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FORUM REVIEW ARTICLE

Antioxidant and Anti-Inflammatory Effects of Resveratrol in Airway Disease

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Abstract

Respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are a significant and increasing global health problem. These diseases are characterized by airway inflammation, which develops in response to various stimuli. In asthma, inflammation is driven by exposure to a variety of triggers, including allergens and viruses, which activate components of both the innate and acquired immune responses. In COPD, exposure to cigarette smoke is the primary stimulus of airway inflammation. Activation of airway inflammatory cells leads to the release of excessive quantities of reactive oxygen species (ROS), resulting in oxidative stress. Antioxidants provide protection against the damaging effects of oxidative stress and thus may be useful in the management of inflammatory airways disease. Resveratrol, a polyphenol that demonstrates both antioxidative and anti-inflammatory functions, has been shown to improve outcomes in a variety of diseases, in particular, in cancer. We review the evidence for a protective role of resveratrol in respiratory disease. Mechanisms of resveratrol action that may be relevant to respiratory disease are described. We conclude that resveratrol has potential as a therapeutic agent in respiratory disease, which should be further investigated. *Antioxid. Redox Signal.* 13, 1535–1548.

Introduction

Airway diseases, including asthma and COPD, are a significant and increasing global health problem. Both of these diseases are characterized by inflammation of the respiratory tract. In asthma, this occurs because asthmatic patients have an exaggerated response to triggers such as viruses and allergens, leading to the activation of both the innate and acquired immune systems. In COPD, inflammation occurs primarily because of exposure to noxious particles and gases, in particular, to cigarette smoke. These various stimuli result in activation of inflammatory cells, which release excessive quantities of reactive oxygen species (ROS), leading to oxidative stress. Inflammation due to both asthma and COPD results in increased production of ROS, irrespective of the initiating event. Various endogenous and exogenous antioxidants can protect against the damaging effects of ROS. Resveratrol is a polyphenol that demonstrates both antioxidative and anti-inflammatory functions. Resveratrol has been shown to improve outcomes in a variety of diseases, in particular, in cancer. *In vitro* and animal studies suggest that resveratrol may also protect against various inflammatory stimuli that are important in respiratory disease, including viruses, lipopolysaccharide (LPS), smoking, and allergens. Thus, resveratrol may also have a therapeutic role in respiratory disease.

Respiratory Disease and Inflammation

Respiratory diseases, including asthma and COPD, involve airway inflammation and oxidative stress (Figs. 1 and 2). Asthma is a chronic inflammatory disorder of the airways in which many cells and elements play a role. A number of features characterize asthma, including airway hyperresponsiveness (AHR), reversible airflow obstruction, and airway inflammation. Airway inflammation in asthma is heterogeneous and may involve activation of both the acquired and innate immune systems (50). Allergens trigger a Th2 response in the airways (22), involving increased production of the cytokines interleukin (IL)-4, IL-5, IL-9, and IL-13, in association with eosinophil and mast cell influx into the airways, mucus hypersecretion, and increased bronchial reactivity (53, 165). Triggers such as viruses, bacteria, and endotoxin induce an IL-8–mediated neutrophilic response, which is associated with innate immune activation. This includes increased expression of several key innate immune receptors: Toll-like receptor (TLR)2, TLR4, cluster of differentiation 14 (CD14), and surfactant protein-A (SP-A), as well

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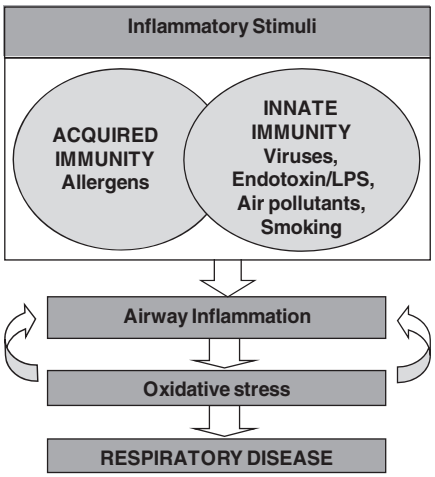

FIG. 1. The role of inflammation and oxidative stress in respiratory disease. Activation of inflammatory cells by stimuli such as allergens, viruses, endotoxin, and smoking leads to production of ROS. Antioxidant defenses are overwhelmed, and oxidative stress occurs, which contributes to the pathophysiology of respiratory disease.

as the proinflammatory cytokines IL-8 and IL-1β (144). Subjects with a neutrophilic asthma phenotype have increased neutrophil counts, which are associated with asthma severity (71) and correlate with both lung function [percentage of predicted forced expiratory volume in 1 s (%FEV1)] and airflow obstruction (145). Stimulation of both the innate and acquired immune pathways in asthma results in infiltration of activated inflammatory cells into the airways (171). Systemic inflammation also occurs in asthma. Plasma C-reactive protein (CRP) is elevated in nonallergic (110) and steroid-naïve asthma, where it correlates with lung function and airway inflammation (149). Serum amyloid A levels are elevated in asthma (24), and increased levels of both serum amyloid A and plasma fibrinogen have been associated with increased asthma prevalence (73). Furthermore, circulating IL-6 (175) and tumor necrosis factor (TNF)-α (83) are elevated during asthma exacerbation.

