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Therapeutics

REVIEW ARTICLE

Potential Therapeutic Effects of Natural Heme Oxygenase-1 Inducers in Cardiovascular Diseases

Ignazio Barbagallo,[1,*] Fabio Galvano,[1,*] Alessandro Frigiola,[2] Francesco Cappello,[3,4,5] Graziano Riccioni,[6] Paolo Murabito,[7] Nicolantonio D'Orazio,[8] Michele Torella,[9] Diego Gazzolo,[2,10] and Giovanni Li Volti[1,2]

Abstract

Significance: Many physiological effects of natural antioxidants, their extracts or their major active components, have been reported in recent decades. Most of these compounds are characterized by a phenolic structure, similar to that of α-tocopherol, and present antioxidant properties that have been demonstrated both *in vitro* and *in vivo*. Polyphenols may increase the capacity of endogenous antioxidant defenses and modulate the cellular redox state. Such effects may have wide-ranging consequences for cellular growth and differentiation. ***Critical Issues:*** The majority of *in vitro* and *in vivo* studies conducted so far have attributed the protective effect of bioactive polyphenols to their chemical reactivity toward free radicals and their capacity to prevent the oxidation of important intracellular components. One possible protective molecular mechanism of polyphenols is nuclear factor erythroid 2-related factor (Nrf2) activation, which in turn regulates a number of detoxification enzymes. ***Recent Advances:*** Among the latter, the heme oxygenase-1 (HO-1) pathway is likely to contribute to the established and powerful antioxidant/anti-inflammatory properties of polyphenols. In this context, it is interesting to note that induction of HO-1 expression by means of natural compounds contributes to prevention of cardiovascular diseases in various experimental models. ***Future Directions:*** The focus of this review is on the role of natural HO-1 inducers as a potential therapeutic strategy to protect the cardiovascular system against various stressors in several pathological conditions. *Antioxid. Redox Signal.* 18, 507–521.

Introduction

OXIDATIVE STRESS, the result of an imbalance between antioxidants and pro-oxidants (121), is associated with the aging process as well as over 100 human diseases (122). Under physiological conditions, cells maintain the redox balance through generation and elimination of reactive oxygen species (ROS) by scavenging free radicals and up-regulating antioxidant enzymes. At low levels, ROS act as signaling molecules to promote cell survival, while accelerated production of ROS without concomitant increases in antioxidant enzyme capacity can induce damage and cause cell death (98). Cancer (70), diabetes (107), cardiovascular diseases (CVD) (34), pulmonary diseases (78), and neurodegenerative diseases, including Alzheimer's and Parkinson's disease (21), have all been associated with increased ROS, demonstrating the role of oxidative stress in a wide array of pathological processes.

In an effort to counteract the detrimental effects of oxidative stress, investigators have studied antioxidant supplements, including Vitamins C and E and β-carotene. Recent clinical trials have been equivocal, with antioxidant vitamins failing to improve markers of oxidative disease (120), and in some cases, even increasing pro-oxidant concentrations (151). Current research efforts have subsequently turned to novel compounds that increase endogenous antioxidant enzyme

[1]Department of Drug Sciences, University of Catania, Catania, Italy.
[2]Department of Cardiac Surgery, IRCCS Policlinico "S. Donato," Milan, Italy.
[3]Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo, Palermo, Italy.
[4]Euromediterranean Institute of Science and Technology, Palermo, Italy.
[5]Institute "Paolo Sotgiu" for Research in Quantitative and Quantum Psychiatry and Cardiology, L.U.de.S. University of Human Sciences and Technology, Lugano, Switzerland.
[6]San Camillo De Lellis Hospital, Manfredonia, Italy.
[7]Department and School of Anesthesia and Intensive Care, Catania University Hospital, Catania, Italy.
[8]Department of Biochemistry, Human Nutrition Unit, G. D'annunzio University of Chieti, Chieti, Italy.
[9]Department of Cardio-Thoracic and Respiratory Sciences, Monaldi Hospital, Second University of Naples, Naples, Italy.
[10]Department of Maternal Fetal and Neonatal Medicine "Cesare Arrigo Children's Hospital," Alessandria, Italy.
*These two authors contributed equally to this article.

activity, providing the potential for more profound antioxidant protection than that is achieved with supplemental antioxidant vitamins.

Phytochemicals have recently been suggested to be compounds capable of increasing endogenous antioxidants (74, 85, 100) such as heme oxygenase (HO). This is the first and rate-limiting enzyme in the catabolism of heme (85) to yield equimolar amounts of biliverdin, carbon monoxide (CO), and free iron (Fig. 1). To date, two isoforms of HO, designated HO-1 and HO-2, have been identified in mammals (93). HO-1 is also known as heat shock protein-32. Its human form is composed of 288 amino acids with a molecular mass of 32,800 Da and shares about 80% amino acid sequence identity with rat HO-1. On the other hand, human HO-2 is a 36-kDa protein that consists of 316 amino acids with three cysteine residues. HO-1 is highly inducible by hemin and other chemical and physical agents such as ultraviolet rays, hydrogen peroxides, heavy metals, hypoxia, and nitric oxide (NO) (93). HO-1 has been shown to exert cytoprotective properties in various cells, including neurons (88), pancreatic β-cells (51), and cardiomyocytes (138). Under conditions of oxidative stress, hypoxia or hyperthermia, the induction of HO-1 would account for the majority of heme breakdown, leading to the formation of biliverdin and CO. Since HO-1 is induced as a protective mechanism in response to various stimuli, targeted induction of this stress-response enzyme may be considered an important therapeutic strategy for protection against inflammatory processes and oxidative tissue damage. Several original articles and reviews have been published so far regarding the putative role of HO-1 in CVD (13, 33, 39, 73). However, most deal with HO-1 inducers, which are far from being used in everyday clinical practice, such as CoPP, Hemin, $SnCl_2$, L4F, and adeno- or retroviral vectors (Table 1). Therefore, the present review will focus on the effects of natural antioxidants, which are commercially available and ready to be used in a clinical setting (*i.e.*, supplements).

In this review, recent findings on the implications of HO-1 induction in cellular adaptive cytoprotective response to various insults and inflammatory conditions are considered, with particular emphasis placed on targeted HO-1 induction by natural compounds and their potential for cardiovascular protection.

CVD and Antioxidants

CVD and oxidative stress

CVD affect more than 80 million people in the United States and are the leading cause of death and disability in the Western World (149). Recent studies have implicated increased production of ROS in the initiation and progression of CVD (2), specifically in the etiology of hypertension (46), congestive heart failure (131), and stroke (21). These studies suggest an important role for ROS in the development of CVD, and highlight the need for therapeutic methods to counteract the changes in the redox status observed in patients with developing heart disease.

Several antioxidant compounds have been tested for prevention of CVD. These antioxidant compounds include probucol, coenzyme Q-10, Vitamin C, Vitamin E, *N*-acetylcysteine, superoxide dismutase (SOD) mimetics, as well as red-wine polyphenols (49). Administration of some exogenous antioxidant compounds has been used for preventive and/or therapeutic intervention in oxidative cardiovascular disorders in

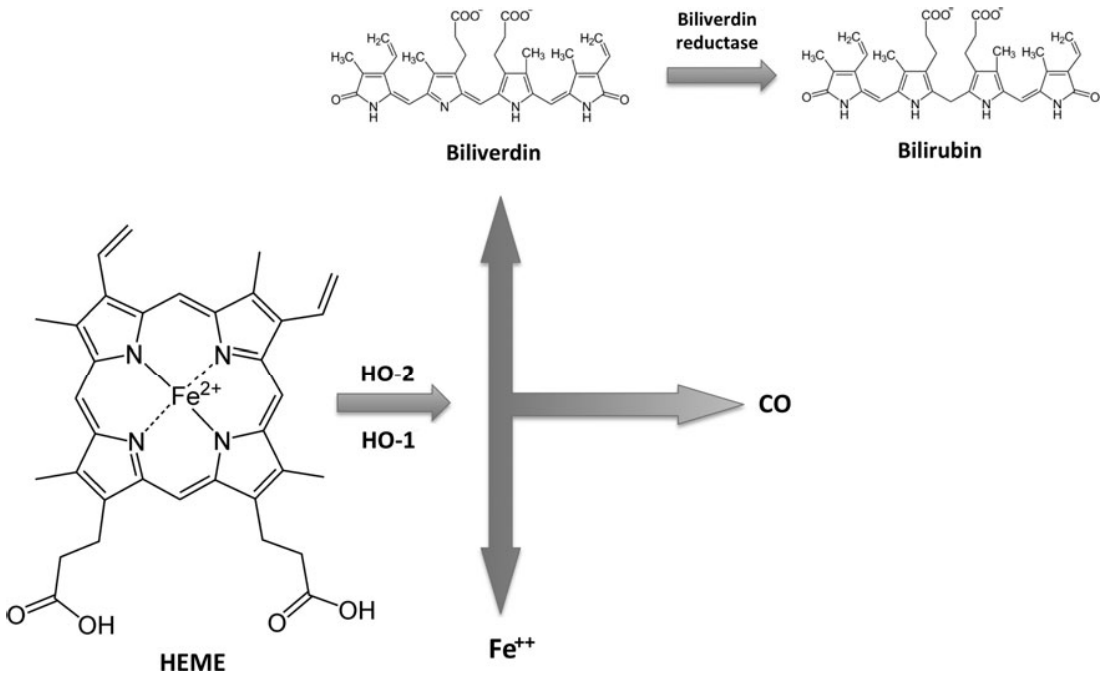

FIG. 1. Schematic representation of the heme-degradative pathway. HO-1/HO-2 degrades heme, which is oxidatively cleaved at the methylene bridge to produce equimolar amounts of CO, biliverdin, and iron. Biliverdin is converted to bilirubin in a stereospecific manner by the cytosolic enzyme, biliverdin reductase. Both CO and bilirubin are bioactive molecules, and the iron generated by HO-1 and HO-2 is immediately sequestered by associated increases in ferritin. CO, carbon monoxide; HO-1, heme oxygenase-1.

Table 1. Commonly Used Heme Oxygenase-1 Inducers

Name of inducer	*Tested models*	*References*
Hemin	Hypertensive rat model, VSMC, cardiac ischemia and reperfusion, endothelial cells, animal model of vascular thrombosis.	(4, 30, 55, 58, 143, 148)
CoPP	SHR, cardiomyocyte, endothelial cells, cardiac ischemia and reperfusion.	(15, 36, 61, 62)
Hemearginate	Mineralocorticoid-induced hypertensive rats, SHR, vascular endothelial cell.	(63, 83, 99)
$SnCl_2$	SHR	(35, 117)
L-4F	Arterioles isolated from hypercholesterolemic $Ldlr^{-/-}$ mice, endothelial cells, cardiac ischemia/reperfusion.	(101, 102, 136)
Adeno/retro/ lentivirus	MSC-treated hearts, rat aortic transplant model, vascular endothelial cells.	(14, 32, 77, 146, 152)

SHR, spontaneously hypertensive rats; VSMCs, vascular smooth muscle cells; MSC, mesenchymal stem cell.

animal models (60). Another strategy for protecting against oxidative cardiac injury may be *via* chemically mediated upregulation of endogenous antioxidants and Phase II enzymes in the cardiac tissue. Such a strategy relies on a profound understanding of the chemical inducibility of cardiac antioxidant and Phase II enzymes, as well as the underlying signaling mechanisms (155). In general, the antioxidant defense mechanism includes enzymes such as SOD, which removes superoxide; glutathione peroxidase (GPx), which converts hydrogen peroxide into water and various hydroperoxides into less-harmful hydroxides; catalase (CAT), which can also break down hydrogen peroxide; and HO. Phenolic acids are a group of phenolic compounds that are widely distributed in foodstuffs, mostly in whole grains, fruits, vegetables, and beverages. Epidemiological studies have suggested an association between the consumption of phenolic acid-rich foods or beverages and the prevention of many diseases (130). These phenolic compounds exhibit good *in vitro* antioxidant and chemoprotective properties, which may have beneficial effects *in vivo* (24).

