ANTIOXIDANTS & REDOX SIGNALING
Volume 3, Number 6, 2001
Mary Ann Liebert, Inc.

Forum Review

Biological Effects of Resveratrol

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ABSTRACT

Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) is a common phytoalexin that is found in a few edible materials, such as grape skins, peanuts, and red wine. It has been speculated that dietary resveratrol may act as an antioxidant, promote nitric oxide production, inhibit platelet aggregation, and increase high-density lipoprotein cholesterol, and thereby serve as a cardioprotective agent. Based on epidemiological data, carcinogenesis and coronary heart disease are linked to dietary lifestyle and share a number of common pathways. Recently, it has been demonstrated that resveratrol can function as a cancer chemopreventive agent, and there has been a great deal of experimental effort directed toward defining this effect. Resveratrol has been reported to be estrogenic in transfected mammary cancer cells; however, there are conflicting results with respect to its actual estrogenic properties. In addition, resveratrol exhibits antiinflammatory, neuroprotective, and antiviral properties. In future work, some controversial *in vitro* biological effects need to be explored in animal models, and relevant physiological and pharmacological concentrations need to be used when assessing biological activities. This review focuses on various biological aspects of resveratrol and some issues that need to be addressed to gain a fuller appreciation of potential health benefits for human beings. Antioxid. Redox Signal. 3, 1041–1064.

INTRODUCTION

THE FIRST KNOWN USE OF GRAPE EXTRACTS for the benefit of human health can be dated back over 1,000 years. Darakchasava, an ayurvedic medicine wherein the main constituent is *Vitis vinifera* L., is prescribed as a cardiotonic in India (103). A significant portion of this preparation is resveratrol (3,4′,5-trihydroxy-*trans*-stilbene), a polyphenolic phytoalexin that is generated in response to stress in specific plants and is found in grape skins, peanuts, and red wine, as well as a host of nonedible plants (78). This compound is abundant in grapevines compared with other flowering plants, but is relatively low in fruits and vegetables (116). Resveratrol is produced preferentially in response to fungal infections as seen in mature vine berries, whereas it is virtually absent in unchallenged berries (79). Resveratrol is not the only stilbene involved in the fight against these infections, but is the parent viniferin from which several stilbene derivatives can be formed (33). Stilbenes are derived from the enzyme stilbene synthase using one molecule of 4-coumaroyl-CoA and three molecules of malonyl-CoA as substrates (116). Gene transplant experiments, with stilbene synthase transfected into tobacco germ lines, have resulted in an increased resistance to

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Botrytis cinerea, the pathogen that commonly infects grapevines (56).

One primary use of grapes is the preparation of wine. It has been proposed that moderate drinking of wine in French populations has led to a decreased risk of morbidity and mortality from coronary heart disease (CHD), a phenomenon that has been dubbed the "French paradox" (77). Several studies have shown that moderate wine drinkers are healthier than their heavy or nondrinking counterparts with respect to CHD (31, 117). High amounts of resveratrol in wine (as compared with other alcoholic beverages) have been speculated to be responsible for the decreased risk of CHD. Resveratrol was studied in rats for inhibition of cholesterol and triglyceride deposition in liver, and subsequent studies established that resveratrol was an inhibitor of platelet aggregation at physiologically relevant concentrations found after moderate wine drinking (1, 74). The fact that red wine is more beneficial than white wine further adds to the evidence that polyphenols, anthocyanins, tannins, and flavonoids (which are higher in concentration in red than white wine) may be the bioactive components (32). These classes of compounds possess antioxidant properties, and red wine extracts, not white, have been shown to inhibit platelet aggregation and protect against ischemic injury (36).

Resveratrol is unique as it is virtually absent in most fruits and vegetables that form a major portion of the human diet. The substance is found in a soluble form in wine. Wine may be considered the predominant bioavailable dietary source (117), but obviously ingestion of grapes or peanuts may be relevant. The compound bears a simple chemical structure that may interact with a variety of receptors and enzymes, thus acting as an activator or inhibitor in a number of pathways. Recently, a great amount of work has been directed toward understanding the cancer chemopreventive effects of resveratrol (68). There are several parallels between carcinogenesis and CHD, as both conditions have epidemiological evidence establishing correlations with dietary lifestyle. Further, there are a number of common mechanisms of etiology [*e.g.*, oxidative events, adhesion molecules, mitogen-activated protein kinase (MAPK) activation, etc.]. Another significant finding is that resveratrol exhibits estrogenic activity in transfected mammary cancer cell lines (52). However, conflicting results have been reported with respect to its actual estrogenic properties. In addition, resveratrol exhibits antiinflammatory, neuroprotective, and antiviral properties.

The wide array of biological activities mediated by resveratrol suggest its mode of action may be complex, and this has been of great interest to scientists working in the areas of basic biology and pharmacology. This review will focus on the biological activities of resveratrol and highlight further studies required to understand the pharmacological effects in human beings.

CARDIOPROTECTIVE EFFECTS OF RESVERATROL

Polyphenolics are suspected to afford cardioprotective effects owing to their spectrum of biological activities, especially as antioxidants. Relative to some areas of the world, the French population has a reduced incidence of CHD in spite of a high-fat diet and heavy smoking tendencies. This has been attributed to the consumption of red wine, which is rich in polyphenolics. In a study conducted in humans to understand the platelet aggregatory effects of different beverages, it was noteworthy that whereas a commercially available grape juice caused an increase in the ratio of thromboxane B2/12-hydroxyeicosatetraenoate, a resveratrol-enriched grape juice showed a decrease when tested in *ex vivo* experiments (101). Also, the commercial juice promoted thrombin-induced platelet aggregation, whereas the resveratrol-enriched juice had inhibitory activity. Moreover, platelets from subjects consuming the commercial juice had a higher cyclooxygenase (COX) to lipoxygenase ratio compared with those consuming resveratrol-enriched grape juice. In an independent study, it was shown that resveratrol, proanthocyanidins, and red wine extract were equally effective in reducing myocardial ischemic reperfusion injury in rats (34), whereas the importance of alcohol as a cardioprotectant in wines is questionable. For ex-

ample, Sato *et al*. (110) have shown that resveratrol, either in a red wine extract or as a single agent, protected the heart from ischemic injury in an isolated rat heart model. Malonaldehyde is a suitable marker for monitoring the extent of lipid peroxidation. In the above study, it was shown that resveratrol was as effective as red wine extract in reducing malonaldehyde content in coronary effluents. Although an interaction between the components of wine cannot be completely ruled out, as shown by Chan *et al*. (25), the concentration of ethanol used in these studies (0.1–0.75%) is much less than that found in alcoholic beverages. These studies suggest that resveratrol forms a major cardioprotective constituent in red wine.

Several mechanisms have been proposed that may be responsible for these cardiovascular effects. It has been hypothesized that a short-term provoked ischemia followed by reperfusion significantly increases the resistance of target tissues to severe ischemia; this process, called "ischemic preconditioning," is accompanied by an increase in adenosine levels. Blardi *et al*. (14) have shown that resveratrol increases endogenous plasma adenosine levels in humans for a period of 120 min. Although this is a short-term effect, this novel mechanism may contribute to its cardioprotective effects. In isolated rat heart experiments, it was shown that resveratrol, when administered before ischemic injury, attenuated the effect, and a corresponding increase in adenosine levels was observed (16). Resveratrol has also been shown to inhibit the peroxidation of low-density lipoproteins (LDL) by both chelating and free radical scavenging mechanisms (8). It was also a potent chelator of copper but not iron, indicating that it might play a role in accelerating removal of copper from LDL particles without affecting iron absorption from the intestines, unlike other polyphenols and tannins (17). In a similar study, resveratrol was shown to be more effective than flavonoids as a chelator of copper, and less effective as a free-radical scavenger (47). Tadolini *et al*. (128) have shown that resveratrol is an effective inhibitor of Fe^{2+}-catalyzed peroxidation of sonicated liposomes, less effective against peroxidation by 2,2′-azo*bis*(2-aminopropane) dihydrochloride (AAPH), but more effective against that initiated by 2,2′-azo*bis*(2,4-dimethylvalero)nitrile (AMVN) radicals. In all these studies, it has been demonstrated that resveratrol is effective as an antioxidant in a lipid environment.

Resveratrol has been shown to associate with very low-density lipoprotein to a greater extent than LDL, and least with high-density lipoprotein (7). Equal distribution was observed in the protein and lipid moieties of LDL after scavenging free radicals in the aqueous phase. The authors report that resveratrol first scavenges free radicals in the aqueous environment and then traps polyunsaturated fatty acids within membranes. It was also shown that resveratrol inhibits the formation of thiobarbituric acid-reactive substances (TBARS) induced by Cu^{2+} and azo compounds in human LDL (148). However, when rats were injected with doses of 20 and 40 mg/kg body weight, no effect on the lipid profile or the formation of TBARS from lipoproteins was observed (136).

