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Review Article

Biological activities of resveratrol and its analogs

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CONTENTS

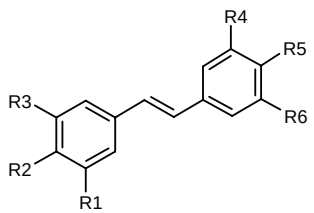
Abstract

Resveratrol (3,4',5-trihydroxy-*trans*-stilbene), a phytoalexin found in grape skins, peanuts, and red wine, has been reported to exhibit a wide range of biological and pharmacological properties. 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, thereby serving as a cardioprotective agent. Recently, resveratrol was shown to function as a cancer chemopreventive agent, and there has been a great deal of experimental effort directed toward defining this effect. In addition, resveratrol exhibits antiinflammatory, neuroprotective and antiviral properties. This review summarizes the recent advances that have provided new insights into the molecular mechanisms underlying the promising properties of resveratrol, including cyclooxygenase, nitric oxide synthase and cytochrome P450 inhibition, as well as cell cycle effects, apoptosis modulation and hormonal activity.

Introduction

Resveratrol (3,4',5-trihydroxystilbene; molecular weight = 228.2; Fig. 1) is a polyphenol that has been classified as a phytoalexin because it is synthesized in spermatophytes in response to certain types of stress. It is the active ingredient of the dried roots of *Polygonum cuspidatum*, which is known in traditional Asian medicine as Ko-jo-kon (1, 2) (Table I). Resveratrol-containing foods include grapes (3, 4), wine (5) and peanuts (6, 7). In the case of grapes, especially when infected with *Botrytis cinerea*, resveratrol is exclusively synthesized in grape skins, which contain 50-100 mg resveratrol/g when they are fresh. Because grape skins are not fermented in the production process of white wines, only red wines contain considerable amounts of resveratrol. It has been proposed that resveratrol is, at least in part, responsible for the beneficial effects of moderate red wine consumption on preventing the development of cardiovascular diseases. Resveratrol inhibited platelet aggregation (8), protected porcine low density lipoproteins against polyunsaturated fatty acid peroxidation (9) and exerted vasorelaxing effects on endothelium-intact aorta rings of rats (10).

The inhibitory potency of resveratrol in various stages of tumor development has attracted much attention (11).



	R1	R2	R3	R4	R5	R6
Stilbene	-H	-H	-H	-H	-H	-H
Resveratrol	-H	-OH	-H	-OH	-H	-OH
Piceatannol	-OH	-OH	-H	-OH	-H	-OH
Piceid	-H	-OH	-H	-OH	-H	-O-Gluc
Pterostilbene	-H	-OH	-H	$-OCH_3$	-H	$-OCH_3$
Rhapontigenin	-OH	$-OCH_3$	-OH	-OH	-H	-OH

Fig. 1. Chemical structures of resveratrol and its analogues.

Table I: Resveratrol and piceid concentrations of selected foods and beverages.

Product	*Trans*-resveratrol	*Trans*-piceid	Ref.
Red grape juice	0.5 mg/l	3.38 mg/l	4
White grape juice	0.05 mg/l	0.18 mg/l	4
Pinot noir red wine, 1994	10.57 mg/l	ND	2
Merlot red wine, 1994	0.48 mg/l	ND	2
Cabernet Sauvignon white wine, 1995	0.53 mg/l	ND	2
Natural peanut butter	0.652 μg/g	0.143 μg/g	7
Blended peanut butter	0.409 μg/g	0.128 μg/g	7
Ko-jo-kon root	523 μg/g	1653 μg/g	2

ND = not detectable

Because many reviews regarding the preventive effect of resveratrol on cardiovascular diseases have been published, this review will focus mainly on the cancer chemopreventive effects of the compound.