COPD is another chronic inflammatory airways disease, involving poorly reversible airflow limitation. In COPD, the inflammatory response is driven primarily by exposure to noxious particles or gases, particularly cigarette smoke (123). Once established, other factors, such as chronic bacterial infection, further stimulate airway inflammation in COPD (134). As a result, the airways contain increased numbers of macrophages, T lymphocytes, and neutrophils (44, 76) and increased levels of proinflammatory mediators, including sputum TNF-α (76), monocyte chemoattractant protein-1 (MCP-1) (40), growth-related oncogene (GRO)-α (152), and IL-8 (15). Subjects with COPD also have higher expression of transforming growth factor (TGF)-β1 messenger ribonucleic acid (mRNA) and protein in airway and alveolar epithelial cells and increased expression of TGF-β receptors in macrophages (41). Subjects with COPD also have evidence of systemic inflammation, with elevated circulating inflammatory markers, including IL-6 (174), TNF-α (43), IL-1β, fibrinogen (92), and CRP (74). During exacerbation, inflammation is further increased, with higher levels of serum IL-6 (162), fibrinogen (162), and leptin (34).

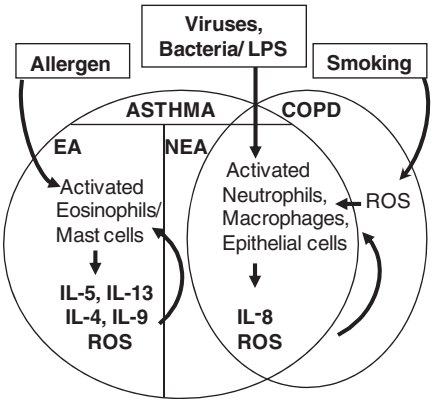

FIG. 2. Triggers of airway inflammation in respiratory disease. In asthma, airway inflammation can be triggered by stimulants of the acquired immune response (*i.e.*, allergens), leading to eosinophilic asthma (EA). Alternatively, airway inflammation may be driven by stimulants of the innate immune response (*e.g.*, viruses and bacteria/LPS) leading to neutrophilic, or non-eosinophilic inflammation (NEA). In COPD, airway inflammation is driven primarily by smoking, which also leads to neutrophilic inflammation. Resveratrol has been shown to block inflammation driven by each of these triggers; this may be beneficial in respiratory disease.

Respiratory Disease and Oxidative Stress

The inflammatory environment in asthma and COPD leads to oxidative stress, as activated cells recruited to the airways produce excessive quantities of reactive oxygen species (ROS) (Fig. 3). Activated eosinophils, neutrophils, monocytes, and macrophages can generate superoxide anions through the membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH)-dependent complex. Superoxide dismutase reacts with the superoxide radical to form hydrogen

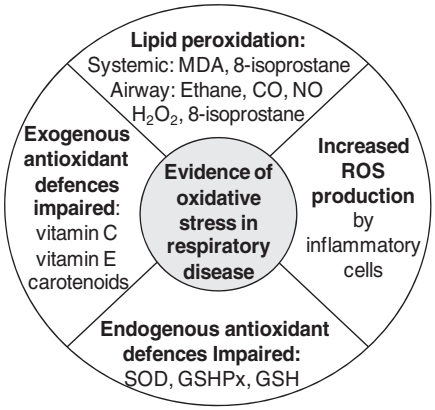

FIG. 3. Evidence of oxidative stress in respiratory disease. Numerous studies have demonstrated that respiratory diseases, such as COPD and asthma, involve oxidative stress. Examples include increased generation of ROS by circulating leukocytes, increased levels of lipid peroxidation, and reduced levels of endogenous and exogenous antioxidant defenses.

peroxide (H_2O_2). H_2O_2 interacts with halide ions (Cl^- and Br^-) in a reaction catalyzed by myeloperoxidase (MPO) provided by neutrophils and monocytes, or eosinophil peroxidase (EPO) from eosinophils (96). The end products of this reaction are other potent cytotoxic radicals, the hypohalous acids, HOCl and HOBr. In addition, nitrite, the end product of nitric oxide ($^{\cdot}NO$) metabolism, is used by MPO and EPO together with H_2O_2, to promote formation of reactive nitrogen species (173). These processes lead to excessive quantities of reactive oxygen and nitrogen species in asthma and COPD, which overwhelm host antioxidant defense, leading to oxidative stress. Oxidative stress is undesirable and leads to various pathophysiologic features that contribute to the symptoms of asthma and COPD, including airway smooth muscle contraction (132), induction of AHR (75), mucus hypersecretion (3), epithelial shedding (48), and vascular exudation (151). In addition, ROS amplify airway inflammation by activating redox-sensitive transcription factors, such as NF-κB (17), JAK-STAT (143), and Raf-1 (2), which leads to further amplification of the transcription of proinflammatory genes.

Much evidence indicates increased oxidative stress in asthma (171). Evidence of oxidative stress includes increased concentrations of 8-iso-$PGF_{2\alpha}$ in plasma (167), induced sputum (170) and exhaled breath condensate (106), increased concentrations of malondialdehyde (MDA) in both plasma (112) and breath condensate (7), and increased concentrations of ethane (116), carbon monoxide (65), NO (62, 65, 116), nitrotyrosine (62), and H_2O_2 (65) in exhaled breath. It has also been demonstrated that airway inflammatory cells from subjects with asthma, such as neutrophils, macrophages, and eosinophils, release increased quantities of ROS compared with those in healthy controls (25). Antioxidant depletion is also commonly reported in asthma, which is an indirect marker of oxidative stress. Vitamin C concentrations have been reported to be low in circulation (159) and in the airways (77) of asthmatic patients versus controls. Vitamin E concentrations have been shown to be reduced in circulation (169) and in the airways of asthmatic patients (77). Circulating levels of carotenoids, including lycopene, α- and β-carotene, lutein, and β-cryptoxanthin have also been shown to be low in asthma versus in controls (168). Disturbed glutathione (GSH) status is reported in asthma, with total (169), oxidized (77, 169) and reduced (169) GSH being elevated in the airways, suggesting that GSH synthesis and/or transport has increased in response to oxidative stress. The status of the antioxidant enzymes is also often disturbed in asthma, including superoxide dismutase (SOD) (138), glutathione peroxidase (GSHPx) (138), and catalase (138) activities.