Another mechanism that may account for a cardioprotective effect is vasorelaxation. Naderali *et al*. (97) have shown that resveratrol induces vasorelaxation in mesenteric and uterine arteries isolated from female guinea pigs, irrespective of the stage of the estrous cycle. Significantly, this effect was not inhibited by indomethacin, indicating that the vasorelaxation was not prostanoid-mediated and may be nitric oxide (NO)-mediated. In support of this observation, Chen and Pace-Asciak (26) have shown that pretreatment of isolated rat aorta with a NO synthase inhibitor antagonized the vasorelaxation caused by resveratrol. The authors suggest, however, that other mechanisms may play a role in vasodilation. For example, resveratrol has a stimulatory effect on Ca^{2+}-activated K^+ (BK_{Ca}) channels found in human vascular endothelial cells (81). It is postulated that increased K^+ efflux following the activation of BK_{Ca} channels by resveratrol may increase K^+ concentration in the myoendothelial space followed by hyperpolarization of vascular myocytes, leading to dilation of blood vessels.

In addition, a steroidal pathway for resveratrol-induced relaxation of porcine coronary arteries has been suggested (65). Resveratrol caused a dose-dependent inhibition of contractions induced by histamine, in the presence of

F^- ions, at physiological concentration, whereas higher doses were required to inhibit ouabain and tetraethylammonium-induced contractions. It was hypothesized, based on the estrogenic effects of resveratrol (52), that the relaxation induced by resveratrol could be mediated through activation of steroid-like membrane receptors that may impact inducible NO synthase (iNOS) leading to the production of NO. In addition, it may also enhance cycle GMP-mediated phosphorylation of BK_{Ca} channels. Further evidence for the induction of NO synthase and the consequent cardioprotective effects of resveratrol was provided by Hung *et al.* (63). In an anesthetized rat model, resveratrol decreased the incidence and duration of ventricular fibrillation and tachycardia with a concomitant increase in NO production.

An additional possibility to consider is that polymorphonuclear leukocytes (PMN) can contribute to the pathogenesis of acute CHD by formation of reactive oxygen species (ROS). Therefore, reduction of this response might be beneficial in preventing CHD (106). Resveratrol inhibited ROS generated by PMN and also the secretion and release of elastase and β-glucuronidase stimulated with formyl methionyl leucyl phenylalanine. In addition, resveratrol decreased the expression of β_2 integrin MAC-1 on the PMN surface, which is crucial for adhesion-mediated PMN functions (106). Ferrero *et al.* (43) have shown that resveratrol significantly inhibited the intracellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) expression in tumor necrosis factor-α (TNFα)-stimulated human endothelial cells, thus indirectly blocking the adhesion of monocytes and granulocytes to endothelial cells. As an extension of the above study, it was shown that resveratrol impairs TNFα-stimulated granulocyte adhesion to EA.hy926 endothelial cells and lipopolysaccharide (LPS)-stimulated monocyte adhesion to human saphenous vein endothelial cells, similar in fashion to anti-VCAM-1 antibody (44). In a recent study, resveratrol was also shown to inhibit the adhesion of blood platelets to fibrinogen (143).

The most widely accepted mechanism of resveratrol-mediated cardioprotection is its ability to inhibit platelet aggregation. Resveratrol, at a physiological concentration of 3.56 μg/L, was able to lower platelet aggregation by ~50% in healthy volunteers (11). Red wine containing ~1.2 mg/L resveratrol was diluted 1,000-fold and inhibited platelet aggregation by ~41%. Similarly, when the concentration of resveratrol was increased in the wine, the effect was raised to 78.5%, thus indicating that the amount of resveratrol in wine is important in determining its antiplatelet aggregatory activity. It was also shown in an independent study that *cis*-resveratrol might have a slightly higher antiaggregating activity than the *trans* isomer (12). Resveratrol may also act by inhibition of induction of tissue factor, a cell-surface glycoprotein that acts as an initiator of the coagulation cascade in hemostasis and pathogenesis (104). With endothelial cells, resveratrol inhibited the induction of tissue factor by a variety of factors, such as LPS, TNFα, and interleukin β, at a transcriptional level. However, resveratrol was not effective in inhibiting the binding of transcription factors c-fos/c-jun and c-rel/p65 (required for induction of tissue factor promoter) in either endothelial cells or monocytes. It also did not significantly affect the binding of nuclear factor κB (NFκB) in endothelial cells.

Another important stimulus for platelet aggregation is an increase in cytosolic Ca^{2+} levels in platelets (107). Resveratrol inhibits Ca^{2+} influx in thrombin-stimulated platelets with an IC_{50} of 0.5 μM (38). It is evident from this study that resveratrol operates through store-operated calcium channels, because thapsigargin, whose stimulation of Ca^{2+} influx was inhibited by resveratrol, operates through store-operated calcium channels. Endothelin-1 is a mediator of cardiovascular disorders, and endothelin-1 receptor blockers can alleviate symptoms of spasm-related cardiovascular diseases (54). A recent study identified resveratrol as an inhibitor of endothelin-1 stimulatory effects in coronary artery smooth muscle as seen by decreased MAPK activity (42). As speculated in previous reports, this effect could not be blocked by tamoxifen, suggesting an estrogen receptor (ER)-independent effect. Likewise, resveratrol had no effect on cyclic AMP levels, a down-regulator of the MAPK cascade.

In pig blood platelets, resveratrol inhibited the production of various ROS at high concen-

trations (25, 50, and 100 μg/ml) (99). However, Kirk *et al*. (75) caution that the inhibition of platelet aggregation by resveratrol may be observed only in washed platelets rather than in circulation. Resveratrol was also shown to inhibit MAPK activation induced by collagen, thrombin, and ADP. Most of the work described thus far has been in either cultured endothelial cells or isolated arteries. The relevance of these *in vitro* studies to an *in vivo* situation is not conclusive. For example, there has been one study in which resveratrol was shown to enhance atherosclerotic development in hypercholesterolemic rabbits (140). Although previous studies with polyphenolics have established their potential as antiatherosclerotic agents, and resveratrol (in particular) was effective in protecting against LDL peroxidation in a number of *in vitro* situations (8, 148), the authors of this report suggest that resveratrol may not be the active polyphenolic. On the other hand, in a stroke-prone spontaneously hypertensive rat model, resveratrol (5 mg/kg/day) exhibits estrogenic effects as seen by a blockade of ovariectomy-induced hypertension and bone loss (93). This is consistent with earlier observations indicating that resveratrol exhibits vasorelaxation in a NO-mediated manner. Resveratrol also enhanced acetylcholine-mediated vasodilatory responses similar to estrogens in the same model. Although mechanistic differences exist between the two models, both are designed to identify agents that are beneficial to the heart. Species differences may play a crucial role in these kinds of studies.

CANCER PREVENTIVE AND THERAPEUTIC EFFECTS OF RESVERATROL

Cancer chemopreventive agents are designed to reduce the incidence of tumorigenesis by intervening at one or more stages of carcinogenesis (9). The cancer preventive and therapeutic potential of resveratrol has been extensively studied in recent years. Significantly, this activity has been much less debated than its estrogenic or cardioprotective properties. Systematic studies in a wide range of cell lines and carcinogenesis checkpoints have established its utility as a chemopreventive agent. It was shown to affect three major stages of carcinogenesis by Jang *et al*. (68), and to inhibit the formation of preneoplastic lesions in a mouse mammary organ culture model. Resveratrol also inhibited the formation of 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-promoted mouse skin tumors in the two-stage model, and pretreatment of mouse skin with resveratrol negated several of the TPA-induced effects including inhibition of the mRNA expression of *c-fos* and *transforming growth factor-β1* (*TGF-β1*) (67).

Apoptotic cell death is a natural process by which genetically damaged and unwanted cells are eliminated in an orderly manner. Loss of apoptosis in certain cell populations could be the result of transformation to a malignant phenotype. Selective induction of apoptosis offers a promising strategy for prevention of this transformation and treatment of cancer, in addition to other pathological disorders (70). Resveratrol has been shown to induce apoptosis in HL-60 cells as demonstrated by DNA fragmentation, increased proportion of subdiploid cell population, and a time-dependent decrease in Bcl-2 expression (125). In the same cell line, Clement *et al*. (30) reported that resveratrol caused a dose-dependent increase in cleavage of caspase substrate poly(ADP-ribose) polymerase (PARP), and caspase inhibitors could block this effect. Another mechanism by which apoptosis inducers operate is by up-regulation of CD95-CD95L and its signaling pathway (48). The up-regulation of CD95-CD95L system was also shown to be one of the mechanisms of resveratrol-induced cell death in HL-60 cells. However, in a human monocyte leukemic cell line (THP-1), resveratrol caused apoptosis in a CD95-CD95L-independent manner (134). Similarly, Berhard *et al*. (10) observed resveratrol-induced apoptosis in CEM-C7H2 leukemia cells in a CD95-independent manner, as judged by lack of change in apoptosis in the presence of antibodies to CD95 or CD95L. Moreover, resveratrol was effective in inducing apoptosis in a CD95-resistant Jurkat cell line. In addition, resveratrol caused an S-phase arrest in these cells prior to apoptosis. The differences between apoptotic mechanisms in var-

ious cell lines can be inferred as cell line-specific effects. Also, a number of chemotherapeutic agents, such as doxorubicin, are known to function without affecting the CD95-CD95L system (88).