Metabolism

Hydroxystilbenes permeate through cell membranes and are stable and not cytotoxic (12). Oral daily administration of 20 mg/kg body weight of resveratrol over a period of 28 days did not lead to any toxic effects in rats (13). In the perfused small intestine of the rat, a model of intestinal absorption, the bioavailability of luminally administered resveratrol was 20.5%. On the vascular side, 16.8% of the resveratrol was found to be conjugated to yield resveratrol glucunoride, 0.3% was found conjugated as resveratrol sulfate and 3.4% was absorbed as free resveratrol (14). Kuhnle *et al.* used the same model to show that 96.5% of the absorbed resveratrol is conjugated as a glucuronide in enterocytes (15). The glucuronidation is mediated by UDP-glucuronyltransferase 1A1, preferentially at the 3-hydroxygroup (16). A conjugation with sulfate has also been reported (17, 18).

After feeding rats red wine with known resveratrol concentrations *ad libitum* the highest plasma concentration was reached after 1 h. The concentration was sufficient to induce physiological effects such as inhibition of thrombocyte aggregation (19). The concentrations detected in the liver and kidneys were comparable to the plasma concentration. A significant absorption could also be found in the heart tissue (20). When known amounts of resveratrol were administered to rats, a bioavailability of 38.1 ± 13.5% was determined. Measurable amounts of glucuronidated and unglucuronidated resveratrol were secreted with bile and reached the enterohepatic cycle. The enterohepatic circulation of resveratrol seemed to influence the plasma half-life (21). After oral administration of 25 mg resveratrol, the highest plasma concentration in humans was detected after 30 min (7.1 μg/l free resveratrol and 338 μg/l conjugated resveratrol) which returned to baseline after 2 h. The rate of conjugated resveratrol was 30-50 times higher than the concentration of free resveratrol. During 24 h, 24.6% of the stilbene was excreted with urine (22). To our knowledge, no data exist concerning the bioavailability of stilbene glucosides. Because glucosides of flavonoids are absorbable, it is likely that stilbene glucosides are bioavailable as well (23). So far no data are available regarding the absorption and metabolism of piceatannol. The extent of absorption of resveratrol from the normal diet is largely unknown and may also depend on the degradability of resveratrol glucosides (*e.g.,* piceid) and resveratrol polymers (*e.g.*, viniferins) in the gut.

In vivo effects

Oral administration of resveratrol inhibited tumor growth of T241 fibrosarcoma in mice (24). Rats inoculated with Yoshida AH-130 hepatoma cells and treated with resveratrol (i.p.) had a decreased number of tumor cells (25). Lung cancer development in A/J mice induced by benzo[*a*]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone was not inhibited by oral administration of resveratrol (500 ppm) (26), but the compound did reduce the number of aberrant crypt foci in azoxymethane-induced tumorigenesis in the rat colon, which led to enhanced expression of the proapoptotic protein Bax in these crypt foci (27). In Min mice, an animal model of familiar adenomatous polyposis, the number of adenomas was reduced by 70% (colons contained no polyps following treatment) in animals given a diet containing resveratrol. The intestinal mucosa of treated mice was subjected to DNA array analysis. Downregulation of the mRNAs encoding for cyclin D1, cyclin D2, DP-1, YB1 and RNA polymerase termination factor TTF-1 could be monitored along with an increase of transforming growth factor (TGF)-β, thrombopoietin, glutamate receptor, MAPK (mitogen activated protein kinase), TSG101 tumor susceptibility protein and other targets (28). The mean survival time of mice inoculated with 32Dp210 leukemia cells and treated with up to 80 mg/kg body weight resveratrol was not significantly different from untreated controls, even though resveratrol exerted antileukemic properties on 32Dp210 cells *in vitro* (29).

In mice bearing highly metastatic Lewis lung carcinoma tumors, resveratrol inhibited DNA synthesis of tumor cells with an IC_{50} value of 6.8 μM. No effects were detected on $CD4^+$, $CD8^+$ and natural killer cells, leading the authors to conclude that these cells are not responsible for the effects of resveratrol on DNA synthesis (30). The

Table II: Overview of the effects of resveratrol on human cancer cell lines.