Several mechanisms have been suggested to explain a direct or indirect action of antioxidants.

Direct antioxidants. Antioxidants, defined as any substance that decreases the severity of oxidative stress by forming less-active radicals or by quenching damage created by free-radical chain reactions, broadly include any substances that delay or prevent the oxidation of a substrate (72). Antioxidant effects of a compound may act by two mechanisms: the compound itself may exhibit direct antioxidant effects through scavenging ROS or inhibiting their formation, or the compound may indirectly upregulate endogenous antioxidant defenses. Direct exogenous antioxidants include Vitamin C, which reacts stoichiometrically with ROS to scavenge aqueous-state free radicals, β-carotene, and Vitamin E, a membrane-bound antioxidant scavenger.

Although supplementation of direct antioxidants is a highly researched topic, the compounds are still only presumed effective (1). Studies of supplementation with a single antioxidant vitamin have shown that this intervention either has no effect or results in increased levels of all-cause mortality (1).

Indirect antioxidants. As a result of the apparent ineffectiveness of supplemental antioxidant vitamins in decreasing oxidative stress, recent research has focused on novel ways to induce an endogenous antioxidant response. Current research efforts have turned to compounds that can be used to increase endogenous antioxidant enzyme activity, providing the potential for more profound antioxidant protection than the traditional approach of antioxidant vitamin supplementation. Phytochemicals, chemical compounds derived from plants, have been examined as a class of these novel inducers of antioxidant enzymes. Also described as indirect antioxidants due to their role in activating Phase II cytoprotective enzymes, phytochemicals stimulate a battery of antioxidant responses in addition to directly scavenging ROS (Fig. 2). Indirect antioxidant compounds act catalytically and are therefore not consumed in the reaction. Unlike direct antioxidants, they have long half-lives, and are unlikely to evoke pro-oxidant effects (132), suggesting the ability to promote a response to oxidative stress, which is both more efficient and longer lasting.

Additionally, studies on polyphenols support the ability of these compounds to activate the nuclear factor erythroid 2-related factor (Nrf2) (7), a critical step in the induction of antioxidant-response mechanisms. By coordinating the expression of cytoprotective proteins, indirect antioxidants provide the potential for greater and more profound upregulation of antioxidant properties and cell protection.

Induction of these cytoprotective proteins is regulated at transcriptional level and is mediated by a specific enhancer, the antioxidant-response element (ARE), found in the promoter of the enzyme's gene.

The ARE. The first experimental evidence for the existence of ARE was found in the late 1980's. Indeed, during studies of xenobiotic metabolism, a group of compounds was found to induce Phase I and II xenobiotic metabolizing enzymes (Fig. 2). Many natural and synthetic phenols and thiol-containing compounds can increase transcription of the genes regulated by the ARE, as well as heavy metal atoms, thiol-containing compounds, hydroperoxides, and heme complexes. Although all activators differ structurally, they all share the property of electrophilicity (42).

Located in the 5'-flanking regulatory region of Phase II target antioxidant genes, the *cis*-acting ARE is a DNA site containing the nucleotide sequence 5'-AGTGACTnnnGCAG-3' (38). This site binds nuclear transcription factor Nrf2, resulting in transcription in a number of xenobiotic and antioxidant enzymes (Fig. 2).

Nrf2: the master regulator of the antioxidant cellular defense system. Nrf2 is a member of the basic leucine-zipper (bZip) transcription factor family (128). Under normal

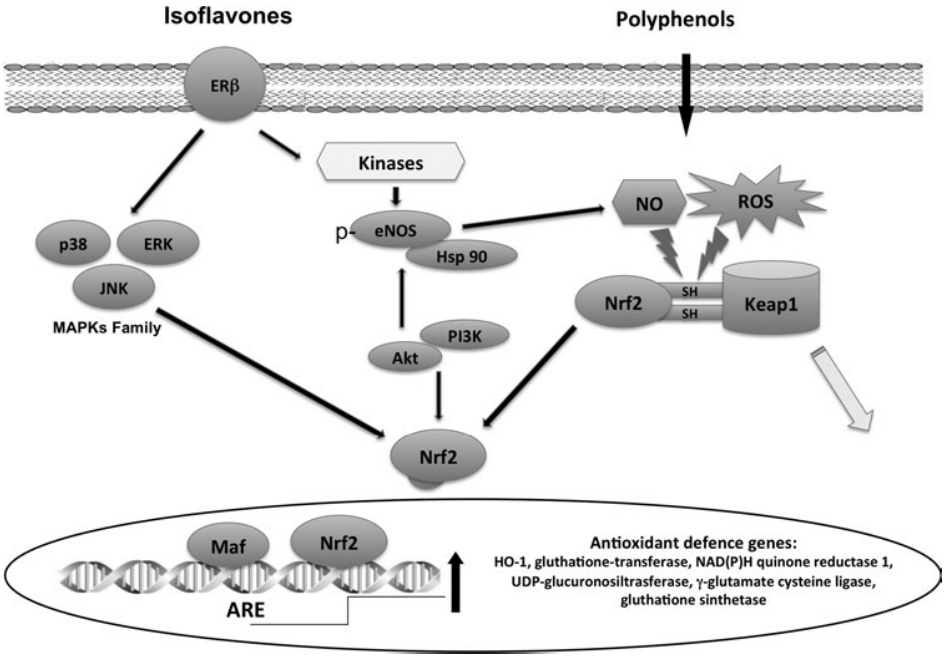

FIG. 2. Transcriptional activation of antioxidant genes by phytochemicals *via* the Nrf2-Keap1 pathway. Isoflavones and other polyphenols activate intracellular kinase cascades, leading to acute activation of eNOS, MAPKs, and NO and/or ROS generation. Increased NO, ROS will modify cysteine residues on Keap1 leading to nuclear traslocation of the redox-sensitive transcription factor Nrf2. After translocation, Nrf2 forms a heterodimer with Maf and Jun bZip transcription factors, which bind to the ARE and induce transcription of Phase II antioxidant enzymes and HO-1. ARE, antioxidant-response element; bZip, basic leucine zipper; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH2- terminal kinase; Keap1, Kelch-like ECH-associated protein 1; MAPKs, mitogen-activated protein kinases; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor; PI-3K, phosphatidylinositol-3 kinase; ROS, reactive oxygen species.

conditions, Nrf2 is sequestered in the cytoplasm by its involvement in an inactive complex with Kelch-like ECH-associated protein 1 (Keap1) (128). Initially thought to passively sequester Nrf2 in the cytoplasm, it is now known that Keap1 plays an active role in targeting Nrf2 for ubiquitination and proteasomal degradation by functioning as a component of the Cul3 E3 ubiquitin ligase complex (84).

Regulation of Nrf2

Nrf2 can be induced injuriously by ROS (41) or non-injuriously by phytochemicals such as curcumin and sulforophane (64, 145) (Fig. 2). Upon exposure to oxidants or chemoprotective compounds, cysteine residues on the Keap1/Nrf2 complex sense cellular redox changes, resulting in an alteration in the structure of Keap1. As shown in Figure 1, modification of the Keap1 cysteine residues stabilizes Nrf2, facilitating its translocation into and accumulation in the nucleus. After translocation, Nrf2 forms a heterodimer with Maf and Jun bZip transcription factors, which bind to the 5′-upstream *cis*-acting regulatory sequence known as the ARE (45) and induce transcription of Phase II antioxidant enzymes.

Natural Inducers of HO-1

A number of natural antioxidant compounds contained in foods and plants have been demonstrated to be effective nonstressful and noncytotoxic inducers of the response protein HO-1 in various cellular models (Table 2). Most of these compounds are contained in plants, which besides having been widely used as food, spices, or flavoring since time immemorial, also represent locally traditional medicinal plants.

Curcumin

Curcumin (diferuloylmethane) (Fig. 3) is the most investigated natural HO-1 inducer. Curcumin is an yellow pigment obtained by populations living in Asian tropical regions by drying and powdering the rhizome of turmeric *(Curcuma longa Linn).* Widely used as food flavoring, it also plays an important role in traditional medicine due to its anti-inflammatory, anticarcinogenic, and antioxidant properties. The major components of turmeric are the curcuminoids that include curcumin, demethoxycurcumin (DMC), and bis-demethoxycurcumin (BDMC) (16). Their chemical structures are illustrated in Figure 3. Curcumin has been demonstrated to be a potent HO-1 inducer in several cellular models (90). At a cellular level, curcumin has been shown to inhibit expression of adhesion molecules (11), possibly by inhibition of stress transcription factors (89). Ongoing experimental and clinical studies suggest that curcumin and its curcuminoids exhibit unique cytoprotective (114), anti-inflammatory (118), and anticancer properties (19). In recent years, it has also been reported that curcumin acts as a nonstressful and non-cytotoxic inducer of the cytoprotective HO-1 and can maximize the intrinsic antioxidant potential of cells (114) (Fig. 4).

In particular, some authors tested various concentrations of curcumin (0–30 μM) on endothelial HO activity and HO-1 protein expression (7). Exposure of endothelial cells to curcumin (1–15 μM) for 18 h resulted in a concentration-

TABLE 2. NATURAL INDUCERS OF HEME OXYGENASE 1, ACTIVE METABOLITES AND BIOLOGICAL EFFECTS IN VARIOUS EXPERIMENTAL MODELS

Compound	*Active metabolites*	*Experimental models*	*Biological effects*	*References*
Caffeic acid phenethyl ester	Caffeic acid phenethyl ester glutathione conjugate	Ischemia/reperfusion	Protective effect on atherosclerosis and ischemia/reperfusion injury	(47, 75)
Cyanidin-3-O-glucoside	Protocatechuic acid	Endothelial cells	Upregulation prosurvival genes.	(125)
Curcumin	Diferuloylmethane	Endothelial cells	Antioxidant properties	(89)
Delphinidin	4′-O-methyl-delphinidin	HUVEC	Antiproliferative effect	(52)
Enterolactone	(3*R*,4*R*)-3,4-bis[(3-hydroxyphenyl) methyl]oxolan-2-one	HUVEC	Inhibits LDL peroxidation and coronary heart disease.	(68)
Epigallocatechin-3-gallate	3′, 4′, 5′-trihydroxyphenyl-γ-valerolactone	Aortic endothelial cells, cardiomyocytes	Improves endothelial function and induces anti-inflammatory vascular events.	(116)
Esculetin	6,7-dihydroxycoumarin	VMSC	Inhibition of vascular smooth muscle cells proliferation.	(50)
Fraxetin	Unknown	VMSC	Inhibits vascular proliferation, atherosclerosis, and LDL oxidation.	(142)
Magnesium lithospermate B	Unknown	Otsuka long-evans Tokushima Fatty rats	Endothelium vasodilation.	(66)
Quercetin	Quercetin 3-O-sulfate Quercetin 3-O-glucoside	Apo E (−/−) mice	Attenuates atherosclerosis and endothelial dysfunction.	(75)
Resveratrol	Piceatannolo, DH-diglucuronide DH-sulfoglucuronide and DH-disulfate	Vascular smooth muscle cells, ischemia/reperfusion	Antiatherogenic activity, general protective effects in coronary artery disease and others vascular disease	(6, 37)

DH, dihydroresveratrol; HUVEC, human umbilical vein endothelial cells; LDL, low density lipoprotein.

dependent increase in HO activity, showing a maximal effect at 15 μM. In the same set of experiments, the authors showed that curcumin attenuates oxidative stress after hypoxia in endothelial cells, and this effect is dependent on increased HO activity (56).