Another study in a rat colon carcinogenesis model has shown that resveratrol induced proapoptotic Bax expression in colon aberrant cryptic foci (130). p53, a highly mutated tumor suppressor gene in some forms of cancer, is known to be crucial for induction of apoptosis. Radiation-induced apoptosis was blocked in p53-deficient mice (89) and, in another study, a high number of spontaneous tumors were observed in these p53-deficient mice (141). Huang *et al.* (62) have shown with JB6 C1 41 cells that resveratrol suppresses cell transformation and induces apoptosis in a p53-dependent manner. Significantly, apoptosis was induced at the same concentration that was required to inhibit cell transformation. To the contrary, in erythroleukemic cells, apoptosis is a result of oxidative stress and is 5-lipoxygenase-dependent (83). Programmed cell death is induced in these cells by activation of 5-lipoxygenase, and resveratrol was shown to inhibit this effect in dose-dependent manner (84). In addition, resveratrol inhibited the activity of 15-lipoxygenase, COX, and peroxidase activity in these cells with IC_{50} values ranging from 4.5 to 40 μM.

In vivo evidence for the potential of resveratrol to induce apoptosis was obtained in a tumor model in which rats were inoculated with Yoshida AH-130 acites hepatoma cells. Resveratrol administered intraperitoneally caused an increase in the G_2/M phase of the cell cycle, apoptosis, as judged by an aneuploid peak, and a decrease in tumor growth (23). There is also an increasing body of evidence suggesting that formaldehyde generators or capturers can play a role in cell proliferation, differentiation, and apoptosis. Szende *et al.* (126) have shown that resveratrol has an effect on the formaldehyde cycle, and some resveratrol derivatives can mediate apoptotic effects in a variety of cell lines. It has also been shown in various cancer cell lines that resveratrol induces apoptosis at high concentrations, decreases mitotic activity, and decreases cell number in a formaldehyde-dependent manner (127).

Aryl hydrocarbons (AH) are activated to genotoxic metabolites that potentially bind to DNA, causing damage. One of the most important enzymes responsible for this activation is cytochrome P-4501A (CYP1A). Resveratrol was recently shown to be a selective inhibitor of this enzyme by using human liver microsomes and *E. coli* membranes coexpressing CYP1A1 and CYP1A2 as models (28). Casper *et al*. (24) have shown that resveratrol serves as an antagonist for the AH receptor. It promotes AH receptor translocation to the nucleus, but it inhibits transactivation of dioxin-responsive genes such as CYP1A1 and interleukin β. In a subsequent study, it was shown that resveratrol was effective in suppressing benzo[*a*]pyrene (B[*a*]P)-induced expression of CYP1A1/CYP1A2 (29). The binding of B[*a*]P-activated nuclear AH receptor to the xenobiotic response element of the CYP1A1 promoter was also inhibited. In addition, resveratrol caused inhibition of CYP1A1 transcriptional activation by 7,12-dimethylbenz[*a*]anthracene in MCF-7 cells. Another study showed that resveratrol could antagonize most responses mediated by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in a chicken periosteal osteogenesis model (114). TCDD suppressed the mRNA levels of several bone-associated proteins such as collagen type I and osteopontin, and resveratrol reversed these effects. Resveratrol inhibited the activity of cytochrome P450-linked enzymes, including benzylresorufin *O*-dealkylase, ethoxyresorufin *O*-deethylase, and methoxyresorufin *O*-demethylase in liver microsomal fractions (129). These mechanisms add to our understanding of antiinitiation effects mediated by resveratrol in procarcinogen models.

The second and crucial stage of carcinogenesis is promotion whereby initiated cells are expanded to form a population of transformed, premalignant cells manifested by changes in oncogenes and tumor suppressor genes (124). Phorbol ester-mediated tumor promotion was shown to be inhibited by resveratrol as seen by suppression of COX-2 mRNA expression induced by TPA in a mouse skin cancer model (67, 68). Stewart *et al.* (119) have shown that resveratrol inhibits the phorbol ester tumor-promoter receptor protein kinase C (PKC)-catalyzed phosphorylation of arginine-rich pro-

tein substrate in a noncompetitive manner. It was also shown that resveratrol exhibits a broad spectrum of inhibition against a variety of PKC isozymes, such as cPKC, nPKC, and aPKC. Stewart *et al*. (120), however, found that resveratrol exhibits a more distinguished inhibitory effect on the autophosphorylation reactions of protein kinase D. In another study, Garcia-Garcia *et al*. (50) have shown that resveratrol affects model membrane organization by obstructing the formation of an inverted hexagonal H_{II} phase and thus acting as an inhibitor of PKC. It was also suggested in this study that resveratrol might act as a direct inhibitor of PKCα activity. Gap junctional intracellular communication (GCIC) is important for normal cell growth, and suppression can lead to transformation. Many tumor promoters are known to inhibit GCIC, and Nielsen *et al*. (98) have shown that resveratrol antagonizes TPA-mediated inhibition of GCIC.

Resveratrol has also been shown to affect the growth and tumorigenic potential of several cancer cell lines. For example, resveratrol suppresses the expression and function of androgen receptor (AR) in LNCaP (prostate cancer) cells (91). Resveratrol down-regulated the expression of androgen-induced genes such as PSA and p21, in addition to mediating several other effects. The response could be mediated by an AR-independent mechanism, as shown by Hseih and Wu (60). In the same cell line, it was found that resveratrol neither affects the expression of AR nor binds to the AR, but mediates antiandrogenic effects. In a related study, it was found that resveratrol mediated growth inhibition and apoptosis in LNCaP cells (59). The authors extended these observations to some androgen-nonresponsive cell lines, whereby resveratrol caused growth inhibition and disrupted the G_1/S phase transition of the cell cycle without causing apoptosis.

Ulsperger *et al*. (137) reported that resveratrol desensitized AHTO-7 human osteoblasts to growth stimulation in response to carcinoma cell supernatants upon pretreatment. Greatest inhibition was observed with pancreas, breast, and renal carcinoma-derived supernatants, whereas colon and prostate had minimal effects. In another study with MC3T3-E1 osteoblast cells, resveratrol stimulated proliferation and differentiation as indicated by increased DNA synthesis, alkaline phosphatase, and prolyl hydroxylase activity (92). At lower concentrations, the production of prostaglandin E_2 (PGE_2) was reduced in these cells.

In a B[*a*]P plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumorigenesis A/J mice model, dietary resveratrol (500 ppm) had no effect (57). All chemopreventive agents in this study were administered during the postinitiation period. The authors conclude that antioxidants like resveratrol and curcumin were ineffective in this model as there was no indication of B[*a*]P plus NNK-induced oxidative damage. Further evidence for its antioxidant role was shown in a kidney carcinogenesis model. An oxidizing agent, potassium bromate, is used as a food additive, and has been shown to be carcinogenic in rats and mutagenic in the Ames test (64, 109). This agent has also been shown to be a kidney carcinogen whose effects could be attenuated by pretreatment with antioxidants. Resveratrol (injected intraperitoneally at 16 mg/kg body weight) completely abolished the increase in levels of oxo^{8}dG in renal genomic DNA and prevented the increase in kidney weight induced by potassium bromate (21).

In oral squamous cell carcinoma cells, resveratrol caused growth inhibition, both alone and in combination with quercetin, as shown by a decrease in DNA synthesis (41). Resveratrol was found to be more potent against human gingival epithelial cells than other cells of the oral cavity (3). In addition, resveratrol caused a decrease in DNA synthesis and irreversible damage to cell proliferation. It is noteworthy that resveratrol did not mediate any antioxidant effects in this cell line compared with quercetin and *N*-acetyl-L-cysteine. Also, resveratrol significantly inhibited the growth, but not the invasion, of highly metastatic B16-BL6 melanoma cells (22). Intraperitoneal administration of resveratrol to syngeneic mice inhibited the growth of melanoma cells injected intramuscularly without toxicity. In CaCo-2 colon cells, resveratrol caused 70% growth inhibition when tested at 25 μM, with a corresponding decrease in ornithine decarboxylase activity (111).