Cell line	Proliferation	Apoptosis	Cell cycle arrest	Differentiation	$p21^{Waf1/Cip1}$ expression	Ref.
Acute lymphoblastic leukemia cells from patients	–	↑	–	–	–	71
HL-60 (leukemia)	↓	↑	–	–	–	70
HL-60 (leukemia)	↓	↑	S-phase	↑	Unmodified	33
CEM-C7H2 (leukemia)	–	↑	S-phase	–	–	56
THP-1 (leukemia)	↓	↑	S-phase	–	–	74
U937 (leukemia)	–	↑	S-phase	–	–	75
U937 (leukemia)	↓	–	S-phase	–	–	60
LNCaP (prostate cancer)	↓	↑	–	–	↓	68
LNCaP (prostate cancer)	↓	–	S-phase	–	↓	59
LNCaP (prostate cancer)	↓	↑	Unmodified	–	–	65
DU 145 (prostate cancer)	–	↑	–	–	↑	78
Caco-2 (colon carcinoma)	↓	↑	S-phase	Unmodified	Unmodified	62
Caco-2 (colon carcinoma)	↓	No	S-phase	–	–	60
HCT-116 (colon carcinoma)	–	↑	–	↑	↑	35
HCT-116 (colon carcinoma)	↓	↑	–	–	–	81
HCT-116 (colon carcinoma)	–	–	S-phase	–	–	62
MCF-7 (mammary carcinoma)	↓	–	S-phase	–	–	55
MDA-MB-435 (mammary carcinoma)	↓	–	S-phase	–	–	55
A431 (epidermoid carcinoma)	↓	↑	G_0/G_1-phase	–	↑	63
Diverse (thyroid carcinoma)	–	↑	–	–	↑	77

↑ induction; ↓ inhibition; – not investigated.

trans-resveratrol-3-*O*-D-glucoside (piceid) also inhibited the proliferation of Lewis lung cancer cells inoculated into mice, but only at a concentration of 1000 μM. 2,3,5,4'-Tetrahydroxystilbene-2-*O*-D-glucoside was more effective with an IC_{50} of 81 μM (31). The natural resveratrol analog pterostilbene (3,5-dimethoxy-4'-hydroxystilbene) inhibited the development of mammary lesions in a mouse mammary gland organ culture treated with 7,12-dimethylbenz[*a*]anthracene (32).

Differentiation

Resveratrol induced differentiation of promyelocytic HL-60 cells (33). Whereas resveratrol did not affect differentiation when applied alone, it potentiated the differentiation-inducing effect of the short-chain fatty acid butyrate on Caco-2 colonic carcinoma cells and enhanced butyrate-upregulated E-cadherin and cell cycle inhibitor $p21^{Waf1/Cip1}$ expression without increasing $p27^{Kip1}$ levels (34). In HCT-116 colon cancer cells treatment with 100 μM resveratrol led to an increase in microvilli density and villin expression, both signs of terminal differentiation (35).

An overview of *in vitro* anticancer effects of resveratrol is given in Table II.