Successive experiments tested whether other derivatives of curcumin present in turmeric, such as DMC and BDMC (Fig. 3), would also stimulate this enzyme induction. The authors found that pure curcumin, DMC, and BDMC all significantly increased HO-1 expression after 6-h incubation. However, despite displaying a similar basic chemical structure, the three compounds affected the pattern of HO-1 protein inducibility in a different fashion. For example, removal of one methoxy group from the molecule of curcumin, as in DMC, affected HO-1 expression slightly. Removal of both methoxy groups, as in BDMC, significantly decreased HO-1 expression. Consistent with these results, HO activity also differed for each curcuminoid tested in this study, the order being curcumin > DMC > BDMC (56). Generally, HO-1 expression is induced by stimuli that activate the mitogen-activated protein kinases (MAPKs) (20, 53) (Fig. 4). Three major subgroups of the MAPK family have been identified to include extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun NH2- terminal kinase (JNK), and p38 MAPK. Depending on the stimuli specificity, contradictory results on the regulatory role of different MAPK pathways for HO-1 expression were observed (53). In the case of curcumin, the activation of the p38 MAPK pathway was found to be involved in HO-1 expression (7, 92). To investigate the signal transduction pathways involved in regulating HO-1 expression in response to curcuminoids, some authors examined the effects of three pharmacological inhibitors of signaling intermediates on HO-1 protein levels. Treatment of endothelial cells with the p38 MAPK inhibitor (SB203580) reduced curcuminoid-induced HO-1 expression. Neither JNK inhibitor (SP600125) nor MAP/ERK kinase inhibitor (U0126) had a significant effect. However, these results clearly show that the pattern of HO-1 protein inducibility differed for each curcuminoid tested in the study, indicating that even subtle changes in the chemical structure can significantly affect the potency of curcuminoids to enhance endothelial HO-1 expression and HO activity (7).

Resveratrol

Resveratrol (*trans*-3,4,5-trihydroxystilbene) is a natural polyphenolic stilbene that is frequently found in grapes and other food products (103) (Fig. 5). It is present in *cis*- and *trans*-isoforms, with the latter being the biologically active form. Resveratrol has been identified in more than 70 species of plants, including grapevines (*Vitis vinifera*), mulberries (*Morus rubra*), *Vaccinum* species, and peanuts (*Arachis hypogea*), and it is thought to have diverse antiatherogenic activities (80, 123), such as the inhibition of low density lipoprotein (LDL) oxidation (9) and platelet aggregation (147) and regulation of vascular smooth muscle proliferation (153). Epidemiological studies have shown that in southern France and other Mediterranean territories, the morbidity and mortality rate of coronary artery disease is low, despite a diet rich in saturated fats and smoking habits (10). This unexpected epidemiological finding was termed the French paradox (137). Exactly how resveratrol exerts its cardioprotective effects is not completely understood, but they have been ascribed to its ability to block

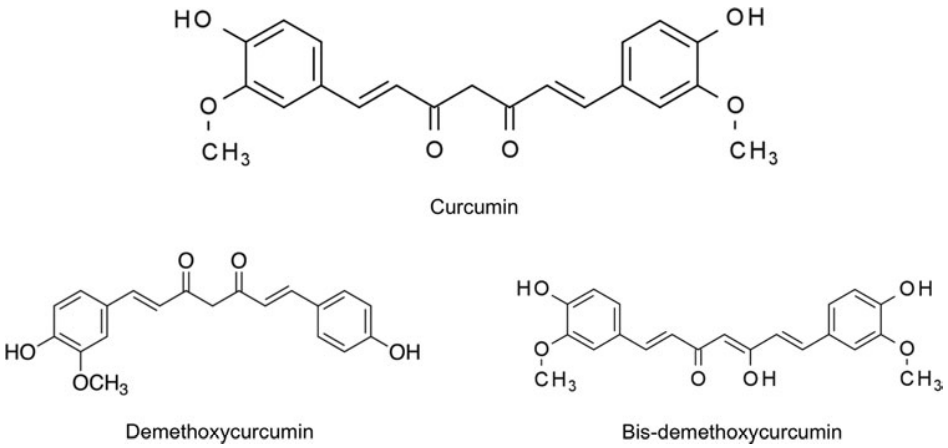

FIG. 3. Chemical structures of curcumin, demethoxycurcumin, and bis-demethoxycurcumin.

platelet aggregation, inhibit oxidation of low-density lipoprotein, and induce NO production. Several studies within the last few years have shown that resveratrol protects against coronary heart disease due to its significant antioxidant properties (22, 108). Additionally, several studies have reported that resveratrol at high concentrations possesses anti-inflammatory activity attributed to blockage of NF-kB activation by inhibiting phosphorylation and degradation of IkBa, thereby preventing nuclear translocation of p65 and p50 (Fig. 6) (94, 104).

Resveratrol-mediated HO-1 induction has been reported in neuronal cultures and has been considered to have potential neuroprotective action (8, 112). The compound is the principal active component of red wine, and its intake is inversely correlated with the incidence of chronic CVD such as atherosclerosis and vascular thrombosis (12). Many studies have found that *trans*-resveratrol prevents the progression of CVD. *Trans*-resveratrol attenuates cardiac hypertrophy in spontaneously hypertensive rats *via* AMP kinase activation (17) and decreases blood pressure in hypertensive rats (97). The compound also suppresses development of myocarditis (150) and

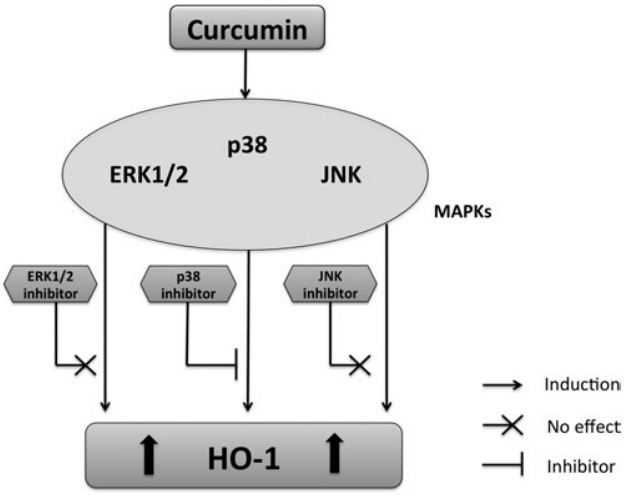

FIG. 4. Induction of heme oxygenase by curcumin. HO-1 expression is induced by stimuli that activate the MAPKs. In the case of curcumin, the activation of the p38 MAPK pathway was found to be involved in HO-1 expression.

atherogenic lesion formation (31). Resveratrol has also been shown to modulate diverse cell cycle regulatory genes (*e.g., p53, Rb,* and cyclins) and these are related to its anticancer or antiproliferation effect (44).

Substantial evidence indicates that resveratrol pharmacologically preconditions the heart to resist ischemia/reperfusion insults. Both NO-dependent pathways (140) and the activation of adenosine receptors (27) are mechanisms that could be mediating the heart preconditioning by resveratrol. In cardiomyocytes, the NO-mediated regulation of cardioprotective enzymes by NO-mediated mechanisms is crucial for cell survival. Resveratrol (*trans*-3,5,4′-trihydroxystilbene), a polyphenolic compound and a naturally occurring phytoalexin, has been designated the active agent (48). The beneficial effect of resveratrol on coronary disease may be attributable, in part, to its ability to retard the progression of early atherosclerotic lesions (111). It also possesses many other biologic activities, including an estrogenic property (28), antiplatelet activity (119), an anti-inflammatory function (25), and a cancer chemopreventive property that has the ability to inhibit angiogenesis and induce apoptosis (29).

Juan *et al.* (59) assessed the induction of HO-1 by resveratrol in human aortic smooth muscle cells at both the mRNA and protein levels (Fig. 6). Northern blot analysis showed that resveratrol at concentrations of 1 and 10 μM significantly induced HO-1 induction, but not at concentrations of 20 and 40 μM. In particular, induction of HO-1 mRNA by resveratrol was observed at 4 h and increased with time up to 24 h of treatment. Consistently, western blot analysis showed that HO-1 was highly expressed in cells exposed to resveratrol at the concentrations of 1 and 10 μM, but not at the concentrations of 20 and 40 μM. To reveal the molecular mechanism of resveratrol-mediated HO-1 induction, MAPK and NF-kB inhibitors were employed (Fig. 6). The level of resveratrol-induced HO-1 expression was attenuated by TPCK (a protease inhibitor that blocks activation of NF-kB) and BAY 11-7082 (an inhibitor of IkBα phosphorylation), but not by MAPK inhibitors, including U0126, curcumin, and SB202190, which are inhibitors of Erk1/2, JNK, and p38 MAPK, respectively. Similarly, previous reports also showed that rats receiving resveratrol (gavage, 2.5 mg/kg) exhibited a significant cardioprotection as evidenced by superior postischemic ventricular recovery, reduced myocardial infarct size, and decreased number of apoptotic cardiomyocytes. Resveratrol induced the

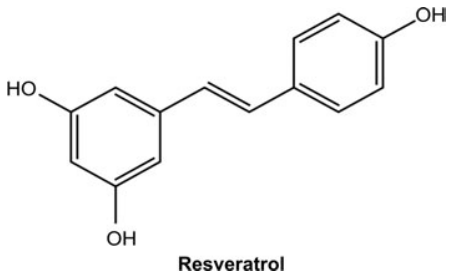

FIG. 5. Chemical structure of resveratrol.

activation of nuclear factor kappa-b (NFkB), the phosphorylation of p38MAP kinase β and Akt, as well as the inhibition of p38 MAPKα; all these effects, except the activation of NFkB, were completely reversed by treatment with Sn-protoporphyrin IX (SnPP). These results indicate that resveratrol generates cardioprotection by preconditioning the heart by HO-1-mediated mechanisms, which are regulated by p38MAP kinase and Akt survival signaling, but nondependent on NFkB activation (Fig. 6). On the other hand, resveratrol inhibits Akt and STAT3 through an increase in oxygen free-radical generation, thus suggesting that resveratrol impacts on Akt activation in a cell-specific manner. Consistent with these results, Kaga *et al.* (59a) showed that resveratrol (10 and 50 μM) induced HO-1 in human coronary arteriolar endothelial cells. The effect of HO-1 induction accounted for increased VEGF production and increased angiogenesis. The authors further tested their hypothesis *in vivo* in a model of descending coronary artery occlusion and demonstrated that the beneficial effects of resveratrol are abolished after HO enzyme inhibition. Similarly, resveratrol (1–100 μM) dose-dependently inhibited IL-1β-stimulated MCP-1 secretion, with almost 45% inhibition at 50 μM resveratrol. Furthermore, the authors showed that this effect was dependent on G_i protein and NO (26). Interestingly, the beneficial effects of resveratrol under these experimental conditions were not abolished by HO activity inhibition or HO-1 silencing, suggesting that the effects on MCP-1 synthesis are mediated *via* distinct signaling pathways.

Further, Ungvari *et al.* found that oxidized LDL and TNF-α elicited significant increases in caspase-3/7 activity in endothelial cells and cultured rat aortas, which were prevented by resveratrol pretreatment (10^{-6}–10^{-4} *M*) (134). The protective effect of resveratrol was attenuated by inhibition of GPx and HO-1, suggesting a role for antioxidant systems in the anti-apoptotic action of resveratrol (134).

Maulik and coworkers showed that resveratrol-treated diabetic rats demonstrated significant reduction in glucose levels as compared to the nontreated diabetic animals, and improved left ventricular function throughout reperfusion compared to diabetic or L-NAME-treated animals (127). Furthermore, the authors showed that cardioprotection from ischemic injury in resveratrol-treated diabetic rats showed decreased infarct size and cardiomyocyte apoptosis compared to diabetic animals. Resveratrol produced significant induction of p-AKT, p-eNOS, Trx-1, HO-1, and VEGF in addition to increased activation of MnSOD activity in diabetic animals compared to nondiabetic animals. However, treatment with L-NAME in resveratrol-treated and nontreated diabetic animals demonstrated significant downregulation of the protein expression profile and MnSOD activity (127), suggesting that the beneficial effects of resveratrol are dependent on NO production.