Similarly, there is evidence of oxidative stress in COPD which is enhanced by smoking (125) and during exacerbation (121). Cigarette smoke itself contains multiple oxidative moieties, including superoxide and nitrogen oxides. These ROS have the ability to damage lipids, proteins, DNA, and the extracellular matrix directly (80). Markers of airway oxidative stress in COPD include elevated 8-isoprostane (105), hydrogen peroxide (42), carbon monoxide (CO), ethane, and NO (117) in exhaled breath. 4-Hydroxy-2-nonenal (4-HNE)–modified protein levels are also increased in airway epithelial cells, endothelial cells, and neutrophils from subjects with COPD (128). Systemic markers of oxidative stress in COPD include increased levels of urinary 8-isoprostane (121) and lipid peroxides (specifically plasma malondialdehyde) (126) in subjects with both stable and exacerbating COPD. Changes in peripheral blood inflammatory cells, in particular, in neutrophils and lymphocytes (172), are observed in COPD. Furthermore, blood neutrophils from both stable (109) and exacerbating (126) COPD subjects, spontaneously generate more ROS than do control subjects. Disturbed antioxidant status is also reported in COPD. Interestingly, after smoking cessation and resolution of an exacerbation, antioxidant capacity improves rapidly toward normal (127).The majority of studies that have examined plasma levels of exogenous antioxidants, including vitamin C, vitamin E, β-carotene, and Se, have shown a depletion in COPD and in smokers (99). Vitamin E and vitamin C levels have also been shown to be reduced in leukocytes and bronchoalveolar lavage (BAL) fluid from smokers (20). Some evidence suggests that smokers may evoke adaptive mechanisms to restore antioxidant defenses, as vitamin C levels were reported to be increased in BAL fluid (125) and in alveolar macrophages from smokers (125). Similarly, evidence suggests that smoking causes an increase in endogenous antioxidant activity, including increased levels of GSH in epithelial lining fluid (107), increased SOD and catalase activity in alveolar macrophages (97), and increased activity of SOD and GSHPx enzymes in lung tissue (176). As occurs in asthma, some inconsistency is found in the available data. One study reported that activities of SOD and GSHPx are decreased in alveolar macrophages from elderly smokers, suggesting that this particular subject group is not able to modify enzyme activity in response to the increased oxidative burden of smoking (58).

Inflammation and oxidative stress also play an important role during clinical exacerbations of respiratory disease. Virus infections, and in particular, human rhinovirus (RV), are associated with the majority of exacerbations of asthma and chronic obstructive pulmonary disease (COPD) (108). RVs target epithelial cells, in which they replicate (147) and initiate innate immune responses (56), resulting in the production of various inflammatory mediators in the airways (146), including IL-6 (81), IL-8 (81) interferon-γ–induced protein (IP)-10 (146), and intercellular adhesion molecule-1 (ICAM-1) (114). RV infection also leads to the production of ROS and increased oxidative stress (115). ICAM-1, the receptor of 90% of RVs, is an adhesion protein that has a central role in inflammatory cell recruitment after RV infection. The expression of ICAM-1 in respiratory epithelial cells is through a mechanism that is nuclear factor (NF)-κB dependent and thus is activated by ROS (115).

In summary, subjects with asthma and COPD clearly demonstrate increased oxidative stress and disturbed antioxidant status, particularly in times of disease exacerbation. This suggests a potential role for antioxidant supplementation in the management of these diseases.

Resveratrol: An Important Antioxidant and Anti-Inflammatory Agent

Increasing scientific evidence describes the importance of polyphenols in protecting against inflammation and oxidative stress. Numerous dietary plants, including grains, legumes, fruits, vegetables, and their products, such as tea and chocolate, contain polyphenols (19). Plant polyphenols can be divided into two major groups, flavonoids and nonflavonoids. The flavonoid family includes the flavonols, flavon-3-ols, and

the anthocyanins. The nonflavonoids include hydroxybenzoic acids such as gallic acid, hydroxycinnamates, caffeic and caftaric acids, and the stilbenes, *trans*- and *cis*-resveratrol (104). Resveratrol (3,4′, 5-trihydroxystilbene) is a naturally occurring phytoalexin present in ≥72 plant species, with relatively high concentrations found in grapes (*Vitis* spp.), berries (*Vaccinium* spp.), and peanuts (*Arachis* spp.). This molecule is synthesized in response to fungal, viral, and bacterial attacks and damage from exposure to ultraviolet radiation (UV), thereby conferring disease resistance to the host (141). Resveratrol exists in two isomeric forms, *cis*- and *trans*-, with isomerization of *trans* to *cis* facilitated by UV exposure. The resveratrol molecule comprises two phenol rings linked by a styrene double bond.