In some cell lines, resveratrol has been

shown to affect cell-cycle distribution in a tissue-specific mechanism. For example, in cultured bovine pulmonary artery epithelial cells, resveratrol induced NO synthase activity and caused accumulation of NO, which may explain the cardioprotective properties of resveratrol as seen by vasodilation, and inhibition of platelet aggregation induced by NO (61). It also caused a suppression of cell-cycle progression through the S and G_2 phases accompanied by elevated levels of p53 and p21 in these cells. Zou *et al*. (147) have shown that resveratrol inhibits proliferation of cultured smooth muscle cells induced by mitogens. It did not cause apoptosis in these cells, rather a $G_1 \rightarrow S$ cell-cycle block was observed. Both of the above studies further support the cardioprotective action of resveratrol.

In another study with HL-60 cells, resveratrol caused cell-growth arrest, induced differentiation, and enhanced cells in the G_1 and S phases of the cell cycle (105). There was also a corresponding increase in the levels of cyclins A and E, and cdc2 in the inactive phosphorylated form. Fontecave *et al*. (45) suggested a novel mechanism that may explain most of the cell-cycle effects of resveratrol. At a concentration of 100 μM, resveratrol inhibited ribonucleotide reductase, an enzyme that is required for the reduction of ribonucleotides to deoxyribonucleotides, in L1210-R2 cells. This was accompanied by a corresponding decrease in DNA synthesis. Resveratrol was also shown to inhibit DNA polymerase activity in SV-40-infected monkey kidney cells (122).

Resveratrol has been proposed to affect proinflammatory mechanisms, thereby acting as an antiinflammatory agent. Interleukin-6 has been shown to be activated in immune responses. Resveratrol caused dose-dependent inhibition of interleukin-6 release by cultured macrophages, with a concomitant blockade of Ca^{2+} influx into cells (145). In RAW 264.7 macrophages, resveratrol suppressed the activity of iNOS as seen by a decrease in NO generation in the culture medium (133). The effect was mediated through down-regulation of iNOS expression at the mRNA and protein levels. Resveratrol, at a concentration of 30 μM, also suppressed activation of NF-κB by LPS, and inhibited phosphorylation and degradation of inhibitory $\kappa B\alpha$ (I$\kappa B\alpha$). Chemopreventive effects of resveratrol have also been attributed to effects on NF-κB. Holmes-McNary and Baldwin (58) reported that resveratrol is a potent inhibitor of IκB kinase activity and thus inhibits NF-κB activation and NF-κB-dependent gene expression.

Evidence for antiinflammatory activity was also obtained by inhibition of ROS production in zymosan-stimulated murine macrophage RAW 264.7 cells, human neutrophils, and monocytes (66). Manna *et al*. (86) have shown that resveratrol suppressed TNF-induced NF-κB activation in a variety of cell lines. In addition, resveratrol inhibited TNF-induced activation of activator protein-1, MAPK kinase, c-JNK, ROS generation, lipid peroxidation, and caspase activation. Wadsworth and Koop (138) suggest that resveratrol (at a concentration as high as 100 μM) does not inhibit the LPS-induced activation of NF-κB complex. However, resveratrol operates by a unique mechanism whereby it was shown to induce TNFα in RAW 264.7 macrophages, which may have cytostatic and cytotoxic properties, inhibits the production of NO, but slightly enhances iNOS mRNA expression. The authors hypothesized that by acting as a COX-1 inhibitor, resveratrol further blocks the negative feedback loop of prostaglandins that down-regulate TNFα production. Palmieri *et al*. (102) have shown that 50% of erythrocyte lysis due to H_2O_2-lactoperoxidase–KI incubation resulted in production of ROS. Resveratrol prolonged this effect to 240 min and, in addition, caused inhibition of tyrosine kinase activity in cytosolic and particulate fractions of prostatic adenoma.

As a unifying hypothesis for its antiinflammatory and chemopreventive properties, resveratrol has been shown to affect the activity and expression of both COX-1 and COX-2. These enzymes are important for the production of prostaglandins under physiological conditions. COX-1 is implicated in inflammation and is constitutively expressed (115), whereas COX-2 is an inducible enzyme that responds to mitogens and growth factors (108). COX-2 is up-regulated in tumorigenesis, and $APC^{\Delta 716}$ knockout mice, having a null mutation for COX-2, have a lower incidence of intestinal tumors (139). Resveratrol has been shown to in-

hibit the activity of the COX-1 enzyme derived from sheep seminal vesicles (68, 112). It was also shown in rats that resveratrol reversed mild water immersion and restraint stress (WRS)-induced gastric protection and blood flow, and attenuated the increase in PGE_2 caused by WRS, demonstrating it was a specific COX-1 inhibitor (19). However, recent studies highlight the importance of resveratrol as a COX-2 inhibitor as well. Subbaramaiah *et al*. (121) have shown that resveratrol suppressed COX-2 expression by inhibiting PKC signal transduction. Resveratrol inhibited the phorbol 12-myristate 13-acetate (PMA)-induced activation of PKC- and activator protein-1-mediated gene expression in human mammary epithelial cells. Overexpression of PKCα, extracellular-regulated kinase (ERK)1, and c-jun led to an increase in COX-2 promoter activity, all of which were suppressed by resveratrol when tested at a concentration of 15 μM. In addition, resveratrol inhibited the activity of COX-2 enzyme in a dose-dependent manner.

It was also shown in other studies that resveratrol (in addition to other resorcin-type molecules) suppressed both basal levels and TGFα-induced COX-2 promoter-dependent transcriptional activity in colon cancer cells (96). Significantly, resveratrol administered at 200 μg/kg/day in drinking water was shown to suppress the formation of colorectal aberrant crypt foci (ACF) in a rat carcinogenesis model (130). This was accompanied by up-regulation of *bax* in ACF but not in normal mucosa, and down-regulation of p21 expression in normal mucosa but not in ACF. Mietus-Snyder *et al.* (90) recently showed the importance of COX-2 in oxidative stress of smooth muscles and its suppression by resveratrol. The authors showed that SR-A, a gene whose expression correlates well with redox activation in smooth muscles, is greatly enhanced in oxidative stress and is accompanied by an increase in COX-2 expression. Other groups have also shown that resveratrol inhibits both protein tyrosine kinase and PKC activity purified from bovine thymus (69). Moreno (95) has shown that resveratrol inhibits ROS production, phospholipase A_2 activity, arachidonic acid release, and PGE_2 synthesis stimulated by fetal calf serum or platelet-derived growth factor in 3T6 fibroblasts. The COX-2 protein induced by these agents was also down-regulated by resveratrol leading to decreased growth and DNA synthesis. The same observations were extended in murine resident peritoneal macrophages. It was shown that resveratrol inhibited LPS- and PMA-induced formation of ROS, inhibited COX-2 induction, and caused marked reduction of prostaglandin synthesis and arachidonic acid release (87).

Johnson and Maddipati (71) have dissected the COX inhibitory effects of resveratrol. They have shown that resveratrol inhibits the peroxidase but not the COX activity of prostaglandin H synthase-2, leading to the accumulation of prostaglandin G2, which is a toxic endoperoxide. In a study conducted with rats, resveratrol augmented acute gastric lesions induced by ischemia–reperfusion and delayed the progress of these lesions into ulcers (18). The role of prostaglandins in the progress of lesions was confirmed by resveratrol intervention. Bertelli *et al*. (13) have shown that resveratrol inhibits *Candida albicans*-facilitated intracellular killing by macrophage-like cells in the U937 human promonocytic cell line. Low values of phagocytosis were observed in these cells compared with macrophages from healthy human subjects owing to their poorly differentiated state; however, on treatment with 1 μM resveratrol, differentiation was induced as well as the phagocytic activity against *C. albicans*. Resveratrol at the same concentration has induced differentiation in other cell lines (105). Intracellular killing was also enhanced at this concentration to levels comparable to healthy subjects. At a higher concentration (10 μM), resveratrol had opposite effects, as seen by decreased intracellular killing with a concomitant decrease in ROS production in these cells. Differentiation was induced in these cells by resveratrol (1 μM) just 20 min after infection with *C. albicans.* The authors also compared the differentiation-inducing effect of resveratrol in HL-60 and U937 cells. Resveratrol, at a concentration of 32 μM, caused phosphatidylserine externalization in HL-60 cells after 18 h of treatment. Much lower doses (100 nM–1 μM) were required to observe the same effect starting 4 h after treatment in U937 cells.

Resveratrol affects various pathways in different stages of carcinogenesis, modulates the cell cycle, and causes apoptosis in various cancer cell lines. A summary of the events reported to be altered by resveratrol is illustrated in Fig. 1 (apoptosis pathways) and Fig. 2 (carcinogenesis and cell cycle). Although all sequences leading to carcinogenesis and apoptosis have not been described, the schemes represent an overview of specific checkpoints where resveratrol intervenes.