Finally, Penumathsa *et al.* showed that high cholesterol-induced complications such as increased lipid levels, Cav1/endothelial nitric oxide synthase (eNOS) association, and decreased HO-1 expression, as well as reductions in myocardial functions, can be normalized with resveratrol therapy (106). The authors documented that resveratrol regulates HO-1 conversely in disruption of the Cav-1/eNOS association in a hypercholesterolemic myocardium. They further validated their results using HO-1 transgenic mice. HO-1 overexpression

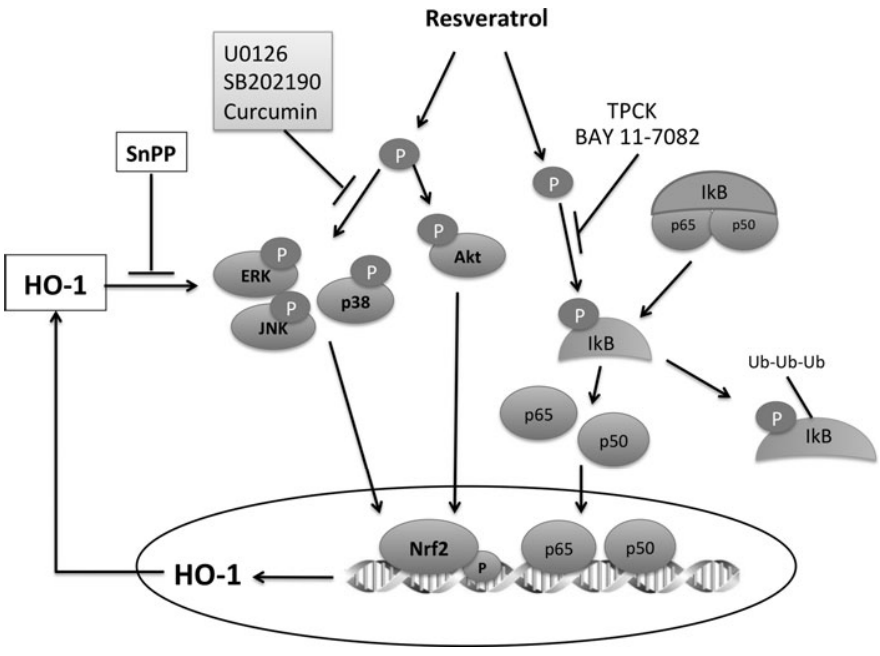

FIG. 6. Anti-inflammatory activity of resveratrol and HO-1 expression. Resveratrol induced the activation of NFkB, the phosphorylation of p38MAP kinase β and Akt, all these effects were completely reversed by treatment with SnPP. These results indicate that resveratrol generates cardioprotection by preconditioning the heart by HO-1-mediated mechanisms, which are regulated by MAPKs and Akt survival signaling, but nondependent on NFkB activation. NFkB, nuclear factor kappa-b; SnPP, Sn-protoporphyrin IX.

resulted in a significant decrease in Cav-1/eNOS association, thus demonstrating that HO-1 regulates Cav-1/eNOS conversely (106). Recently, resveratrol has also been shown to prevent doxorubicin toxicity and apoptosis by an HO-1-dependent pathway (43).

The role of HO-1 in mediating the beneficial effect of resveratrol is further substantiated by a number of studies with pharmacological inhibitors of HO, HO-$1^{-/-}$ animals, and siRNA. Furthermore, in a wire-injured femoral artery mouse model, oral administration of *trans*-resveratrol significantly suppressed intimal hyperplasia. The same authors demonstrated that this effect was reversed by an HO activity inhibitor ZnPPIX (65).

Flavonoids

Flavonoids are naturally occurring antioxidants belonging to the large family of polyphenols. They are widely distributed in plants used as food, as well as traditional medicines, due to their particular variety of clinically relevant properties, such as antitumor, antiplatelet, anti-ischemic, and anti-inflammatory activities.

Quercetin (Fig. 7) is one of the most common flavonoid, and probably, overall the most investigated. In an experimental model of atherosclerosis, quercetin (1.3 mg/day), but not (−)-epicatechin, significantly increased the expression of HO-1 protein in lesions *versus* ApoE(−/−) controls (91).

Anthocyanins are water-soluble plant pigments responsible for the blue, purple, and red color of many plant tissues. They occur primarily as glycosides of their respective aglycone anthocyanidin chromophores (Fig. 7), with the sugar moiety mainly attached at the 3-position on the C-ring or the 5, 7-position on the A-ring. Anthocyanins have been shown to be strong antioxidants, and may exert a wide range of health benefits through antioxidant or other mechanisms (71). It has been suggested that anthocyanins play an important role in the prevention of human diseases associated with oxidative stress, for example, coronary heart disease and cancer (95). The antioxidant properties of anthocyanins have been demonstrated by both *in vitro* and *in vivo* experiments (54, 95, 110, 113, 115).

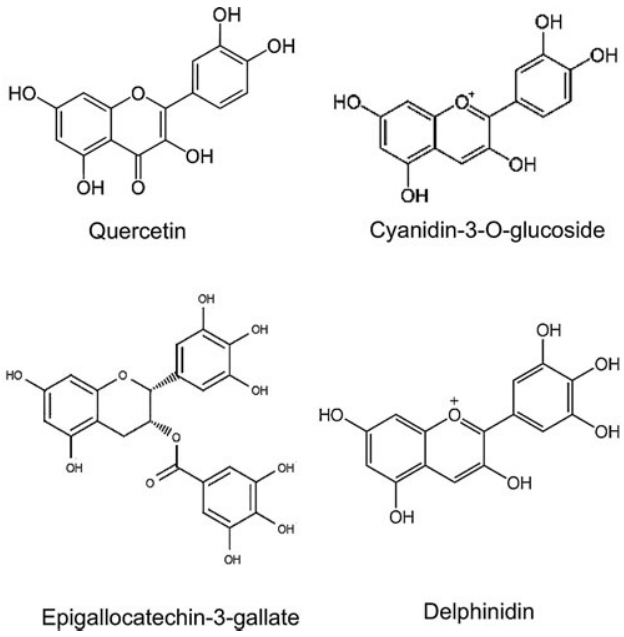

FIG. 7. Chemical structures of quercetin, cyanidin-3-*O*-glucoside, epigallocatechin-3-gallate, and delphinidin.

In this regard, previous studies showed that delphinidin (50 and 100 μM) (Fig. 7) significantly induced HO-1 (1.5-fold increase), whereas cyanidin exhibited this effect only at 100 μM concentration (1.2-fold increase) (79).

Examples of flavonoids include flavonols, isoflavones, flavonones, and flanan-3-ols (*e.g.*, catechins). Epidemiologic studies have shown that green tea rich in catechins may be protective against coronary atherosclerosis (76). In fact, green tea consumption is usually higher in healthy subjects compared with those with coronary artery disease (76), suggesting that green tea and its polyphenols, for example, catechins, can attenuate risk factors associated with the pathology of atherosclerosis (76). The majority of catechins in green tea include epigallocatechin-3-gallate (EGCG) (Fig. 7), which has been shown to improve endothelial function and to induce anti-inflammatory vascular events. Zheng *et al.* (154) showed that pretreatment with EGCG inhibited the secretion of MCP-1 and the activation of activator protein-1 in porcine aortic endothelial cells stimulated with TNF-α. Moreover, EGCG upregulated the expression of HO-1 and further induced the secretion of bilirubin. The observed anti-inflammatory effects of EGCG were mimicked by the HO-1 inducer cobalt protoporphyrin and abolished by HO-1 gene silencing.

These results are consistent with previous data showing that while mRNA levels of GPx3, SOD1, and CAT were not influenced by EGCG and theaflavin-3,39-digallate (TF3), HO-1 was selectively upregulated by EGCG, but not by TF3. However, inhibition of HO-1 did not diminish polyphenol-mediated cardioprotection. While EGCG and TF3 activated Akt, ERK1/2, and p38 MAPK, inhibition of these kinases did not attenuate polyphenol-mediated protection. In this regard, previous studies showed that EGCG-induced phosphorylation of Erk and Akt occurs *via* activation of the mitogen-activated protein kinase-kinase (MEK) and phosphatidylinositol-3 kinase (PI-3K) pathways, respectively (23). Loading of cardiomyocytes with dichlorofluorescein revealed that intracellular levels of ROS were significantly reduced after treatment with EGCG or TF3 as early as 30 min after induction of oxidative stress. In conclusion, activation of prosurvival signaling kinases and upregulation of antioxidant enzymes do not play a major role in tea polyphenol-mediated cardioprotection. In addition, EGCG inhibits STAT-1 activation and reduces cell death after cardiac ischemia/reperfusion injury (129).

Other compounds and plant extracts

Plant lignans are a group of phenolic compounds that can be found in diets rich in fiber. Enterolactone (Fig. 8) is a breakdown product of plant lignans. The production of mammalian lignans from dietary precursors by intestinal bacteria occurs mainly in the large intestine. After removal of methyl and hydroxyl groups in precursors, enterolactone is absorbed from the gut into the circulation and then excreted in urine, where enterolactone primarily exists as glucuronides (5). Recent studies have shown that high serum enterolactone levels reduce LDL peroxidation *in vivo*, assessed by serum

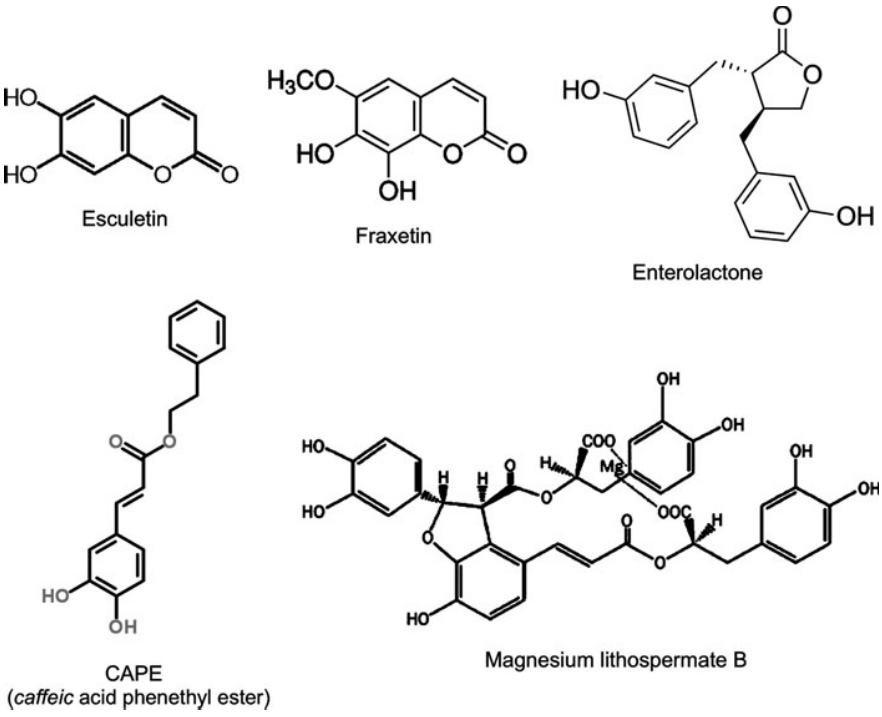

FIG. 8. Chemical structures of esculetin, fraxetin, enterolactone, caffeic acid phenethyl ester (CAPE), and magnesium lithospermate B.

isoprostane levels (135). Enterolactone also reduced lipid peroxidation *in vitro via* direct scavenging of a hydroxyl radical (68). This association implies a protective role of enterolactone against oxidative injury. In addition, estrogen-like biological effects of enterolactone have been reported, which may also result in protection against coronary heart disease (105, 139). Kivela *et al.* showed that enterolactone induced HO-1 in human umbilical vein endothelial cells (HUVEC) in a time- and concentration-dependent manner (50–150 μM for 16 h) (69). Induction appeared to be mediated *via* the transcription factor Nrf2, as Nrf2 siRNA abolished HO-1 induction by enterolactone. The authors also showed that exposure to enterolactone increased the binding of Nrf2 to the promoter region of HO-1 (69).