Arachidonic acid metabolism

Arachidonic acid is released from phospholipid membranes by phospholipase A_2 and subsequently converted by two major pathways. The lipoxygenase pathway results in production of immunomodulatory leukotrienes, whereas the cyclooxygenase (COX) pathway leads to production of prostaglandins, prostacyclins and thromboxanes. COX has been implicated in inflammatory processes and tumorigenesis of the colon and the mammary gland. Resveratrol is an inhibitor of the constitutively expressed COX-1 isoenzyme. This inhibition is exerted on the COX activity as well as on the hydroperoxide activity of COX-1. The hydroperoxide activity of the inducible COX-2 isoform was also inhibited, but only with 20-fold higher concentrations of resveratrol than for COX-1; the COX activity of COX-2 was not affected (11). Whereas inhibition of COX-1 by resveratrol was confirmed by other authors, stimulation of COX-2 activity was also reported (36). In contrast to these results, Subbaramaiah *et al.* demonstrated that resveratrol inhibits prostaglandin (PG) production via recombinant COX-2. In addition, resveratrol suppressed basal and phorbol 12-myristate 13-acetate (PMA)-induced COX-2 activity of 184B5/HER mammary epithelial cells. This effect was accompanied by reduced COX-2 mRNA levels and inhibition of COX-2 promoter activity. Resveratrol also inhibited COX-2 promoter activity induced by overexpression of ERK1, c-Jun and PKCα (37). In DLD-1 colon cancer cells COX-2 promoter activity induced by TGF-α was also inhibited by resveratrol (38). Treatment with resveratrol led to diminished PGE_2 production in murine peritoneal macrophages stimulated with lipopolysaccharides (LPS). In addition, resveratrol downregulated COX-2 levels induced by PMA, LPS or O^-_2 (39). In the erythroleukemia cell line K562, resveratrol suppressed H_2O_2-induced leukotriene

B_4 and PGE_2 production. Dioxygenation of linoleic acid by purified 5-lipoxygenase or 15-lipoxygenase was inhibited as well (40). Induction of phospholipase A_2-association with membranes induced by fetal calf serum (FCS) or platelet derived growth factor (PDGF) was inhibited by resveratrol in 3T6 murine fibroblasts. Resveratrol also suppressed [^{3}H]-arachidonic acid release from membranes and PGE_2 synthesis induced by FCS and PDGF (41).

Inflammation

Resveratrol has been demonstrated to exhibit antiinflammatory properties by suppressing carrageenan-induced paw edema (11). The nuclear factor (NF)-κB is a mediator of inflammation and exerts antiapoptotic activities. Normally, transcription factor NF-κB is sequestered in the cytoplasm by its inhibitor IκB. NF-κB release and translocation to the nucleus occurs when IκB is degraded by proteasomes after phosphorylation by IKK (IκB kinase) following an inflammatory stimulus. Tumor necrosis factor (TNF)-α-induced NF-κB-activation was inhibited by pretreatment of U937 histiocytic lymphoma cells, Jurkat T-cells, HeLa uterus carcinoma cells and H4 glioma cells with resveratrol. In U937 cells, NF-κB-induction by PMA, LPS, okadaic acid, ceramide and H_2O_2 was suppressed as well. Resveratrol did not modify the ability of NF-κB to bind to DNA of U937 cells and did not directly interfere with TNF-α-induced NF-κB-binding to DNA (42). In contrast to these results, Holmes-McNary and Baldwin (43) demonstrated that resveratrol inhibits DNA-binding of NF-κB induced by TNF-α and LPS in U937 cells and THP-1 monocytes. NF-κB-dependent transcription, IκBα degradation, and IKK activation induced by TNF-α in THP-1 cells were inhibited by pretreatment with resveratrol. In LPS-activated RAW 264.7 macrophages, resveratrol inhibited generation of nitric oxide (NO). This effect was due to downregulation of the inducible NO synthase (iNOS) protein and mRNA. An upstream event of LPS-induced iNOS-activation is the activation of NF-κB. Resveratrol treatment inhibited LPS-induced nuclear localization and DNA-binding of NF-κB and suppressed phosphorylation and degradation of the NF-κB-inhibitory protein IκBα (44).