Ex vivo, resveratrol is stable for ≤5 days at 4°C when protected from light (161). Resveratrol is stable to moderate heating, but will react when exposed to low or high pH (153). The literature on bioavailability and metabolism of resveratrol is somewhat inconsistent, with a wide range of concentrations reported to achieve *in vivo* effect (from ∼100 ng to 1,500 mg/kg body weight in animals) (14). Resveratrol metabolism in humans is known to be rapid, with the majority of resveratrol converted to metabolites, in the form of sulfate and glucuronide conjugates, within 30 min (160). The serum half-life of total resveratrol metabolites has been reported to be ∼9 h (160). Thus, considering the established efficacy of resveratrol in various *in vivo* situations, it appears likely that resveratrol metabolites retain some activity. Belguendouz *et al*. (16) showed that resveratrol must be bound with some protein or conjugated to remain at a high concentration in serum, or both, as it is almost insoluble in water. Albumin is one of the plasma transporters of resveratrol in blood circulation (70). Bioavailability appears to vary, depending on the delivery agent. For example, in whole foods such as grape juice, resveratrol exists in the glycoside form, which appears to have very low bioavailability compared with the pure aglycone form of resveratrol (98). Tissue affinity also plays an important role in the bioavailability of resveratrol, which has been shown to accumulate in the liver (158).

Resveratrol: Mechanisms of Action

Resveratrol as an antioxidant

Numerous studies have shown the effectiveness of polyphenols in limiting the progression of chronic diseases. This is likely to occur, at least in part, because of the antioxidant capacity of these molecules, which extends from the availability of hydroxyl groups (-OH) and the presence of conjugated double bonds. It is likely that resveratrol acts by a variety of antioxidative mechanisms, including inhibiting production of reactive oxygen species by inflammatory cells (95), scavenging free radicals, and stimulating biosynthesis of endogenous antioxidants by mechanisms such as stimulation of nuclear erythroid-related factor (Nrf2) activity (84). Resveratrol has been reported to increase antioxidant capacity and reduce various markers of oxidative stress. For example, resveratrol administration led to a dose-dependent decrease in malondialdehyde (MDA) levels and an increase in endogenous antioxidant defenses in rats that were healthy (103) and with cholestasis (8). Resveratrol has been reported to prevent LDL oxidation *in vitro* (148), and in a clinical trial, consumption of red wine led to an increase in concentration of resveratrol in LDL particles (155). Resveratrol also has been shown to reduce urinary 8-hydroxydeoxyguanosine and serum levels of glycated albumin in hypertensive rats (102).

Resveratrol as an anti-inflammatory agent

Polyphenols are also able to modulate cellular signalling processes, thereby reducing inflammation (4). A variety of dietary antioxidants, such as vitamin C (27), lycopene (79), β-carotene (9), and a combination of vitamins C and E (150) show anti-inflammatory effects, through suppression of NF-κB activity. Resveratrol has also demonstrated antiinflammatory effects through inhibition of transcription factors such as NF-κB and activator protein-1 (AP-1) (91). Resveratrol has been shown to inhibit TNF-α–mediated matrix metallopeptidase (MMP)-9 expression by downregulating NF-κB activity (177). Zhu *et al*. (179) reported that resveratrol suppressed NF-κB binding activity, thereby reducing TNF-α–induced MCP-1 expression in adipocytes. Other groups have demonstrated that resveratrol has inhibitory effects on cell adhesion (118), probably through inhibition of NF-κB. Resveratrol appears to modulate mitogen-activated protein (MAP) kinase signalling in a dose-dependent manner (124), with low doses being stimulatory (39), and high doses, inhibitory (51). The anti-inflammatory effects of resveratrol also occur through inhibition of the cyclooxygenase (COX) enzymes (78), as resveratrol inhibits both COX-2 transcription (95) and COX-1 activity (69). Modification of these enzymes has numerous effects on the production of proinflammatory molecules by both the cyclooxygenase and 5-lipoxygenase pathways (142). For example, COX-1 is preferentially inhibited over COX-2 (68), which leads to reduced production of the vasoconstrictors, thromboxane A2 and leukotriene B_4 (140). Resveratrol may also exhibit anti-inflammatory effects by activating the peroxisome proliferator–activated receptor (PPAR)-α (67). In addition, it has been reported that resveratrol protects against virus infection (45), increases apoptosis (85), and reduces cell proliferation (85).

Epidemiologic evidence for a protective role of resveratrol in respiratory disease

The prevalence of respiratory disease has increased dramatically over recent decades, particularly in westernized countries, suggesting that environmental factors must play a role in disease onset and development. Several large epidemiologic studies have indicated that a Western-style dietary pattern, high in fat and low in antioxidant content, increases the risk of both asthma (164) and COPD (157). Dietary intake and/or serum levels of various antioxidants, including vitamin C (60), vitamin E (130), β-carotene (59, 60, 130), lutein (133), lycopene (59), and α-carotene (59), have been associated with improved lung health. Although no studies specifically examine resveratrol concentrations in relation to respiratory disease risk, a number of epidemiologic studies have identified that consumption of various antioxidant-rich foods, many of which are known to contain resveratrol, are protective against asthma outcomes. In a case–control study involving 607 asthmatic patients and 864 controls, aged 16–50 years, red wine consumption was found to be inversely correlated with asthma severity, whereas total fruit and vegetable intake and apple intake were protective against asthma onset (136). Fresh fruit intake has been shown to be inversely