An attractive candidate antioxidant to treat diabetes is magnesium lithospermate B (MLB) (Fig. 8). MLB is the active component of the water-soluble fraction of the Chinese medicine Danshen, a root preparation of Red Sage (*Salvia mitorrhizae*) (67). MLB is an antioxidant worth further study because of its interesting secondary effects in cells. MLB inhibits the enzyme aldose reductase, which is a key component in the polyol biochemical pathway involved in the pathogenesis of diabetic complications (67). Previous research has shown that MLB has antifibrotic, myocardial salvage, and neuroprotective effects (133). MLB prevents hepatitis, uremia, and improves blood circulation, arrhythmia, and renal function (18, 40). Recent work in our laboratory showed that MLB could prevent the development of neointimal hyperplasia in animal models of diabetes and after balloon-induced injury. Starting at 12 weeks, 20-week MLB treatment attenuated the decrease in endothelium-dependent vasodilation in rats. MLB treatment also increased the serum nitrite level and reduced serum concentration of advanced glycation end products. The effect of MLB was greater than an equivalent dose of α-lipoic acid, a popular antioxidant treatment. MLB rescued the inhibition of eNOS activity and eNOS phosphorylation in endothelial cells cultured in hyperglycemia. This effect was dependent on Akt phosphorylation and associated with decreased *O*-linked *N*-acetylglucosamine protein modification of eNOS. MLB also increased nuclear factor erythroid 2-related factor (Nrf-2) activation in a phosphoinositide 3-kinase/Akt pathway-dependent manner. MLB treatment induced the expression of HO-1, and previous studies demonstrated that HO-1 silencing abolished the protective effect of MLB (81).

Fraxinus rhynchophylla DENCE (Oleaceae) is a traditional medicinal plant from East Asia (144). Diverse compounds have been isolated from the plant. Among them, ferulaldehyde and scopoletin have inhibitory activity against induction of inducible NO synthase (66), and antitoxoplasmosis effect of oleuropein was reported (57). During the course of characterizing biologically active compounds from natural products, two major coumarins were isolated, esculetin and fraxetin (Fig. 8). Despite numerous studies on the inhibitory activities of natural antioxidants against LDL oxidation, reports on the effects of coumarinoids are still scarce. Lee *et al.* have shown that esculetin inhibits LDL oxidation and Apo-B fragmentation (82). Low concentrations (1–5 mM) of fraxetin potently inhibited LDL oxidation induced by metal and free radicals. Moreover, treatment of vascular smooth muscle cells with higher concentrations (above 30 mM) of fraxetin significantly increased the protein level of HO-1, a key enzyme that inhibits vascular proliferation and atherosclerosis. Subcellular fractionation and reporter gene analysis using an ARE construct revealed that fraxetin increased the level of Nrf2 and reporter activity, and these were associated with the induction of antioxidant enzymes, such as HO-1 and glutathione *S*-transferase-a.

Caffeic acid phenethyl ester (CAPE) (Fig. 8), a polyphenolic compound concentrated in honeybee propolis, has been reported to exhibit numerous bioactive properties, including

antioxidant (124) and anti-inflammatory activities (96), which may contribute to its protective effects in various pathophysiological processes such as ischemia/reperfusion injury (126, 142) and atherosclerosis (47). To ascertain the involvement of HO-1 induction in the cytoprotective effects of CAPE analogs, their ability to induce HO-1 at 20 μM was determined by reverse transcriptase–polymerase chain reaction, western blotting, and the use of HO-1 inhibitor tin protoporphyrin IX (10–40 μM) (141). There was significant induction of HO-1 by CAPE derivatives. Inhibition of HO-1 enzymatic activity resulted in reduced cytoprotection. Modification of the catechol ring of CAPE by introduction of fluorine at various positions resulted in dramatic changes in cytoprotective activity. The maintenance of at least one hydroxyl group on the CAPE catechol ring and the phenethyl ester portion was required for HO-1 induction. CAPE and its derivatives were screened for their ability to scavenge intracellular ROS generated in HUVECs by measuring 5-(and-6)-chlormethyl-2′, 7′-dichlorodihydrofluorescein diacetate oxidation. The maintenance of 3, 4-dihydroxyl groups on the catechol ring was required for antioxidant activity, but antioxidant activity did not guarantee cytoprotection. Methylation or replacement of one hydroxyl group on the catechol ring of CAPE however provided both pro-oxidant and cytoprotective activities. These results indicate that the induction of HO-1 plays a more important role in the cytoprotective activity of CAPE derivatives than their direct antioxidant activity.

Critical considerations and future studies. The amount of experimental data evidencing important properties of many ingredients and/or bioactive substances from plants and food plants is vast and continues to increase rapidly. The use of terms such as nutraceuticals, functional foods, herbal extracts, bioactive dietary constituents, phytochemicals, and similar is becoming copious. In many cases, marketing strategies abuse these terms and health properties are claimed while far from scientifically demonstrated. Thus, researchers require severe scientific objectivity in evaluating the health properties of food ingredients. It is possible to maintain that diverse bioactive substances from plants and food plants are promising candidates as natural HO-1 inducers to be used in CVD. However, some critical evaluations of the literature data are necessary. It is important to note that the majority of studies were conducted in cellular models, whereas few studies were conducted on rats. Thus, the reproduction of natural HO-1 cardiovascular inducers in more relevant *in vivo* models is certainly necessary. With regard to the inductive mechanism of natural HO-1 inducers, although other pathways cannot be excluded, it seems quite clear that the prevalent mechanism is an ARE-mediated HO-1 gene transcription through the Nrf2/ARE signaling pathway.

Other uncertainties derive from the fact that the referred studies report data on natural HO-1 inducers considered both as single chemicals and food extracts. In some cases, little or no information was provided regarding (i) the quantitative measurements of the proposed active compound; (ii) methods of analysis, and (iii) extraction procedures. Obviously, these details are essential for other researchers to reproduce the experiments and to obtain comparable data.

When considering a possible therapeutic use of future natural HO-1 inducer-based drugs, the amount of work yet to be performed is even more significant. Indeed, there is largely insufficient exhaustive information on absorption, distribution, metabolism, and excretion by main possible routes (oral, intraperitoneal, intravenous, and intratecal). One possible limitation of HO-1 inducers that should be taken into due account is the concomitant reduction of the amounts of intracellular heme, necessary for the assembly of many proteins, including cytochromes (109), cyclooxygenase (86), and NO synthase (87), and the production of ferrous iron, which can trigger oxidative stress through to the Fenton and Haber–Weiss reactions (3).

References

1. Abner EL, Schmitt FA, Mendiondo MS, Marcum JL, and Kryscio RJ. Vitamin E and all-cause mortality: a meta-analysis. *Curr Aging Sci* 4: 158–170, 2011.
2. Abrescia P and Golino P. Free radicals and antioxidants in cardiovascular diseases. *Expert Rev Cardiovasc Ther* 3: 159–171, 2005.
3. Alam J, Igarashi K, Immenschuh S, Shibahara S, and Tyrrell RM. Regulation of heme oxygenase-1 gene transcription: recent advances and highlights from the International Conference (Uppsala, 2003) on Heme Oxygenase. *Antioxid Redox Signal* 6: 924–933, 2004.
4. Awede B, Lemaire MC, Hyvelin JM, Halimi JM, Bonnet P, and Eder V. Hemin, a carbon monoxide donor, improves systemic vascular compliance by inhibiting the RhoA-Rhokinase pathway in spontaneous hypertensive rats. *Eur J Pharmacol* 626: 256–261, 2010.
5. Axelson M and Setchell KD. The excretion of lignans in rats—evidence for an intestinal bacterial source for this new group of compounds. *FEBS Lett* 123: 337–342, 1981.
6. Azorin-Ortuno M, Yanez-Gascon MJ, Vallejo F, Pallares FJ, Larrosa M, Lucas R, Morales JC, Tomas-Barberan FA, Garcia-Conesa MT, and Espin JC. Metabolites and tissue distribution of resveratrol in the pig. *Mol Nutr Food Res* 55: 1154–1168, 2011.
7. Balogun E, Hoque M, Gong P, Killeen E, Green CJ, Foresti R, Alam J, and Motterlini R. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. *Biochem J* 371: 887–895, 2003.
8. Bastianetto S and Quirion R. Heme oxygenase 1: another possible target to explain the neuroprotective action of resveratrol, a multifaceted nutrient-based molecule. *Exp Neurol* 225: 237–239, 2010.
9. Berrougui H, Grenier G, Loued S, Drouin G, and Khalil A. A new insight into resveratrol as an atheroprotective compound: inhibition of lipid peroxidation and enhancement of cholesterol efflux. *Atherosclerosis* 207: 420–427, 2009.
10. Bertelli AA and Das DK. Grapes, wines, resveratrol, and heart health. *J Cardiovasc Pharmacol* 54: 468–476, 2009.
11. Bhandarkar SS and Arbiser JL. Curcumin as an inhibitor of angiogenesis. *Adv Exp Med Biol* 595: 185–195, 2007.
12. Bradamante S, Barenghi L, and Villa A. Cardiovascular protective effects of resveratrol. *Cardiovasc Drug Rev* 22: 169–188, 2004.
13. Calabrese V, Cornelius C, Trovato A, Cavallaro M, Mancuso C, Di Rienzo L, Condorelli D, De Lorenzo A, and Calabrese EJ. The hormetic role of dietary antioxidants in free radical-related diseases. *Curr Pharm Des* 16: 877–883, 2010.
14. Cao J, Sodhi K, Inoue K, Quilley J, Rezzani R, Rodella L, Vanella L, Germinario L, Stec DE, Abraham NG, and