ESTROGEN RECEPTOR-MODULATORY EFFECTS

The most controversy exists with respect to the estrogenic/antiestrogenic properties of resveratrol. A report by Gehm *et al*. (52) indicates that resveratrol, at a concentration required for other biological effects, acts as a strong estrogen agonist in transfected MCF-7 cells. The authors attributed the estrogenic effects to its structural similarity with diethylstilbestrol, a synthetic estrogen. When combined with estradiol (E_2), resveratrol exhibited superagonist activity, as seen by a maximal transcriptional response greater than that mediated by E_2 alone. Subsequent studies led to controversy. For example, Lu and Serrero (82) report that resveratrol in the same cell line shows antiestrogenic activity as seen by a suppression of progesterone receptor expression induced by E_2. In addition, resveratrol down-regulated the basal levels of TGFα1 and insulin-like growth factor-1 and up-regulated TGFβ2 mRNA. On the other hand, a study by Basly *et al*. (4) compared the *trans*- and *cis*-resveratrol estrogenic effects in MCF-7 cells. They report that both isoforms of resveratrol exhibit superestrogenic activity at moderate concentrations (10 and 25 μM), whereas at low concentrations (0.1 and 1 μM), antiestrogenic effects are mediated in transfected estrogen response element (ERE)-luciferase reporter experiments. Gehm *et al*. (52) have also shown that resveratrol binds to partially purified ER from rat uterus at a concentration (10 μM) re-

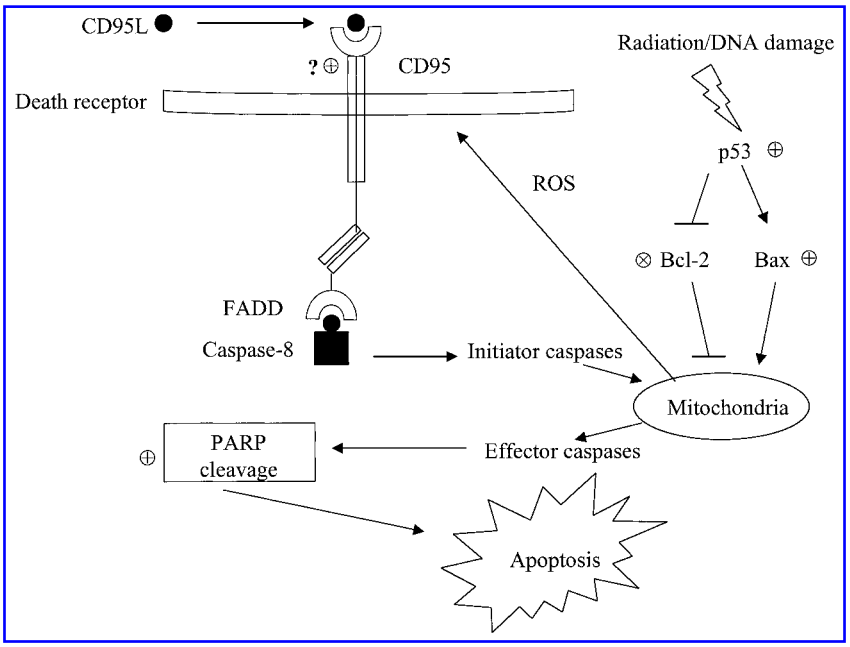

FIG. 1. Schematic respresentation of the effect of resveratrol on various mediators of apoptotic cell death. The plus symbol (⊕) indicates targets of resveratrol that are either enhanced or activated, and the cross (⊗) indicates targets that are either suppressed or inhibited. A question mark indicates controversial data. Resveratrol has been shown to up-regulate the CD95-CD95L system in HL-60 cells, but not in other leukemic cell lines. Resveratrol also enhanced PARP cleavage in HL-60 cells. In JB6 C1 41 cells, resveratrol induced apoptosis in a p53-dependent manner. In a colon carcinogenesis model, resveratrol induced proapoptotic *bax* expression, whereas *bcl-2* expression was down-regulated in HL-60 cells.

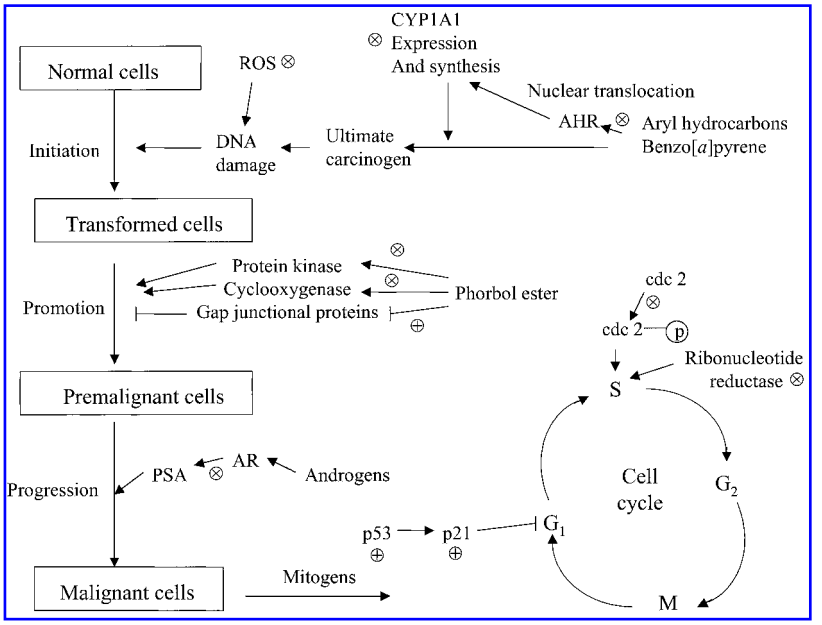

FIG. 2. Schematic representation of carcinogenesis and cell-cycle intervening points of resveratrol. The plus symbol (⊕) indicates targets of resveratrol that are either enhanced or activated, and the cross (⊗) indicates targets that are either suppressed or inhibited. See text for details.

quired for estrogenic activation in transfection studies. This activity was not confirmed in subsequent studies, although different sources of ER were used. For example, resveratrol showed no binding to ER in cell extracts of the PR1 pituitary cell line (118), but enhanced prolactin secretion without causing growth stimulation. Strikingly, the induction of prolactin secretion was blocked by a pure antiestrogen in this study. Further work in MC3T3-E1 osteoblastic cells has shown that resveratrol increased alkaline phosphatase and prolyl hydroxylase activity in these cells, indicating an estrogenic and bone loss preventive effect. Both activities could be antagonized by tamoxifen, signifying an estrogenic pathway. In another study by Yoon *et al*. (142), resveratrol did not show any binding to partially purified mouse uterine ER. In U2 osteogenic cancer cells transfected with ER-activation function 1-luciferase plasmid, resveratrol caused an estrogenic response, whereas in HepG2 liver cells, resveratrol antagonized the action of E_2 in a dose-dependent manner.

In vivo experiments with resveratrol designed to establish estrogenic effects have also led to indefinite conclusions. At least three separate studies have been conducted with ovariectomized rats using a range of doses. Ashby *et al*. (2) have shown in ovariectomized rats treated with resveratrol at concentrations ranging from 0.3 to 70 mg/kg body weight/day, s.c., no estrogenic effects were mediated as judged by several endpoints, including uterine weight. Another study with weanling rats confirmed the lack of effect of resveratrol (administered in the diet at concentrations ranging from 1 to 1,000 μg/day) on uterine weight, epithelial cell height, and mRNA levels of insulin-like growth factor-1 (135). To the contrary, resveratrol, at higher concentrations (1,000 μg/day), antagonized the cholesterol-lowering effect of E_2. The only reported study where resveratrol was shown to have estrogenic properties was in stroke-prone spontaneously hypertensive rats (93). Resveratrol administered in the diet at a concentration of 5 mg/kg/day to ovariectomized rats attenuated the increase in systolic blood pressure. It also enhanced the endothelin-dependent vascular relaxation in response to acetylcholine and prevented ovariectomy-induced decreases in femoral bone strength in a manner similar to E_2. These authors further extended their observations to study advanced glycation end-products (AGEs) of plasma proteins in vascular

smooth muscles from normal and stroke prone rats. AGEs are potent mediators of vascular disorders like atherosclerosis. Resveratrol caused a suppression of AGEs-stimulated cell proliferation, DNA synthesis, and prolyl hydroxylase activity in a dose-dependent manner (94). Significantly, these effects could be partially antagonized with the pure antiestrogen, ICI 182780.

Recently, Bowers *et al*. (15) showed that resveratrol acts as a mixed agonist/antagonist in transiently transfected cells. Resveratrol could bind to both ER-α and ER-β with comparable affinity, but with 7,000-fold lower affinity than E_2. It was also shown that the type of estrogen modulatory activity of resveratrol depends on the ERE sequence and ER subtype. Resveratrol was shown to have higher transcriptional activity when liganded to ER-β than ER-α. Moreover, resveratrol showed antagonist activity for ER-α but not for ER-β. All these effects (estrogenic or antiestrogenic) were significant at concentrations 10 μM or higher.