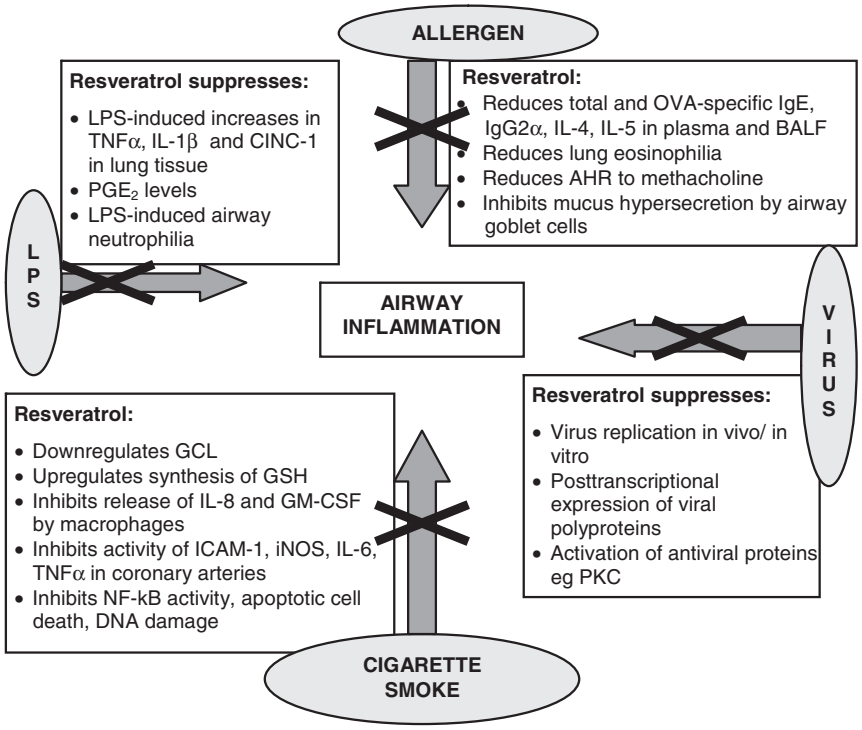

FIG. 4. Demonstrated effects of resveratrol in models of airway inflammation.

related to wheeze (23) and chronic lung disease onset (100), and positively associated with FEV_1 (28, 30). Another study reported that a high consumption of "fruity vegetables," including tomatoes, eggplants, cucumbers, green beans, and zucchini (5), reduced wheeze in children (31). In other studies, vegetables and vegetable products have been inversely associated with wheeze (52) and asthma (86). It is likely that a combination of antioxidants in these whole foods, including resveratrol, provide a beneficial effect.

Mechanisms by which resveratrol may modulate respiratory disease

Resveratrol has been shown to have properties that protect against various inflammatory stimuli that are particularly relevant in respiratory disease, such as allergens, viruses, cigarette smoke, and lipopolysaccharide (LPS) (Fig. 4). The relative importance of these different stimuli varies with disease (Fig. 5). The airway epithelium is the primary site for these inflammatory insults. Recently, it was demonstrated that in epithelial cells, resveratrol exhibits anti-inflammatory activity (49). In an A549 epithelial cell line, resveratrol inhibited cytokine-stimulated IL-8 release (with an $IC_{50} = 72 \; 11\,\mu M$) and granulocyte-macrophage colony-stimulating factor release (GM-CSF) (with an $IC_{50} = 24.3 \pm 5.5\,\mu M$) (49). These mediators are important, as IL-8 is involved in the recruitment of inflammatory cells, in particular neutrophils, and GM-CSF prolongs the resident time of inflammatory cells. The glucocorticoid antagonist mifepristone did not alter the inhibitory effect of resveratrol, suggesting that resveratrol acts by mechanisms different from those of glucocorticoids. The mechanism of resveratrol action was investigated further by using luciferase reporter genes stably transfected into A549 cells. Resveratrol inhibited NF-κB, AP-1, and cyclic adenosine monophosphate (cAMP) response element–binding protein-dependent transcription to a greater extent than did the glucocorticosteroid dexamethasone. Resveratrol inhibited IL-1β–induced expression of luciferase in a dose-dependent manner, with an IC_{50} of $41 \pm 10\,\mu M$, and 100% inhibition of this reporter gene activity in the presence of $100\,\mu M$ resveratrol. Although dexamethasone inhibited expression of the NF-κB reporter, the maximum inhibition observed was only 41% ($IC_{50} = 10 \pm 6\,nM$). The effect of these compounds also was examined by using an AP-1 luciferase reporter. Resveratrol inhibited AP-1–dependent luciferase expression ($IC_{50} = 28 \; 13\,\mu M$ and $20 \pm 12\,\mu M$) by stimulated cells. Dexamethasone also inhibited AP-1–dependent luciferase expression, but the maximal inhibition was less than that seen with resveratrol. In a similar experiment, resveratrol inhibited *cis*-acting replication element (CRE)-dependent expression, with IC_{50} values of $46 \pm 23\,\mu M$. Dexamethasone also inhibited CRE-dependent transcription, but with a maximum inhibition of 50% in the presence of $100\,\mu M$ dexamethasone. These results suggest that resveratrol inhibits inflammatory gene transcription and, although not as potent as dexamethasone, inhibits transcription factor activity to a greater extent (49). In primary airway epithelial cells, resveratrol inhibited cytokine-stimulated inducible nitric oxide synthase (iNOS) expression and nitrite production ($IC_{50} = 3.6 \pm 2.9\,\mu M$), GM-CFS release

ASTHMA	TRIGGER	COPD
++	Smoking	+++
+++	Virus Infection	+++
+	Bacterial Infection	+++
++	Air pollution	++
+++	Allergens	+

FIG. 5. Relative importance of inflammatory triggers in asthma and COPD.