Kappas A. Lentiviral-human heme oxygenase targeting endothelium improved vascular function in angiotensin II animal model of hypertension. *Hum Gene Ther* 22: 271–282, 2011.
15. Cao J, Sodhi K, Puri N, Monu SR, Rezzani R, and Abraham NG. High fat diet enhances cardiac abnormalities in SHR rats: protective role of heme oxygenase-adiponectin axis. *Diabetol Metab Syndr* 3: 37, 2011.
16. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). *J Altern Complement Med* 9: 161–168, 2003.
17. Chan AY, Dolinsky VW, Soltys CL, Viollet B, Baksh S, Light PE, and Dyck JR. Resveratrol inhibits cardiac hypertrophy via AMP-activated protein kinase and Akt. *J Biol Chem* 283: 24194–24201, 2008.
18. Chen CG and Wang YP. Magnesium lithospermate B ameliorates renal cortical microperfusion in rats. *Acta Pharmacol Sin* 27: 217–222, 2006.
19. Chen J, Bai H, Wang C, and Kang J. Trichostatin A improves the anticancer activity of low concentrations of curcumin in human leukemia cells. *Pharmazie* 61: 710–716, 2006.
20. Chen YC, Chow JM, Lin CW, Wu CY, and Shen SC. Baicalein inhibition of oxidative-stress-induced apoptosis via modulation of ERKs activation and induction of HO-1 gene expression in rat glioma cells C6. *Toxicol Appl Pharmacol* 216: 263–273, 2006.
21. Chrissobolis S, Miller AA, Drummond GR, Kemp-Harper BK, and Sobey CG. Oxidative stress and endothelial dysfunction in cerebrovascular disease. *Front Biosci* 16: 1733–1745, 2011.
22. Chu LM, Lassaletta AD, Robich MP, and Sellke FW. Resveratrol in the prevention and treatment of coronary artery disease. *Curr Atheroscler Rep* 13: 439–446, 2011.
23. Chung JH, Han JH, Hwang EJ, Seo JY, Cho KH, Kim KH, Youn JI, and Eun HC. Dual mechanisms of green tea extract (EGCG)-induced cell survival in human epidermal keratinocytes. *FASEB J* 17: 1913–1915, 2003.
24. Cos P, Rajan P, Vedernikova I, Calomme M, Pieters L, Vlietinck AJ, Augustyns K, Haemers A, and Vanden Berghe D. *In vitro* antioxidant profile of phenolic acid derivatives. *Free Radic Res* 36: 711–716, 2002.
25. Csiszar A. Anti-inflammatory effects of resveratrol: possible role in prevention of age-related cardiovascular disease. *Ann N Y Acad Sci* 1215: 117–122, 2011.
26. Cullen JP, Morrow D, Jin Y, Curley B, Robinson A, Sitzmann JV, Cahill PA, and Redmond EM. Resveratrol, a polyphenolic phytostilbene, inhibits endothelial monocyte chemotactic protein-1 synthesis and secretion. *J Vasc Res* 44: 75–84, 2007.
27. Das S, Cordis GA, Maulik N, and Das DK. Pharmacological preconditioning with resveratrol: role of CREB-dependent Bcl-2 signaling via adenosine A3 receptor activation. *Am J Physiol Heart Circ Physiol* 288: H328–H335, 2005.
28. De Amicis F, Giordano F, Vivacqua A, Pellegrino M, Panno ML, Tramontano D, Fuqua SA, and Ando S. Resveratrol, through NF-Y/p53/Sin3/HDAC1 complex phosphorylation, inhibits estrogen receptor {alpha} gene expression via p38MAPK/CK2 signaling in human breast cancer cells. *FASEB J* 25: 3695–3707, 2011.
29. de la Lastra CA and Villegas I. Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. *Biochem Soc Trans* 35: 1156–1160, 2007.
30. Desbuards N, Rochefort GY, Schlecht D, Machet MC, Halimi JM, Eder V, Hyvelin JM, and Antier D. Heme oxygenase-1 inducer hemin prevents vascular thrombosis. *Thromb Haemost* 98: 614–620, 2007.
31. Do GM, Kwon EY, Kim HJ, Jeon SM, Ha TY, Park T, and Choi MS. Long-term effects of resveratrol supplementation on suppression of atherogenic lesion formation and cholesterol synthesis in apo E-deficient mice. *Biochem Biophys Res Commun* 374: 55–59, 2008.
32. Du D, Chang S, Chen B, Zhou H, and Chen ZK. Adenovirus-mediated heme oxygenase transfer inhibits graft arteriosclerosis in rat aortic transplants. *Transplant Proc* 39: 3446–3448, 2007.
33. Durante W. Targeting heme oxygenase-1 in vascular disease. *Curr Drug Targets* 11: 1504–1516, 2010.
34. Elahi MM, Kong YX, and Matata BM. Oxidative stress as a mediator of cardiovascular disease. *Oxid Med Cell Longev* 2: 259–269, 2009.
35. Escalante B, Sacerdoti D, Davidian MM, Laniado-Schwartzman M, and McGiff JC. Chronic treatment with tin normalizes blood pressure in spontaneously hypertensive rats. *Hypertension* 17: 776–779, 1991.
36. Ewing P, Wilke A, Eissner G, Holler E, Andreesen R, and Gerbitz A. Expression of heme oxygenase-1 protects endothelial cells from irradiation-induced apoptosis. *Endothelium* 12: 113–119, 2005.
37. Fabre KM, Saito K, DeGraff W, Sowers AL, Thetford A, Cook JA, Krishna MC, and Mitchell JB. The effects of resveratrol and selected metabolites on the radiation and antioxidant response. *Cancer Biol Ther* 12: 915–923, 2011.
38. Favreau LV and Pickett CB. The rat quinone reductase antioxidant response element. Identification of the nucleotide sequence required for basal and inducible activity and detection of antioxidant response element-binding proteins in hepatoma and non-hepatoma cell lines. *J Biol Chem* 270: 24468–24474, 1995.
39. Ferrandiz ML and Devesa I. Inducers of heme oxygenase-1. *Curr Pharm Des* 14: 473–486, 2008.
40. Fish JM, Welchons DR, Kim YS, Lee SH, Ho WK, and Antzelevitch C. Dimethyl lithospermate B, an extract of Danshen, suppresses arrhythmogenesis associated with the Brugada syndrome. *Circulation* 113: 1393–1400, 2006.
41. Florczyk U, Loboda A, Stachurska A, Jozkowicz A, and Dulak J. [Role of Nrf2 transcription factor in cellular response to oxidative stress]. *Postepy Biochem* 56: 147–155, 2010.
42. Giudice A, Arra C, and Turco MC. Review of molecular mechanisms involved in the activation of the Nrf2-ARE signaling pathway by chemopreventive agents. *Methods Mol Biol* 647: 37–74, 2010.
43. Gu J, Song ZP, Gui DM, Hu W, Chen YG, and Zhang DD. Resveratrol attenuates doxorubicin-induced cardiomyocyte apoptosis in lymphoma nude mice by heme oxygenase-1 induction. *Cardiovasc Toxicol* 2012 [Epub ahead of print]; DOI: 10.1007/s12012-012-9178-7.
44. Harikumar KB and Aggarwal BB. Resveratrol: a multitargeted agent for age-associated chronic diseases. *Cell Cycle* 7: 1020–1035, 2008.
45. Hayes JD and McMahon M. Molecular basis for the contribution of the antioxidant responsive element to cancer chemoprevention. *Cancer Lett* 174: 103–113, 2001.
46. Hirooka Y. Oxidative stress in the cardiovascular center has a pivotal role in the sympathetic activation in hypertension. *Hypertens Res* 34: 407–412, 2011.
47. Hishikawa K, Nakaki T, and Fujita T. Oral flavonoid supplementation attenuates atherosclerosis development in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 25: 442–446, 2005.

48. Holthoff JH, Woodling KA, Doerge DR, Burns ST, Hinson JA, and Mayeux PR. Resveratrol, a dietary polyphenolic phytoalexin, is a functional scavenger of peroxynitrite. *Biochem Pharmacol* 80: 1260–1265, 2010.
49. Hu FB and Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 288: 2569–2578, 2002.
50. Huang HC, Lai MW, Wang HR, Chung YL, Hsieh LM, and Chen CC. Antiproliferative effect of esculetin on vascular smooth muscle cells: possible roles of signal transduction pathways. *Eur J Pharmacol* 237: 39–44, 1993.
51. Huang SH, Chu CH, Yu JC, Chuang WC, Lin GJ, Chen PL, Chou FC, Chau LY, and Sytwu HK. Transgenic expression of haem oxygenase-1 in pancreatic beta cells protects non-obese mice used as a model of diabetes from autoimmune destruction and prolongs graft survival following islet transplantation. *Diabetologia* 53: 2389–2400, 2010.
52. Ichiyanagi T, Rahman MM, Kashiwada Y, Ikeshiro Y, Shida Y, Hatano Y, Matsumoto H, Hirayama M, and Konishi T. Absorption and metabolism of delphinidin 3-O-beta-D-glucoside in rats. *Biofactors* 21: 411–413, 2004.
53. Iles KE, Dickinson DA, Wigley AF, Welty NE, Blank V, and Forman HJ. HNE increases HO-1 through activation of the ERK pathway in pulmonary epithelial cells. *Free Radic Biol Med* 39: 355–364, 2005.
54. Jensen GS, Wu X, Patterson KM, Barnes J, Carter SG, Scherwitz L, Beaman R, Endres JR, and Schauss AG. *In vitro* and *in vivo* antioxidant and anti-inflammatory capacities of an antioxidant-rich fruit and berry juice blend. Results of a pilot and randomized, double-blinded, placebo-controlled, crossover study. *J Agric Food Chem* 56: 8326–8333, 2008.
55. Jeon EM, Choi HC, Lee KY, Chang KC, and Kang YJ. Hemin inhibits hypertensive rat vascular smooth muscle cell proliferation through regulation of cyclin D and p21. *Arch Pharm Res* 32: 375–382, 2009.
56. Jeong GS, Oh GS, Pae HO, Jeong SO, Kim YC, Shin MK, Seo BY, Han SY, Lee HS, Jeong JG, Koh JS, and Chung HT. Comparative effects of curcuminoids on endothelial heme oxygenase-1 expression: ortho-methoxy groups are essential to enhance heme oxygenase activity and protection. *Exp Mol Med* 38: 393–400, 2006.
57. Jiang JH, Jin CM, Kim YC, Kim HS, Park WC, and Park H. Anti-toxoplasmosis effects of oleuropein isolated from Fraxinus rhychophylla. *Biol Pharm Bull* 31: 2273–2276, 2008.
58. Johns DG, Zelent D, Ao Z, Bradley BT, Cooke A, Contino L, Hu E, Douglas SA, and Jaye MC. Heme-oxygenase induction inhibits arteriolar thrombosis *in vivo*: effect of the non-substrate inducer cobalt protoporphyrin. *Eur J Pharmacol* 606: 109–114, 2009.
59. Juan SH, Cheng TH, Lin HC, Chu YL, and Lee WS. Mechanism of concentration-dependent induction of heme oxygenase-1 by resveratrol in human aortic smooth muscle cells. *Biochem Pharmacol* 69: 41–48, 2005.
59a. Kaga S, Zhan L, Matsumoto M, and Maulik N. Resveratrol enhances neovascularization in the infarcted rat myocardium through the induction of thioredoxin-1, heme oxygenase-1 and vascular endothelial growth factor. *J Mol Cell Cardiol* 39: 813–822, 2005.
60. Kang YJ. New understanding in cardiotoxicity. *Curr Opin Drug Discov Devel* 6: 110–116, 2003.
61. Katori M, Buelow R, Ke B, Ma J, Coito AJ, Iyer S, Southard D, Busuttil RW, and Kupiec-Weglinski JW. Heme oxygenase-1 overexpression protects rat hearts from cold ischemia/reperfusion injury via an antiapoptotic pathway. *Transplantation* 73: 287–292, 2002.
62. Kawamoto S, Flynn JP, Shi Q, Sakr SW, Luo J, and Allen MD. Heme oxygenase-1 induction enhances cell survival and restores contractility to unvascularized three-dimensional adult cardiomyocyte grafts implanted *in vivo*. *Tissue Eng Part A* 17: 1605–1614, 2011.
63. Kawamura K, Ishikawa K, Wada Y, Kimura S, Matsumoto H, Kohro T, Itabe H, Kodama T, and Maruyama Y. Bilirubin from heme oxygenase-1 attenuates vascular endothelial activation and dysfunction. *Arterioscler Thromb Vasc Biol* 25: 155–160, 2005.
64. Kim AN, Jeon WK, Lee JJ, and Kim BC. Up-regulation of heme oxygenase-1 expression through CaMKII-ERK1/2-Nrf2 signaling mediates the anti-inflammatory effect of bisdemethoxycurcumin in LPS-stimulated macrophages. *Free Radic Biol Med* 49: 323–331, 2010.
65. Kim JW, Lim SC, Lee MY, Lee JW, Oh WK, Kim SK, and Kang KW. Inhibition of neointimal formation by trans-resveratrol: role of phosphatidyl inositol 3-kinase-dependent Nrf2 activation in heme oxygenase-1 induction. *Mol Nutr Food Res* 54: 1497–1505, 2010.
66. Kim NY, Pae HO, Ko YS, Yoo JC, Choi BM, Jun CD, Chung HT, Inagaki M, Higuchi R, and Kim YC. *In vitro* inducible nitric oxide synthesis inhibitory active constituents from Fraxinus rhynchophylla. *Planta Med* 65: 656–658, 1999.
67. Kim SH, Choi M, Lee Y, Kim YO, Ahn DS, Kim YH, Kang ES, Lee EJ, Jung M, Cho JW, Williams DR, and Lee HC. Natural therapeutic magnesium lithospermate B potently protects the endothelium from hyperglycaemia-induced dysfunction. *Cardiovasc Res* 87: 713–722, 2010.
68. Kitts DD, Yuan YV, Wijewickreme AN, and Thompson LU. Antioxidant activity of the flaxseed lignan secoisolariciresinol diglycoside and its mammalian lignan metabolites enterodiol and enterolactone. *Mol Cell Biochem* 202: 91–100, 1999.
69. Kivela AM, Kansanen E, Jyrkkanen HK, Nurmi T, Yla-Herttuala S, and Levonen AL. Enterolactone induces heme oxygenase-1 expression through nuclear factor-E2-related factor 2 activation in endothelial cells. *J Nutr* 138: 1263–1268, 2008.
70. Klaunig JE, Wang Z, Pu X, and Zhou S. Oxidative stress and oxidative damage in chemical carcinogenesis. *Toxicol Appl Pharmacol* 254: 86–99, 2011.
71. Kong JM, Chia LS, Goh NK, Chia TF, and Brouillard R. Analysis and biological activities of anthocyanins. *Phytochemistry* 64: 923–933, 2003.
72. Kostyuk VA and Potapovich AI. Mechanisms of the suppression of free radical overproduction by antioxidants. *Front Biosci (Elite Ed)* 1: 179–188, 2009.
73. Kroon PA, Iyer A, Chunduri P, Chan V, and Brown L. The cardiovascular nutrapharmacology of resveratrol: pharmacokinetics, molecular mechanisms and therapeutic potential. *Curr Med Chem* 17: 2442–2455, 2010.
74. Krzyzanowska J, Czubacka A, and Oleszek W. Dietary phytochemicals and human health. *Adv Exp Med Biol* 698: 74–98, 2010.
75. Kudugunti SK, Thorsheim H, Yousef MS, Guan L, and Moridani MY. The metabolic bioactivation of caffeic acid phenethyl ester (CAPE) mediated by tyrosinase selectively inhibits glutathione S-transferase. *Chem Biol Interact* 192: 243–256, 2011.
76. Kuriyama S. Green tea consumption and prevention of coronary artery disease. *Circ J* 74: 248–249, 2010.
77. Kushida T, Li Volti G, Quan S, Goodman A, and Abraham NG. Role of human heme oxygenase-1 in attenuating