These studies have led us to speculate if resveratrol could function as a selective ER modulator. Considering lack of estrogenic activity in the uterus and mammary gland (and possible antiestrogenic activity in the same tissues), and estrogenic activity in bone and endothelial cells, desirable pharmacological effects could be facilitated by a selective ER modulator. However, controversial ER binding activity and ER-superagonistic effects require thorough investigation.

MISCELLANEOUS BIOLOGICAL ACTIVITIES

Considerable interest has been shown recently in studying resveratrol as a neuroprotectant. Most importantly, these effects have been observed under subphysiological concentrations. Tredici *et al*. (131) have shown that resveratrol induces phosphorylation of MAPK family members, ERK1 and ERK2, in human neuroblastoma cells, at a concentration of 1 pM. Epidemiological studies have also shown an inverse relationship with wine consumption and dementia (80, 100). Owing to its antioxidant properties, resveratrol has been shown to inhibit the peroxidation of LDL in PC-12 cells and protect against neuronal cell death that could manifest Alzheimer's disease (40). The antioxidant properties of resveratrol have been shown to contribute neuroprotective effects in cultured hippocampal neurons (5). In another study, it was shown that cysteamine pretreatment of the astroglial substratum enhances PC-12 cell vulnerability to oxidative injury causing cell death (46). Resveratrol, as an antioxidant, abrogated this effect, pointing to the role of oxidative stress in the injury.

The lipophilic nature of resveratrol and its corresponding ability to cross the blood–brain barrier could explain some of its central nervous system-related biological effects. Zini *et al.* (146) have shown that resveratrol exhibits a biphasic inhibition of the rat brain respiratory chain. Resveratrol inhibits complex III of the respiratory chain, which might explain its suppression of ROS generation, whereas inhibition of complex V is linked to its suppression of ATPase. Karlsson *et al*. (72) have used an electron paramagnetic resonance spin-trapping technique to show the free radical scavenging properties of resveratrol in embryonic mesencephalic cells. It inactivates several complexes induced by glutamate plus malate in a biphasic fashion and acts as a protectant in three models of oxidation. However, in primary cultures of cerebellar granule neurons, it was shown that resveratrol failed to inhibit apoptosis induced by glutamate and low K^+ concentrations, whereas other antioxidants such as ascorbic acid and red wine extracts inhibited this effect (37). It was suggested that the resveratrol, in addition to other antioxidants such as α-tocopherol, might not have the ability to access intracellular sites where ROS formation is prevalent.

Resveratrol also inhibits mitochondrial proton F_0F_1-ATPase activity with rat brain and liver isolates in a noncompetititve and additive manner (144). In another study, it was shown that rat liver mitochondria exposed to AAPH damage F_0F_1-ATPase and form peroxides in the aqueous region without affecting malondialdehyde formation. Resveratrol and α-tocopherol, both hydrophobic antioxidants, could not suppress this effect (6). Resveratrol, and more significantly oxyresveratrol, were shown

to be moderate inhibitors of the dopa oxidase activity of mushroom tyrosinase, an enzyme that plays a role in melanin biosynthesis (113). This enzyme also causes darkening of food products of plant origin. Human amyloid disorders such as familial amyloid cardiomyopathy are caused by insoluble transthyretin fibrils, which deposit in peripheral nerves and heart tissue (76). Resveratrol was shown to significantly reduce transthyretin fibril formation by fitting in the T4 binding site while maintaining its minimum energy conformation, thus representing a new class of drug active against transthyretin-associated human amyloid diseases (76).

In a recent study, relative to normal hematopoietic cells, resveratrol profoundly inhibited the proliferation of mouse and human leukemic cells (51). The moderate effect observed with normal hematopoietic progenitor cells was reversible but, in leukemic cells, resveratrol caused apoptosis in an irreversible manner. In lethally irradiated mice, resveratrol led to significant hematopoietic reconstitution. Thus, it has been suggested that resveratrol may serve as a novel agent for *ex vivo* bone marrow purging. In another study, resveratrol selectively inhibited the proliferation and migration of liver myofibroblasts (53). It decreased the expression of α-smooth muscle actin, an important marker for myofibroblastic cells, but did not affect the expression of other cytoskeletal proteins like vimentin or β-cytoplasmic actin. It also inhibited the expression of type I collagen and matrix metalloproteinase-2, considered two parameters of migration in these cells.

Another report highlights the effect of resveratrol in rat hepatic stellate and Kupffer cells, which play a central role in hepatic fibrogenesis (73). It was shown that resveratrol suppressed thymidine incorporation, BrdU uptake, inositol phosphate metabolism, tyrosine phosphorylation, and MAPK activation in these cells. Resveratrol also selectively inhibited cyclin D1 expression in stellate cells and blocked the production of NO and TNFα by LPS-stimulated Kupffer cells without affecting the mRNA levels. Resveratrol was also shown to inhibit the proliferation of human hepatoblastoma HepG2 cells, causing a delayed entry into mitosis (35).

The effects of resveratrol on viral infections have also been reported recently. The compound was shown to cause reversible inhibition of herpes simplex virus types 1 and 2 replication in Vero cells (39). Effects were prominent 1 h after infection, but not after 9 h, indicating an early event of inhibition that was subsequently shown to be due to a reduction of ICP-4, a major immediate early viral regulatory protein. However, resveratrol did not cause direct inactivation of herpes simplex virus nor did it affect viral attachment to the cell. Resveratrol also caused cell-cycle delay at the S–G_2/M interphase of Vero cells and inhibited the reactivation of virus from latent infections.

Helicobacter pylorus is a major ulcer-causing bacterial strain and is found to be associated with dyspepsia, gastritis, and gastric cancer (55). It has also been shown recently that COX-2 is expressed in various stages of gastrointestinal carcinogenesis as seen in gastric biopsies of infected patients suffering from intestinal metaplasia and gastric adenocarcinoma (122). It is worthwhile investigating the effects of resveratrol in these conditions. Moreover, Mahady and Pendland (85) have shown that resveratrol and red wine extract inhibited the growth of 15 clinical isolates of *H. pylori*.

Resveratrol has been implicated to play a role in the protection against allergic disorders. β-Hexosaminidase is released by mast cells in response to immunological activation. Resveratrol caused a dose-dependent inhibition of this release in cultured RBL-2H3 cells (27). Resveratrol was also shown to be a DNA-cleaving agent in the presence of Cu^{2+} ions enhancing the formation of hydroxyl-radical formation (49). However, Burkitt and Duncan (20) reported that under physiological conditions (in the presence of either ascorbic acid or glutathione) resveratrol behaves as an antioxidant by a hydroxyl-radical scavenging mechanism and, in the presence of glutathione, it inhibited the formation of glutathione disulfide.

CONCLUSIONS—THE ENIGMA OF RESVERATROL

Unlike many drugs used in the prevention or treatment of various disorders, resveratrol

has a remarkably simple structure. This provides a major advantage because sourcing is not a limitation. As demonstrated by a large number of recent reports, resveratrol can mediate a wide range of biological activities, with no obvious toxicity. Thorough preclinical toxicity studies are currently under way, but it is notable that no toxicity reports have been published with respect to resveratrol in animals. As an example, we have incorporated resveratrol into the diets of rats at levels of 3,000 mg/kg diet for 120 days, and no significant changes in body weights were observed nor were there any other signs of overt toxicity (unpublished observations). Thus, in conjunction with human dietary experience, it is relatively clear that resveratrol can be safely administered.

As biologists and chemists are dealing with a common molecule with variable interests, certain practical aspects tend to be neglected. For example, while testing for *in vitro* pharmacological activities, researchers tend to use concentrations as high as 100 μM. Although this might be of interest to understand the preventive effect of resveratrol against a disorder (efficacy), the actual therapeutic benefit may be questionable. Preventive agents need to be tested in physiologically relevant concentrations because a correlation should exist between the experimental concentrations and the amount present in the diet (which is presumably low) or through dietary supplements. Virtually all the evidence supporting notions such as the "French paradox" is from epidemiological studies, and researchers can only try to duplicate such a situation in the laboratory by using either *in vitro* or animal models that can parallel the population study. Clinical studies with chemopreventive agents are also generally more complex than those conducted with their therapeutic counterparts. Therapeutic agents are often administered on a short-term basis (compared with chemopreventive agents that need to be administered for several years), and administered after a disease has been diagnosed. It can be asserted that the dose of a chemopreventive agent should be chosen based on that found in the diet (or through supplementation) and that which is achievable in the plasma. As a generalization, physiological concentrations normally do not exceed 1 μM. With resveratrol, a few studies in rats have shown that the total tissue and plasma concentrations after the administration of red wine is in the 100 nM to 1 μM range. The dosing of rats with red wine was based on that consumed by moderate drinkers. These studies were conducted after a single administration of red wine, and parameters such as long-term effects, bioavailability, and metabolism, remain unknown. Nevertheless, it would be prudent to select appropriate doses for the conduct of *in vitro* experiments.