($IC_{50} = 0.44 \pm 0.17\ \mu M$), IL-8 ($IC_{50} = 4.7 \pm 3.3\ \mu M$) release, and COX-2 expression (49).

Resveratrol in an allergic model of inflammation

Allergic mouse models have been established to explore Th2 inflammatory responses to allergic stimuli. A study by Lee *et al.* (88) used an allergic mouse model to demonstrate that resveratrol inhibits production of total and OVA-specific IgE, IgG2α, IL-4, and IL-5 in plasma and BAL fluid. Resveratrol-treated mice had significantly reduced lung eosinophilia in BAL fluid and lung tissue, which may have resulted from the decrease in the levels of Th2 cytokines responsible for eosinophil recruitment into the lung in asthma. Resveratrol markedly reduced AHR to methacholine, a measure of bronchial-constriction in asthma. This inhibition was likely to be associated with the corresponding reduction in airway inflammation (64). Resveratrol also substantially inhibited mucus hypersecretion by airway goblet cells. The efficacy of resveratrol in the study by Lee *et al*. (88) was similar to that of dexamethasone, a glucocorticoid used as a positive control.

Resveratrol and virus-induced inflammation

Changes in host cell redox pathways after virus infection are known to be critical in inducing changes that allow virus replication to occur (32). As resveratrol is a potent antioxidant, its antiviral effects have been investigated. Palamara *et al.* (113) assessed the effect of resveratrol on the RNA virus influenza. They treated human cells with resveratrol and demonstrated, at doses of 10–40 μg/ml, a 90% reduction in influenza replication, although in doses $>20\ \mu$g/ml, significant cellular toxicity was found. This antiviral effect was not the result of direct toxicity to the virus or reduced virus adhesion, but was the result of the prevention of posttranscriptional expression of viral polyproteins. Resveratrol had only a minimal effect on cell redox state, with minimal alteration of intracellular glutathione levels (113), but instead appeared to have its effect by inhibiting intracellular protein kinase C (PKC) and downstream MAP kinase pathways. In further experiments, BALB/c mice were infected intranasally with influenza, and then resveratrol (20 mg/mouse/day) or placebo was administered 1 h after virus inoculation and daily for the next 7 days. Survival of resveratrol-treated mice was significantly increased, compared with those with placebo. Pulmonary viral titers, determined by the 50% cytopathic effect (CPE_{50}) assay, were lower in the resveratrol-treated mice (113). A similar antiviral effect was also demonstrated *in vitro* against the DNA virus varicella zoster (VZV) (47). Resveratrol inhibited VZV replication in a dose-dependent fashion. Resveratrol, at concentrations of 55, 110, and 219 μM, inhibited VZV at a rate of 86, 93, and 100%, respectively, at the 48-h time point, which was the point of maximal virus production in controls. This resulted in a median effective concentration required to induce a 50% effect (EC_{50}) value for resveratrol of 19 μM, compared with an EC_{50} value of 4 μM for acyclovir (47). Topical preparations of resveratrol (12.5% and 25%) have been shown to have effectiveness similar to that of the antiviral acyclovir (5%) in preventing herpes simplex skin infection in a mouse model, when treatment was begun 1 h after infection and repeated every 3 h, 5 times a day for 5 days (46). Despite these preliminary results, no clinical human study examined the effect of resveratrol.

Resveratrol in a cigarette smoke–induced inflammation

Each puff of cigarette smoke contains 10^{14} to 10^{16} free radicals, including reactive aldehydes, quinines, and benzopyrene (122). As a result, smoking and exposure to cigarette smoke extract (CSE) lead to an increase in ROS production, both systemically and in the airways, which can be attenuated by resveratrol treatment.

Reduced glutathione (GSH) is a key antioxidant in the airways. It has been demonstrated that smoking downregulates glutamate-cysteine ligase (GCL), which is necessary for the synthesis of GSH (63). In a study by Kode *et al*. (84), resveratrol was shown to attenuate cigarette smoke–mediated oxidative stress by quenching ROS and by upregulating the synthesis of GSH through an activation of an Nrf2-dependent mechanism in human lung epithelial cells.

A recent study demonstrated that resveratrol, administered at a concentration range of 10^{-4} to 10^{-8}, inhibited basal and cytokine-stimulated release of IL-8 and GM-CSF by macrophages from both smokers and patients with COPD in a dose-dependent manner (36). Macrophages play an important role in the pathphysiology of COPD, as numbers of alveolar macrophages are increased in COPD airways (1), where they release increased levels of proinflammatory mediators, including neutrophil and macrophage chemotactic factors, such as IL-8 (101) and GM-CSF (37). In contrast to the effects of resveratrol, the glucocorticosteroid dexamethasone does not inhibit IL-8 release by BAL fluid macrophages from patients with COPD, except in a high concentration (10 μM) in smokers (37).

In coronary artery endothelial cells, smoking-induced upregulation of inflammatory markers, including ICAM-1, iNOS, IL-6, and TNF-α, was inhibited by resveratrol (35). These effects corresponded with inhibition of CSE-induced NF-κB activation, apoptotic cell death, DNA damage, and endothelial dysfunction (35). Interestingly, this study demonstrated the central role of silent mating-type information regulation 2 homologue (SIRT1) in maintaining cell homeostasis in the presence of CSE, an environmental stressor. The protective effects of resveratrol were dependent on SIRT1 activity, and SIRT1 overexpression mimicked resveratrol activity (35).