TNF-alpha-mediated inflammation injury in endothelial cells. *J Cell Biochem* 87: 377–385, 2002.
78. Lawless MW, O'Byrne KJ, and Gray SG. Oxidative stress induced lung cancer and COPD: opportunities for epigenetic therapy. *J Cell Mol Med* 13: 2800–2821, 2009.
79. Lazze MC, Pizzala R, Perucca P, Cazzalini O, Savio M, Forti L, Vannini V, and Bianchi L. Anthocyanidins decrease endothelin-1 production and increase endothelial nitric oxide synthase in human endothelial cells. *Mol Nutr Food Res* 50: 44–51, 2006.
80. Lee B and Moon SK. Resveratrol inhibits TNF-alpha-induced proliferation and matrix metalloproteinase expression in human vascular smooth muscle cells. *J Nutr* 135: 2767–2773, 2005.
81. Lee BW, Chun SW, Kim SH, Lee Y, Kang ES, Cha BS, and Lee HC. Lithospermic acid B protects beta-cells from cytokine-induced apoptosis by alleviating apoptotic pathways and activating anti-apoptotic pathways of Nrf2-HO-1 and Sirt1. *Toxicol Appl Pharmacol* 252: 47–54, 2011.
82. Lee MJ, Chou FP, Tseng TH, Hsieh MH, Lin MC, and Wang CJ. Hibiscus protocatechuic acid or esculetin can inhibit oxidative LDL induced by either copper ion or nitric oxide donor. *J Agric Food Chem* 50: 2130–2136, 2002.
83. Levere RD, Martasek P, Escalante B, Schwartzman ML, and Abraham NG. Effect of heme arginate administration on blood pressure in spontaneously hypertensive rats. *J Clin Invest* 86: 213–219, 1990.
84. Li H, Wu S, Shi N, Lian S, and Lin W. Nrf2/HO-1 pathway activation by manganese is associated with reactive oxygen species and ubiquitin-proteasome pathway, not MAPKs signaling. *J Appl Toxicol* 31: 690–697, 2011.
85. Li Volti G, Sacerdoti D, Di Giacomo C, Barcellona ML, Scacco A, Murabito P, Biondi A, Basile F, Gazzolo D, Abella R, Frigiola A, and Galvano F. Natural heme oxygenase-1 inducers in hepatobiliary function. *World J Gastroenterol* 14: 6122–6132, 2008.
86. Li Volti G, Seta F, Schwartzman ML, Nasjletti A, and Abraham NG. Heme oxygenase attenuates angiotensin II-mediated increase in cyclooxygenase-2 activity in human femoral endothelial cells. *Hypertension* 41: 715–719, 2003.
87. Li Volti G, Sorrenti V, Murabito P, Galvano F, Veroux M, Gullo A, Acquaviva R, Stacchiotti A, Bonomini F, Vanella L, and Di Giacomo C. Pharmacological induction of heme oxygenase-1 inhibits iNOS and oxidative stress in renal ischemia-reperfusion injury. *Transplant Proc* 39: 2986–2991, 2007.
88. Li Volti G, Zappala A, Leggio GM, Mazzola C, Drago F, La Delia F, Serapide MF, Pellitteri R, Giannone I, Spatuzza M, Cicirata V, and Cicirata F. Tin chloride enhances parvalbumin-positive interneuron survival by modulating heme metabolism in a model of cerebral ischemia. *Neurosci Lett* 492: 33–38, 2011.
89. Lim JH and Kwon TK. Curcumin inhibits phorbol myristate acetate (PMA)-induced MCP-1 expression by inhibiting ERK and NF-kappaB transcriptional activity. *Food Chem Toxicol* 48: 47–52, 2010.
90. Lin JK. Molecular targets of curcumin. *Adv Exp Med Biol* 595: 227–243, 2007.
91. Loke WM, Proudfoot JM, Hodgson JM, McKinley AJ, Hime N, Magat M, Stocker R, and Croft KD. Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein E-knockout mice by alleviating inflammation and endothelial dysfunction. *Arterioscler Thromb Vasc Biol* 30: 749–757, 2010.
92. Ma J, Phillips L, Wang Y, Dai T, LaPage J, Natarajan R, and Adler SG. Curcumin activates the p38MPAK-HSP25 pathway *in vitro* but fails to attenuate diabetic nephropathy in DBA2J mice despite urinary clearance documented by HPLC. *BMC Complement Altern Med* 10: 67, 2010.
93. Maines MD. The heme oxygenase system: past, present, and future. *Antioxid Redox Signal* 6: 797–801, 2004.
94. Manna SK, Mukhopadhyay A, and Aggarwal BB. Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation. *J Immunol* 164: 6509–6519, 2000.
95. Mazza GJ. Anthocyanins and heart health. *Ann Ist Super Sanita* 43: 369–374, 2007.
96. Michaluart P, Masferrer JL, Carothers AM, Subbaramaiah K, Zweifel BS, Koboldt C, Mestre JR, Grunberger D, Sacks PG, Tanabe T, and Dannenberg AJ. Inhibitory effects of caffeic acid phenethyl ester on the activity and expression of cyclooxygenase-2 in human oral epithelial cells and in a rat model of inflammation. *Cancer Res* 59: 2347–2352, 1999.
97. Mizutani K, Ikeda K, Kawai Y, and Yamori Y. Resveratrol attenuates ovariectomy-induced hypertension and bone loss in stroke-prone spontaneously hypertensive rats. *J Nutr Sci Vitaminol (Tokyo)* 46: 78–83, 2000.
98. Morgan MJ and Liu ZG. Reactive oxygen species in TNFalpha-induced signaling and cell death. *Mol Cells* 30: 1–12, 2010.
99. Ndisang JF and Jadhav A. Heme-arginate suppresses phospholipase C and oxidative stress in the mesenteric arterioles of mineralcorticoid-induced hypertensive rats. *Hypertens Res* 33: 338–347, 2010.
100. Ogborne RM, Rushworth SA, Charalambos CA, and O'Connell MA. Haem oxygenase-1: a target for dietary antioxidants. *Biochem Soc Trans* 32: 1003–1005, 2004.
101. Ou J, Ou Z, Jones DW, Holzhauer S, Hatoum OA, Ackerman AW, Weihrauch DW, Gutterman DD, Guice K, Oldham KT, Hillery CA, and Pritchard KA, Jr. L-4F, an apolipoprotein A-1 mimetic, dramatically improves vasodilation in hypercholesterolemia and sickle cell disease. *Circulation* 107: 2337–2341, 2003.
102. Ou Z, Ou J, Ackerman AW, Oldham KT, and Pritchard KA, Jr. L-4F, an apolipoprotein A-1 mimetic, restores nitric oxide and superoxide anion balance in low-density lipoprotein-treated endothelial cells. *Circulation* 107: 1520–1524, 2003.
103. Paul B, Masih I, Deopujari J, and Charpentier C. Occurrence of resveratrol and pterostilbene in age-old darakchasava, an ayurvedic medicine from India. *J Ethnopharmacol* 68: 71–76, 1999.
104. Pellegatta F, Bertelli AA, Staels B, Duhem C, Fulgenzi A, and Ferrero ME. Different short- and long-term effects of resveratrol on nuclear factor-kappaB phosphorylation and nuclear appearance in human endothelial cells. *Am J Clin Nutr* 77: 1220–1228, 2003.
105. Penttinen P, Jaehrling J, Damdimopoulos AE, Inzunza J, Lemmen JG, van der Saag P, Pettersson K, Gauglitz G, Makela S, and Pongratz I. Diet-derived polyphenol metabolite enterolactone is a tissue-specific estrogen receptor activator. *Endocrinology* 148: 4875–4886, 2007.
106. Penumathsa SV, Koneru S, Samuel SM, Maulik G, Bagchi D, Yet SF, Menon VP, and Maulik N. Strategic targets to induce neovascularization by resveratrol in hypercholesterolemic rat myocardium: role of caveolin-1, endothelial nitric oxide synthase, hemeoxygenase-1, and vascular endothelial growth factor. *Free Radic Biol Med* 45: 1027–1034, 2008.