Some of the *in vitro* activities of resveratrol, the concentrations used, and the corresponding *in vivo* activities are summarized in Table 1. It is obvious that testing of resveratrol at a concentration of 100 μM with *in vitro* models is not relevant to normal dietary levels, and corresponding responses may not be observed in animal models. The lowest concentration reported for the effectiveness of resveratrol has been in neuroprotection. Resveratrol, at a concentration as low as 1 pM, caused phosphorylation of ERK1 and ERK2, a potential prerequisite for normal brain function. Similarly, platelet aggregation was inhibited by resveratrol in nanomolar quantities. It is noteworthy that both of these effects (neuro- and cardioprotection) have epidemiological, *in vitro* and *in vivo* evidence.

In animal studies, such as in the case of chemopreventive agents, it is worthwhile to investigate the maximum tolerated dose of a nutrient. However, using high test concentrations for *in vitro* experiments may only yield nonspecifically active agents. For example, extremely high doses of many drugs can lead to nonspecific and general cytotoxicity and numerous alterations of signal transduction. To date, a consistent maximum concentration, beyond which testing would likely yield pharmacologically irrelevant results, has not been established.

As noted previously, there is considerable controversy regarding the estrogenic potential of resveratrol. Key observations were reported by Gehm *et al.* (52), who demonstrated a superagonistic response with an ERE-based reporter in cultured MCF-7 cells. We have been unable to reproduce these data with the same model system. Rather, a mild agonistic re-

TABLE 1. COMPARISON OF *IN VITRO* AND *IN VIVO* EFFECTS OF RESVERATROL FOR VARIOUS BIOLOGICAL ACTIVITIES*

In vitro *activity*	*Concentration*	*Corresponding* in vivo *activity*
Inhibit TBARS formation	50 μM	Ineffective in rats for reducing TBARS when tested at 20 and 40 mg/kg body weight for 21 days.
Vasorelaxation	0.45–0.75 μM	Attenuates hypertension in ovariectomized rats when administered at 5 mg/kg/day.
Protection against LDL peroxidation	30–200 μM	Promotes atherosclerosis in hypercholesteremic rabbits when administered at 1 mg/kg diet.
Apoptosis induction	10 μM	Administered i.p. at 1 mg/kg body weight; caused apoptosis in ascites hepatoma cells.
Antioxidant effects	250 nM–30 μM	Pretreatment of mouse skin with resveratrol negated TPA-induced oxidative events in a dose-dependent manner. TPA-induced increases in the expression of c-fos and TGF-β1 were selectively inhibited.
COX-2 inhibition	2.5–20 μM	Inhibited ACF formation in rats with 200 μg/kg/day in drinking water.
Estrogenic effects	1–10 μM	Specifically inhibited hypertension induced in ovariectomized rats at 5 mg/kg/day in the diet. Failed in other studies aimed at estrogenic effects on the uterus.

*For literature citations, see text.

sponse was observed in a narrow dose range (~10 μM), but in the presence of E_2, antagonism was observed at all concentrations tested, rather than superagonism. The reason for these differences in results is unknown. One possibility we have explored is the stability of resveratrol to light, heat, pH, and/or oxygen exposure. For example, resveratrol is stable to moderate heating, but will react when exposed to low or high pH (132). Resveratrol exists predominantly as the *trans* isomer, but exposure to light will cause excitation of the electrons in the alkene to undergo a π to π^* transition and induce isomerization through a perpendicular transition state to *cis*-resveratrol (Fig. 3). This occurs readily when resveratrol is exposed to light near its λ_{max} (306 nm for *trans*, 288 nm for *cis*), which is in the near-UV region of the electromagnetic spectrum. Fluorescent lighting, the primary source of illumination in laboratories, is generated by the white phosphor re-emission of UV light from excited mercury vapor. Most of the UV light is absorbed by the phosphor coating; however, spikes in the near-UV (310, 340, and 365 nm) are transmitted and can affect samples that are exposed. Clear borosilicate glass vials provide some protection for wavelengths below 350 nm, but only amber-colored vials insure complete protection. *cis*-Resveratrol is nonplanar due to the steric effects of the aromatic rings and is extremely sensitive to light, thereby converting back to the more stable *trans* isomer. The *cis* isomer is also sensitive to low pH (1.0), with 50% converting to *trans*-resveratrol in 23 h. Both *cis*- and *trans*-resveratrol are stable to pH 3–8, but are degraded at pH 10 and above to unspecified products (132). Resveratrol, especially in solu-

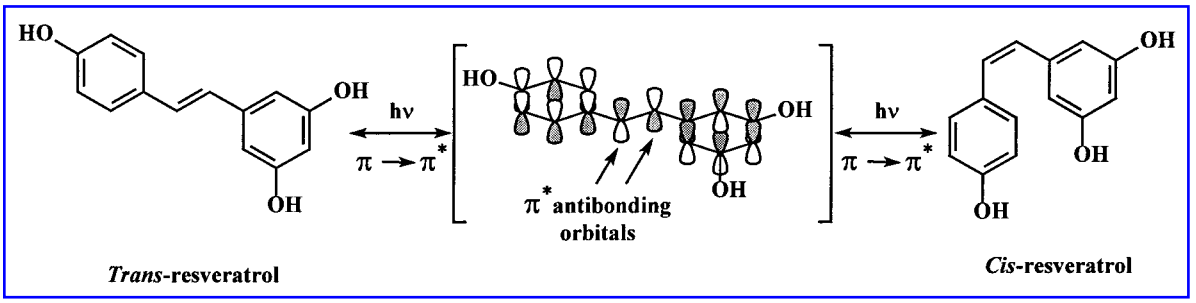

FIG. 3. Mechanism for light-induced isomerization of resveratrol.

tion, should be stored in amber containers to avoid undue exposure to light. In principle, the resulting mixture of isomers from careless handling can have widely different activities and cause significant discrepancies from assay to assay.

Based on these considerations, using the ERE-luciferase transfected MCF-7 cell model, we tested the estrogenic potential of various resveratrol preparations. Resveratrol was dissolved at a concentration of 10 μM in either dimethyl sulfoxide (DMSO) or ethanol and transferred to clear or amber-colored vials. Aliquots were removed on day 0, day 3, and day 6, after exposure to fluorescent light (18 h/day, benchtop height), and stored at −20°C in amber vials with tetrafluoroethylene liners. A separate ethanol solution of resveratrol was exposed to sunlight for 7 days and stored as above.

The resveratrol isomer ratio and overall purity of these preparations were established by analytical HPLC. Analyses were performed on dual Waters 510 pumps and a 991M photodiode array detector. All solutions and solvents were sterile-filtered and degassed with helium. *Trans*- and *cis*-resveratrol were eluted at 8.2 and 11 min, respectively, on a Phenomenex Luna 5-μm phenyl-hexyl stationary phase 4.6 × 150 mm column using a linear gradient of 50% methanol in water to 100% methanol over 20 min at 0.7 ml/min and 20°C. Purity was determined by peak area observed at 220 nm. The *cis*/*trans* ratio was expressed as percent *trans*-resveratrol and calculated using the area of the *trans* peak at 308 nm and the *cis* peak at 288 nm (Table 2).

The plasmid (pUC 18) containing the ERE-luciferase construct consisted of two copies of *Xenopus* vitellogenein A_2 ERE inserted upstream (−331 to −289) of a minimal thymidine kinase promoter (−109 to +45) linked to the luciferase gene. MCF-7 cells were obtained from American Type Culture Committee (ATCC) and grown in minimum essential media containing 5% fetal calf serum, antibiotic–antifungal (penicillin G sodium, 10 units/ml; streptomycin sulfate, 10 μg/ml; amphotericin B, 0.25 μg/ml), 1 mM sodium pyruvate, and 10 mM insulin. For transfection assays, cells were grown in steroid-stripped media for 24 h and then plated in 12-well plates at a density of 10×10^4 cells/well. The experimental media containing various concentrations of resveratrol and E_2 were added 24 h later. Two hours after changing to experimental media, the cells were transfected with the lipid–plasmid complex using FUGene 6 reagent (Roche Biochemicals, Indianapolis, IN, U.S.A.). The luciferase activity was detected by using Luciferase Assay System (Promega Corp., Madison, WI, U.S.A.) ~24 hours after transfection using a TD-20/20 luminometer (Turner Designs, Sunnyvale, CA, U.S.A.). The luciferase induction (AU) was represented as vertical bar graphs and compared.