Resveratrol in an LPS model of inflammation

In another study, Birrell *et al*. (18) demonstrated that resveratrol can inhibit inflammatory responses to lipopolysaccharide (LPS) challenge in rat lungs, by a variety of mechanisms. Resveratrol inhibited LPS-induced increases in lung-tissue levels of TNF-α, IL-1β, and cytokine-induced neutrophil chemoattractant-1 (CINC-1). Resveratrol also affected LPS-induced prostanoid production, by suppressing prostaglandin E_2 levels. It is likely that the suppression of cytokine and prostanoid production contributed to the inhibition of LPS-induced airway neutrophilia that also was observed (18). The magnitude of inhibition of cytokine production and lung-tissue neutrophilia that was achieved by using resveratrol was similar to the inhibition achieved by using the glucocorticoid, budesonide (18).

Other Beneficial Effects of Resveratrol in Human Health and Disease

From a botanic point of view, resveratrol is a toxic compound produced by some plants in response to attack by parasites or under stress conditions. Since its isolation from the roots of white hellebore in 1940s, interest in resveratrol has increased exponentially with the findings that it has remarkable properties, including chemoprevention in some cancer models, cardioprotection, protection against neurologic disorders, and positive effects on several aspects of metabolism, potentially leading to the increased life span of various organisms (119) (Fig. 6).

Resveratrol has been shown to inhibit diverse cellular events by interfering with initiation, promotion, and progression of cancer (68), and therefore can prevent or delay carcinogenesis. Molecular mechanisms underlying the chemopreventive role of resveratrol include inhibition of cyclooxygenase (COX), nitric oxide synthase and cytochrome P450 enzymes, cell-cycle components, apoptosis modulation, and the inhibition of angiogenesis and hormonal activity (57). Resveratrol inhibits the expression of COX-2, long-term inhibition and deletion of which is known to reduce the risk of developing colorectal cancer in a mouse model (111). Antiangiogenic properties have been illustrated by the inhibition of tumor-induced neovascularization essential to support solid tumor growth, through systemic delivery of resveratrol (82, 154). Resveratrol may increase carcinogen detoxification by inhibiting the expression and activity of various cytochrome P450 enzymes (29, 120) or by inducing expression of phase II drug-detoxifying enzymes (26). Resveratrol has been shown to reduce lipid peroxidation and to increase plasma antioxidant activity to mop up reactive oxygen species that are known to damage deoxyribonucleic acid (DNA) and other biomolecules involved in the initiation and progression of cancer (163). Resveratrol, with its abilities to downregulate cell-cycle proteins (178), has also been shown to increase apoptosis (55) and antiproliferative properties in tumor cell lines (33).

People residing in certain parts of France, where red wine rich in resveratrol is a customary meal complement, have a low coronary heart disease mortality, despite living a lifestyle considered to have relatively high risk, compared with those in the United States and many other developed countries: the French Paradox (131). Mechanisms by which resveratrol exerts cardioprotective effects have not been elucidated. It is believed that a suppression of platelet aggregation, dilatation of blood vessels, antiatherosclerotic effects, reduction in endothelin-1, protection of endothelial cells against apoptosis, as well as lowering of plasma lipids (cholesterol and triglycerides) may be involved (14, 94).

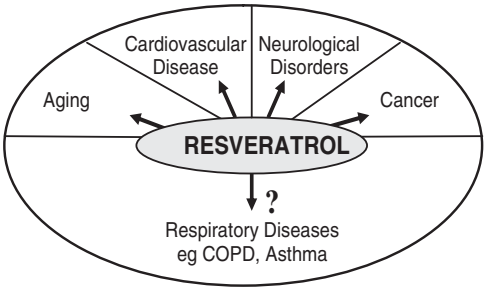

FIG. 6. Health effects of resveratrol. These include protection against a variety of chronic inflammatory diseases and conditions, such as cancer, cardiovascular disease, neurologic disorders, and aging. A growing body of evidence suggests that resveratrol may also be protective against respiratory diseases, such as COPD and asthma.

Resveratrol has been shown to prolong platelet aggregation (139) through inhibition of thromboxane formation (90). Resveratrol increases expression of endothelial nitric oxide synthase and inducible nitric oxide synthase (38, 89), enhancing nitric oxide formation and resulting in vasodilation (129). Resveratrol has been shown to prevent low-density lipoprotein (LDL) oxidation by chelating copper ions and scavenging reactive oxygen species (54). Resveratrol also suppresses the expression of lipoprotein lipase and scavenger receptor AII genes involved in cellular lipid uptake (135). Therefore, it would appear that multiple and highly complex mechanisms exists to result in the beneficial effects of resveratrol on cardiovascular health.

Since 2002, several studies have reported that resveratrol has the potential to extend life span, slow the aging process, and promote longevity in organisms from different phyla, such as yeasts (66), worms and flies (166), and short-lived fish (156). This property of resveratrol has fostered extensive research efforts regarding its effects on aging and metabolism in mammals. When mice were raised on a high-fat diet, resveratrol prevented premature death and restored the normal life span, while improving insulin sensitivity and motor function (13, 87). These effects of resveratrol on life span may be related to the ability of resveratrol to activate the SIRT1 enzyme (21), a deacetylase that may promote survival by regulating the activity of a number of transcriptional factors and enzymes responsive to environmental stresses, such as fluctuations in nutrient availability (61). However, because of the low systemic bioavailability of resveratrol, combined with its extensive metabolism in humans, substantial research efforts are now directed toward identification and testing of more bioavailable/ potent pharmaceutical activators of SIRT1, for use in the prevention of aging and age-related disorders.

