate the serum cholesterol-lowering activity of E2 (96). Resveratrol given orally, as well as subcutaneously, did not affect uterine weight at any concentration ranging from lowest to highest (0.03 mg/kg/day to 120 mg/kg/day) (97), whereas in another related study, resveratrol reduced uterine weight and decreased the expression of ER-α mRNA and protein, as well as progesterone receptor mRNA (98). In contrast, resveratrol was found to possess estrogenic properties in stroke-prone spontaneously hypertensive rats (99). Ovariectomized rats fed resveratrol at a concentration of 5 mg/kg/day showed an attenuation of increases in systolic blood pressure. In concert with this, resveratrol enhanced endothelin-dependent vascular relaxation in response to acetylcholine, and prevented ovariectomy-induced decreases in femoral bone strength in a manner similar to E2. Recently, resveratrol was found to act as an ER agonist in breast cancer cells stably transfected with ER-α (100). In a recent study, we showed a significant induction of ER-α mRNA by resveratrol in rats. On the other hand, there was a decrease in ER-α expression by 13-fold (51). Resveratrol-mediated activation of life-extending genes in human cells may open a totally new horizon for resveratrol research. Preliminary studies with resveratrol have shown promising protective effects of SIRT1 overexpression in vitro, and lifespan extension with intact learning and motor function with age in fish experiments (111,112). The proposed antiaging properties of resveratrol open up exciting possibilities for new discoveries in aging research. However, the application and translation of these data from lower organisms to human studies remain to be seen.

Protection against stroke: Several animal studies have raised the possibility that resveratrol may be useful in protecting against and limiting brain damage following ischemia. Rats treated with resveratrol showed decreased infarct size and motor impairment, and decreased delayed neuronal death. These important findings, observed even at lower doses, offer considerable hope for the therapeutic potential of resveratrol. Recent studies have established that after a stroke, levels of intracellular heme increase. The source of free heme is mainly from several heme-containing enzymes. Heme is a prooxidant and its rapid degradation by HO is believed to be protective against neuronal damage. Studies from our laboratory and others have shown that resveratrol, apart from direct free radical-scavenging activity, also increases HO activity, thus offering neuroprotective actions in ischemic injury of the brain (113).

CONCLUSIONS

From several in vivo, in vitro and human studies, it is evident that resveratrol can protect against a variety of diseases such as ischemic heart disease, cancer, Alzheimer disease, diabetes, inflammation and infection. Even though we do not know the maximum tolerated dose of resveratrol, rodent studies have shown that treatment with up to 300 mg/kg body weight has no side effects, with variable bioavailability in different organs. New studies should be aimed at improving the bioavailability of resveratrol and discovering new analogues to help in finding more potent yet protective compounds in preventing disease. It would be interesting to identify the mechanisms behind these fascinating beneficial effects of resveratrol and other compounds in red wine, and this could herald a new chapter in alternative medicine.

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