107. Rains JL and Jain SK. Oxidative stress, insulin signaling, and diabetes. *Free Radic Biol Med* 50: 567–575, 2011.
108. Robich MP, Osipov RM, Chu LM, Han Y, Feng J, Nezafat R, Clements RT, Manning WJ, and Sellke FW. Resveratrol modifies risk factors for coronary artery disease in swine with metabolic syndrome and myocardial ischemia. *Eur J Pharmacol* 664: 45–53, 2011.
109. Sacerdoti D, Escalante B, Abraham NG, McGiff JC, Levere RD, and Schwartzman ML. Treatment with tin prevents the development of hypertension in spontaneously hypertensive rats. *Science* 243: 388–390, 1989.
110. Saija A, Tomaino A, Lo Cascio R, Rapisarda P, and Dederen JC. *In vitro* antioxidant activity and *in vivo* photoprotective effect of a red orange extract. *Int J Cosmet Sci* 20: 331–342, 1998.
111. Saiko P, Szakmary A, Jaeger W, and Szekeres T. Resveratrol and its analogs: defense against cancer, coronary disease and neurodegenerative maladies or just a fad? *Mutat Res* 658: 68–94, 2008.
112. Sakata Y, Zhuang H, Kwansa H, Koehler RC, and Dore S. Resveratrol protects against experimental stroke: putative neuroprotective role of heme oxygenase 1. *Exp Neurol* 224: 325–329, 2010.
113. Salamone F, Li Volti G, Titta L, Puzzo L, Barbagallo I, La Delia F, Zelber-Sagi S, Malaguarnera M, Pelicci PG, Giorgio M, and Galvano F. Moro orange juice prevents fatty liver in mice. *World J Gastroenterol* 18: 3862–3868, 2012.
114. Scapagnini G, Foresti R, Calabrese V, Giuffrida Stella AM, Green CJ, and Motterlini R. Caffeic acid phenethyl ester and curcumin: a novel class of heme oxygenase-1 inducers. *Mol Pharmacol* 61: 554–561, 2002.
115. Scazzocchio B, Vari R, Filesi C, D'Archivio M, Santangelo C, Giovannini C, Iacovelli A, Silecchia G, Li Volti G, Galvano F, and Masella R. Cyanidin-3-O-beta-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPARgamma activity in human omental adipocytes. *Diabetes* 60: 2234–2244, 2011.
116. Schantz M, Erk T, and Richling E. Metabolism of green tea catechins by the human small intestine. *Biotechnol J* 5: 1050–1059, 2010.
117. Seki T, Naruse M, Naruse K, Yoshimoto T, Tanabe A, Seki M, Tago K, Imaki T, Demura R, and Demura H. Induction of heme oxygenase produces load-independent cardioprotective effects in hypertensive rats. *Life Sci* 65: 1077–1086, 1999.
118. Selvam C, Jachak SM, Thilagavathi R, and Chakraborti AK. Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents. *Bioorg Med Chem Lett* 15: 1793–1797, 2005.
119. Shen MY, Hsiao G, Liu CL, Fong TH, Lin KH, Chou DS, and Sheu JR. Inhibitory mechanisms of resveratrol in platelet activation: pivotal roles of p38 MAPK and NO/cyclic GMP. *Br J Haematol* 139: 475–485, 2007.
120. Sies H, Stahl W, and Sundquist AR. Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. *Ann N Y Acad Sci* 669: 7–20, 1992.
121. Sohal RS and Orr WC. Relationship between antioxidants, prooxidants, and the aging process. *Ann N Y Acad Sci* 663: 74–84, 1992.
122. Sohal RS and Weindruch R. Oxidative stress, caloric restriction, and aging. *Science* 273: 59–63, 1996.
123. Soleas GJ, Diamandis EP, and Goldberg DM. Resveratrol: a molecule whose time has come? And gone? *Clin Biochem* 30: 91–113, 1997.
124. Son S and Lewis BA. Free radical scavenging and antioxidative activity of caffeic acid amide and ester analogues: structure-activity relationship. *J Agric Food Chem* 50: 468–472, 2002.
125. Sorrenti V, Mazza F, Campisi A, Di Giacomo C, Acquaviva R, Vanella L, and Galvano F. Heme oxygenase induction by cyanidin-3-O-beta-glucoside in cultured human endothelial cells. *Mol Nutr Food Res* 51: 580–586, 2007.
126. Tan J, Ma Z, Han L, Du R, Zhao L, Wei X, Hou D, Johnstone BH, Farlow MR, and Du Y. Caffeic acid phenethyl ester possesses potent cardioprotective effects in a rabbit model of acute myocardial ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol* 289: H2265–H2271, 2005.
127. Thirunavukkarasu M, Penumathsa SV, Koneru S, Juhasz B, Zhan L, Otani H, Bagchi D, Das DK, and Maulik N. Resveratrol alleviates cardiac dysfunction in streptozotocin-induced diabetes: role of nitric oxide, thioredoxin, and heme oxygenase. *Free Radic Biol Med* 43: 720–729, 2007.
128. Tkachev VO, Menshchikova EB, and Zenkov NK. Mechanism of the Nrf2/Keap1/ARE signaling system. *Biochemistry (Mosc)* 76: 407–422, 2011.
129. Townsend PA, Scarabelli TM, Pasini E, Gitti G, Menegazzi M, Suzuki H, Knight RA, Latchman DS, and Stephanou A. Epigallocatechin-3-gallate inhibits STAT-1 activation and protects cardiac myocytes from ischemia/reperfusion-induced apoptosis. *FASEB J* 18: 1621–1623, 2004.
130. Tsuda H, Ohshima Y, Nomoto H, Fujita K, Matsuda E, Iigo M, Takasuka N, and Moore MA. Cancer prevention by natural compounds. *Drug Metab Pharmacokinet* 19: 245–263, 2004.
131. Tsutsui H, Kinugawa S, and Matsushima S. Oxidative stress and heart failure. *Am J Physiol Heart Circ Physiol* 301: H2181–H2190, 2011.
132. Turrens JF. The potential of antioxidant enzymes as pharmacological agents *in vivo*. *Xenobiotica* 21: 1033–1040, 1991.
133. Tzen JT, Jinn TR, Chen YC, Li FY, Cheng FC, Shi LS, She H, Chen BC, Hsieh V, and Tu ML. Magnesium lithospermate B possesses inhibitory activity on Na+,K+-ATPase and neuroprotective effects against ischemic stroke. *Acta Pharmacol Sin* 28: 609–615, 2007.
134. Ungvari Z, Orosz Z, Rivera A, Labinskyy N, Xiangmin Z, Olson S, Podlutsky A, and Csiszar A. Resveratrol increases vascular oxidative stress resistance. *Am J Physiol Heart Circ Physiol* 292: H2417–H2424, 2007.
135. Vanharanta M, Voutilainen S, Nurmi T, Kaikkonen J, Roberts LJ, Morrow JD, Adlercreutz H, and Salonen JT. Association between low serum enterolactone and increased plasma F2-isoprostanes, a measure of lipid peroxidation. *Atherosclerosis* 160: 465–469, 2002.
136. Vecoli C, Cao J, Neglia D, Inoue K, Sodhi K, Vanella L, Gabrielson KK, Bedja D, Paolocci N, L'Abbate A, and Abraham NG. Apolipoprotein A-I mimetic peptide L-4F prevents myocardial and coronary dysfunction in diabetic mice. *J Cell Biochem* 112: 2616–2626, 2011.
137. Vidavalur R, Otani H, Singal PK, and Maulik N. Significance of wine and resveratrol in cardiovascular disease: French paradox revisited. *Exp Clin Cardiol* 11: 217–225, 2006.
138. Wang G, Hamid T, Keith RJ, Zhou G, Partridge CR, Xiang X, Kingery JR, Lewis RK, Li Q, Rokosh DG, Ford R, Spinale FG, Riggs DW, Srivastava S, Bhatnagar A, Bolli R, and Prabhu SD. Cardioprotective and antiapoptotic effects of heme oxygenase-1 in the failing heart. *Circulation* 121: 1912–1925, 2010.

139. Wang LQ. Mammalian phytoestrogens: enterodiol and enterolactone. *J Chromatogr B Analyt Technol Biomed Life Sci* 777: 289–309, 2002.
140. Wang S, Qian Y, Gong D, Zhang Y, and Fan Y. Resveratrol attenuates acute hypoxic injury in cardiomyocytes: correlation with inhibition of iNOS-NO signaling pathway. *Eur J Pharm Sci* 44: 416–421, 2011.
141. Wang X, Stavchansky S, Kerwin SM, and Bowman PD. Structure-activity relationships in the cytoprotective effect of caffeic acid phenethyl ester (CAPE) and fluorinated derivatives: effects on heme oxygenase-1 induction and antioxidant activities. *Eur J Pharmacol* 635: 16–22, 2010.
142. Wei X, Zhao L, Ma Z, Holtzman DM, Yan C, Dodel RC, Hampel H, Oertel W, Farlow MR, and Du Y. Caffeic acid phenethyl ester prevents neonatal hypoxic-ischaemic brain injury. *Brain* 127: 2629–2635, 2004.
143. Worou ME, Belmokhtar K, Bonnet P, Vourc'h P, Machet MC, Khamis G, and Eder V. Hemin decreases cardiac oxidative stress and fibrosis in a rat model of systemic hypertension via PI3K/Akt signalling. *Cardiovasc Res* 91: 320–329, 2011.
144. Xiao K, Song QH, Zhang SW, and Xuan LJ. Water-soluble constituents of the root barks of Fraxinus rhynchophylla (Chinese drug Qinpi). *J Asian Nat Prod Res* 10: 205–210, 2008.
145. Yang C, Zhang X, Fan H, and Liu Y. Curcumin upregulates transcription factor Nrf2, HO-1 expression and protects rat brains against focal ischemia. *Brain Res* 1282: 133–141, 2009.
146. Yang L, Quan S, and Abraham NG. Retrovirus-mediated HO gene transfer into endothelial cells protects against oxidant-induced injury. *Am J Physiol* 277: L127–L133, 1999.
147. Yang Y, Wang X, Zhang L, An H, and Zao Z. Inhibitory effects of resveratrol on platelet activation induced by thromboxane a(2) receptor agonist in human platelets. *Am J Chin Med* 39: 145–159, 2011.
148. Yeh CH, Chen TP, Wang YC, Lin YM, and Lin PJ. HO-1 activation can attenuate cardiomyocytic apoptosis via inhibition of NF-kappaB and AP-1 translocation following cardiac global ischemia and reperfusion. *J Surg Res* 155: 147–156, 2009.
149. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, and Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 362: 2155–2165, 2010.
150. Yoshida Y, Shioi T, and Izumi T. Resveratrol ameliorates experimental autoimmune myocarditis. *Circ J* 71: 397–404, 2007.
151. Young AJ and Lowe GM. Antioxidant and prooxidant properties of carotenoids. *Arch Biochem Biophys* 385: 20–27, 2001.
152. Zeng B, Chen H, Zhu C, Ren X, Lin G, and Cao F. Effects of combined mesenchymal stem cells and heme oxygenase-1 therapy on cardiac performance. *Eur J Cardiothorac Surg* 34: 850–856, 2008.
153. Zghonda N, Yoshida S, Araki M, Kusunoki M, Mliki A, Ghorbel A, and Miyazaki H. Greater effectiveness of epsilon-viniferin in red wine than its monomer resveratrol for inhibiting vascular smooth muscle cell proliferation and migration. *Biosci Biotechnol Biochem* 75: 1259–1267, 2011.
154. Zheng Y, Toborek M, and Hennig B. Epigallocatechin gallate-mediated protection against tumor necrosis factor-alpha-induced monocyte chemoattractant protein-1 expression is heme oxygenase-1 dependent. *Metabolism* 59: 1528–1535, 2010.
155. Zhu H, Itoh K, Yamamoto M, Zweier JL, and Li Y. Role of Nrf2 signaling in regulation of antioxidants and phase 2 enzymes in cardiac fibroblasts: protection against reactive oxygen and nitrogen species-induced cell injury. *FEBS Lett* 579: 3029–3036, 2005.

Address correspondence to:
Dr. Giovanni Li Volti
Department of Drug Sciences
University of Catania
Viale Andrea 6
95125 Catania
Italy

E-mail: livolti@unict.it

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Abbreviations Used

ARE = antioxidant-response element
BDMC = bis-demethoxycurcumin
bZip = basic leucine zipper
CAPE = caffeic acid phenethyl ester
CAT = catalase
CO = carbon monoxide
CVD = cardiovascular diseases
DMC = demethoxycurcumin
EGCG = epigallocatechin-3-gallate
eNOS = endothelial nitric oxide synthase
ERK1/2 = extracellular signal-regulated kinase 1/2
GPx = glutathione peroxidase
HO-1 = heme oxygenase-1
JNK = c-Jun NH2- terminal kinase
Keap1 = Kelch-like ECH-associated protein 1
MAPKs = mitogen-activated protein kinases
MLB = magnesium lithospermate B
NO = nitric oxide
Nrf2 = nuclear factor erythroid 2-related factor
ROS = reactive oxygen species
SOD = superoxide dismutase
TF3 = theaflavin-3,39-digallate
VSMCs = vascular smooth muscle cells