In addition to the activation of SIRT1, resveratrol also alters chromatin structure and transcription in mice (10). Resveratrol also extends the life span of mice raised on a high-calorie diet by increasing insulin sensitivity, decreasing IGF-1 expression, and increasing AMP-activated protein kinase and peroxisome proliferator–activated receptor-γ coactivator 1α activity.

Because of its ability to penetrate the blood–brain barrier, resveratrol has been shown to exert neuroprotective effects (14). It is a potential treatment for several neurodegenerative diseases (93) including Alzheimer disease. The neuroprotective effects are mediated through the protection of hippocampal cells against β-amyloid–induced toxicity (12). In a rat model of 6-hydroxydopamine (6-OHDA)-induced Parkinson disease, the administration of resveratrol demonstrated a neuroprotective effect through suppression of inflammation, as indicated by a significant reduction in the levels of COX-2 and TNF-α mRNA (72).

Mechanisms of aging and Alzheimer disease appear to be intricately linked and resemble those that can be modulated by calorie-restriction regimens, the prime mediator of which is the SIRT1 protein (6). Resveratrol-induced SIRT1 suppresses

p53 activity, activates Forkhead box (FOX)O proteins to regulate the expression of genes that contribute to longevity and resistance to various stresses, promotes neuron survival, nitric oxide synthase (iNOS) and cathepsin B, the two toxic factors that mediate neurodegeneration in microglia and astrocytes through inhibition of NF-κB to protect neurons against β-amyloid–induced toxicity. Resveratrol functions as an antioxidant; it may prevent reactive oxygen species–induced β-amyloid production and apoptosis-mediated neurodegeneration. Resveratrol also blocks nitric oxide–induced phospholipase A_2/arachidonic acid cascades and prevents neuron apoptotic death (6, 137).

Therapeutic Implications and Future Directions

A substantial increase in the prevalence and incidence of obstructive lung diseases, such as asthma and COPD, has occurred in recent decades. These diseases involve inflammation of the respiratory tract, which plays a major role in disease progression. Research efforts are focused on identifying and evaluating therapeutic agents to treat these diseases. Resveratrol has been shown to have effects that may be beneficial in a variety of diseases and conditions, including cancer, cardiovascular disease, neurologic disorders, and aging. Natural agents, such as resveratrol, hold great promise, as they have may provide a safe and effective option to complement pharmacologic approaches.

In each of the models reviewed, the effects of resveratrol on inflammation were similar to, or superior to, the effects of glucocorticoids. The clinical use of glucocorticoids is controversial in some settings, such as COPD and non-eosinophilic forms of asthma (11), which are characterized by airway neutrophils. In these diseases, glucocorticoids appear to be ineffective in treating airway inflammation (11). Resveratrol, which has been shown to suppress innate immune activity, may be more effective in reducing airway inflammation if a neutrophilic phenotype exists. Thus, resveratrol, or related compounds, should be further investigated as alternatives to corticosteroids for the treatment of airway inflammation in some settings.

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Abbreviations Used

6-OHDA = 6-hydroxydopamine
AHR = airway hyperresponsiveness
AP-1 = activator protein-1
BALF = bronchoalveolar lavage fluid
cAMP = cyclic adenosine monophosphate
CD14 = cluster of differentiation 14
CINC-1 = cytokine-induced neutrophil chemoattractant-1
COPD = chronic obstructive pulmonary disease
COX = cyclooxygenase
CPE50 = 50% cytopathic effect
CRE = *cis*-acting replication element
CRP = C-reactive protein
CSE = cigarette smoke extract
DNA = deoxyribonucleic acid
EPO = eosinophil peroxidise
%FEV_1 = percentage of predicted forced expiratory volume in 1s
FOX = Forkhead box
GCL = glutamate-cysteine ligase
GM-CSF = granulocyte-macrophage colony-stimulating factor
GRO-α = growth-related oncogene
GSH = glutathione
GSHPx = glutathione peroxidase
H_2O_2 = hydrogen peroxide
ICAM-1 = intercellular adhesion molecule-1
IL = interleukin
iNOS = inducible nitric oxide synthase
IP-10 = interferon-γ–induced protein
LDL = low-density lipoprotein
LPS = lipopolysaccharide
MAP = mitogen-activated protein
MCP-1 = monocyte chemoattractant protein-1
MDA = malondialdehyde
MMP-9 = matrix metallopeptidase
MPO = myeloperoxidase
mRNA = messenger ribonucleic acid
NADPH = nicotinamide adenine dinucleotide phosphate
NF-κB = nuclear factor-κB
NO = nitric oxide
Nrf = nuclear erythroid-related factor
PKC = protein kinase C
PPAR = peroxisome proliferator–activated receptor
RNA = ribonucleic acid
ROS = reactive oxygen species
SIRT1 = silent mating-type information regulation 2 homologue
SOD = superoxide dismutase
SP-A = surfactant protein-A
TGF-β1 = transforming growth factor
TLR = Toll-like receptor
TNF = tumor necrosis factor
UV = ultraviolet radiation
VZV = varicella zoster virus

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