The ligand-activated ER binds to ERE, and

Table 2. Purity and Isomer Ratio for Photolyzed Resveratrol Samples

*Sample**	*% trans/% cis*	*% purity*
Control (day 0)	100/0	95
RC3-ethanol	95.3/4.7	92
RC6-ethanol	76.8/23.2	92
RC3-DMSO	90.4/9.6	91
RC6-DMSO	90.5/9.5	91
RA3, RA6-ethanol or -DMSO	100/0	95
RS	30/70	89

*RC3 and RC6 represent resveratrol stored in clear borosilicate glass vials for 3 and 6 days, respectively; RA3 and RA6 indicate resveratrol stored in amber borosilicate glass vials for 3 and 6 days, respectively. All preparations were exposed to fluorescent light under laboratory conditions. RS represents a solution of resveratrol in ethanol stored in a clear borosilicate glass vial and exposed to sunlight over a period of 7 days.

its functional activation was tested using a luciferase reporter gene linked to its promoter. E_2 (1 n*M*) as a single agent caused a sevenfold increase in luciferase activity compared with control. Freshly dissolved resveratrol was labeled R0 and stored immediately in an amber vial. Resveratrol exposed to laboratory lighting conditions for 3 and 6 days in amber or clear vials was labeled as RA3 and RA6 or RC3 and RC6, respectively. Figure 4A shows the effect of resveratrol preparations on ERE-luciferase activity with or without E_2. All exposures of resveratrol exhibited agonistic activity but, in combination with E_2, antagonized the induction of luciferase. Similarly, photolyzed DMSO solutions of resveratrol exhibited ~50% induction of luciferase activity and antagonized this effect when combined with E_2 (Fig. 4B). There

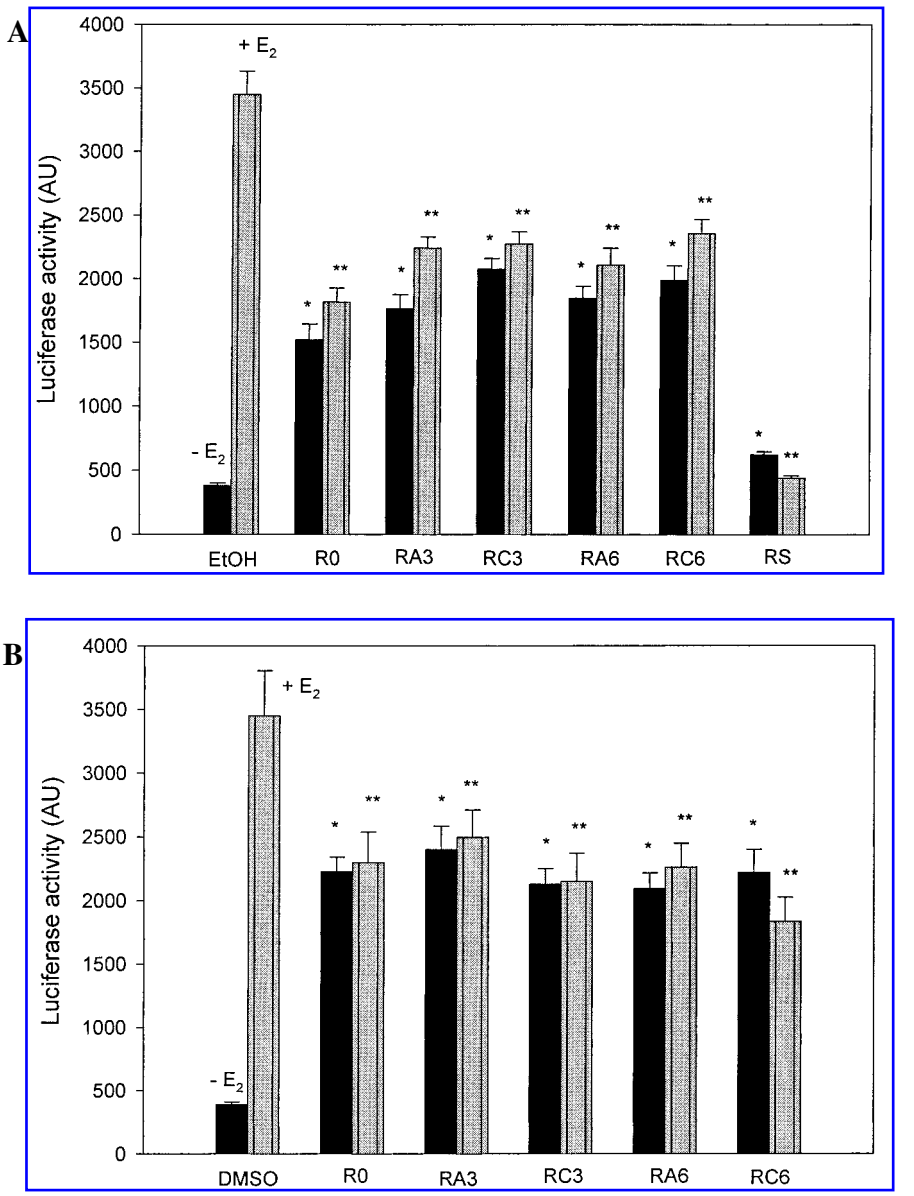

FIG. 4. Effects of resveratrol on ERE-luciferase activity transfected into MCF-7 cells. Cells were treated with 10 μM resveratrol dissolved in either ethanol (EtOH) (**A**) or DMSO (**B**) after exposure to light for various time periods (see Table 2) with or without 1 n*M* E_2, as described in the text. Two hours later, cells were transfected with ERE-luciferase plasmid, and luciferase activity was measured after 24 h. Induction values were averaged from triplicate determinations, and bars indicate SE. *Statistically significant ($p < 0.05$) differences from solvent control ($-E_2$); **statistically significant ($p < 0.05$) differences from E_2 control.

were no major differences among the various groups, except for resveratrol exposed to sunlight (RS). RS did not have any estrogenic effect, compared with control, and showed ~90% inhibition of luciferase activity when combined with E_2.

Thus, although some test concentrations of resveratrol (*e.g.*, 10 μM) can show estrogenic activity when administered as a single agent, the superagonistic activity reported previously could not be confirmed. To the contrary, when combined with E_2, resveratrol antagonized the induction and decreased luciferase activity by ~40%. Further, there was no significant correlation of the luciferase activity with the *cis*/*trans* ratio of resveratrol, as the day 0 control (100% *trans*-resveratrol) activity was essentially the same as sample RC3 (95% *trans*-resveratrol in ethanol) and RC6 (75% *trans*-resveratrol in ethanol). Simliar results were observed with DMSO solutions. For the sample RS, the significant antiestrogenic activity may be due more to decomposition products rather than *cis*-resveratrol. Isolation of the resveratrol byproducts and subsequent analysis of their estrogenic/antiestrogenic effects will answer this question.

To conclude, resveratrol holds great promise for future development as a chemopreventive agent that may be useful for several disorders. Although resveratrol cannot be claimed as a "panacea," the plethora of biological activities demonstrated by this molecule is fascinating. A challenge for the future will be to extrapolate data properly from *in vitro* experiments or animals to the human situation. A further complication is that controversial data have been reported in a few cases. We have explored resveratrol degradation products as a possible explanation for estrogenic effects mediated with a simple reporter gene assay, but we were still unable to reproduce superagonistic activity. In any case, care should be taken to avoid this potential variable in future work. It appears likely that human consumption of resveratrol will continue, so certain benefits may be realized, irrespective of our knowledge of the mechanism. Exploitation in a more directed manner will require the conduct of human clinical trials.

ACKNOWLEDGMENTS

The authors wish to thank Pharmascience (Montreal, Canada) for the supply of resveratrol and Dr. Peter J. Kushner (University of California at San Francisco) for providing ERE-luciferase plasmid. Experimental work in the laboratory of the authors is supported by program project P01 CA48112 funded by the National Cancer Institute.

ABBREVIATIONS

AAPH, 2,2′-azo*bis*(2-aminopropane) dihydrochloride; ACF, aberrant crypt foci; AGEs, advanced glycation end-products; AH, aryl hydrocarbons; AMVN, 2,2′-azo*bis*(2,4-dimethylvalero)nitrile; AR, androgen receptor; B[*a*]P, benzo[*a*]pyrene; BK_{Ca} current, Ca^{2+}-activated K^+ current; CHD, coronary heart disease; COX, cyclooxygenase; CYP1A, cytochrome P-4501A; DMSO, dimethyl sulfoxide; E_2, estradiol; ER, estrogen receptor; ERE, estrogen response element; ERK1, extracellular-regulated kinase 1; GCIC, gap junctional intracellular communication; IκB, inhibitory κB; iNOS, inducible nitric oxide synthase; LDL, low-density lipoproteins; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NO, nitric oxide; PARP, poly(ADP-ribose) polymerase; PGE_2, prostaglandin E_2; PKC, protein kinase C; PMA, phorbol 12-myristate 13-acetate; PMN, polymorphonuclear leukocytes; ROS, reactive oxygen species; TBARS, thiobarbituric acid-reactive substances; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TGF, transforming growth factor; TNFα, tumor necrosis factor α; TPA, 12-*O*-tetradecanoylphorbol 13-acetate; VCAM-1, vascular cell adhesion molecule; WRS, water immersion and restraint stress.

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Received for publication November 17, 2000; accepted April 9, 2001.

This article has been cited by:

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