Signal transduction

The MAPK convert extracellular signals (*e.g.*, growth factor signals) into intracellular events. Three kinase pathways (extracellular signal regulated kinase [ERK], p38 and c-Jun kinase [JNK]) have been identified that follow the same principle of phosphorylation and activation cascades. Targets of the MAPK pathways are transcription factors like activator protein (AP)-1, c-Myc and Elk-1. TNF-α-induced AP-1, JNK and MEK (MAPK kinase) activation were inhibited in U937 lymphoma cells by pretreatment with resveratrol (42). Resveratrol inhibited phosphorylation of ERK1 and ERK2 induced by fibroblast growth factor 2 (FGF-2) in bovine capillary endothelial cells (24) and by human serum in liver myofibroblasts (45). Pretreatment of the cervical squamous cancer cell line HeLa with resveratrol inhibited phosphorylation of p38, ERK2, c-Src and JNK and subsequently activation of AP-1 induced by UV irradiation. PMA-induced ERK2 and c-Src phosphorylation were strongly inhibited by resveratrol, whereas resveratrol had only a weak effect on epidermal growth factor (EGF)-induced ERK2-activation (46). In undifferentiated SH-SY5Y neuroblastoma cells, treatment with resveratrol led to increased ERK1 and ERK2 phosphorylation. ERK phosphorylation was inhibited at concentrations of 50 μM and higher. Resveratrol treatment of retinoic acid-differentiated SH-SY5Y cells decreased ERK phosphorylation at first, but then subsequently markedly increased it (47). In porcine coronary arteries, resveratrol inhibited ERK-activation and tyrosine phosphorylation in a concentration-dependent manner. Pretreatment with resveratrol counteracted endothelin-1-stimulated ERK-activity and tyrosine phosphorylation (48).

Resveratrol inhibited recombinant protein kinase C (PKC) activity induced by sonicated vesicles prepared from 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoserine with an IC_{50} value of 30 μM (49). Resveratrol inhibited the PMA-induced redistribution of PKC from cytosol to membrane (37) and the autophosphorylation of isolated PKD in a dose-dependent manner, whereas it had only negligible effects on PKC isozyme autophosphorylation (50).

The naturally occurring stilbene analog piceatannol (*trans*-3,4',3',5-tetrahydroxystilbene), which shares most of the structural moieties with resveratrol, was first identified as an inhibitor of the tyrosine kinase activity of $p72^{Syk}$ and $p56^{Lck}$ in lymphoid cells (51). In addition, piceatannol inhibits the tyrosine kinase activity of human placenta (52) and the focal adhesion kinase and Src in thrombocytes (53).

Cell cycle

The negative effect of resveratrol on proliferation has in part been attributed to inhibition of ribonucleotide reductase and DNA synthesis (54). Inhibition of cell cycle progression is a possible target for chemopreventive agents like resveratrol. The cell cycle is regulated by cyclins and cyclin-dependent kinases (Cdk), which are primarily modulated by their expression levels and by cell cycle inhibiting proteins ($p21^{Waf1/Cip1}$, $p27^{Kip1}$, and members of the INK family of proteins). The effect of resveratrol on the cell cycle distribution of tumor cells appears to affect the S-phase with a cell cycle arrest in the S-phase reported for different cell types (21, 55-62). Increased cyclin E and cyclin A expression was observed in HL-60 leukemia cells (21), U937 lymphoma cells (60), HCT-116 and Caco-2 colon cancer cells (62). Ragione *et al.* identified inactivation of cdc2 by phosphorylation at tyrosine

residue 15 as a possible pathway by which this S-phase arrest is mediated (21). A concentration-dependent decrease of the $p27^{Kip1}$ expression level was observed in LNCaP, U937 and Caco-2 cells (59, 60, 62). In bovine pulmonary artery endothelial cells (57), HL-60 cells (21), A431 cells (63) and U937 cells (60), resveratrol treatment led to an increased $p21^{Waf1/Cip1}$ expression, whereas the protein level of the cell cycle inhibitor was unmodified in Caco-2 cells (62) and decreased in LNCaP cells (59). The retinoblastoma protein (pRb) sequesters the transcription factor E2F in the cytosol. Phosphorylation of pRb prevents binding of pRb to E2F which leads to the translocation of E2F into the nucleus. Dephosphorylation and thus activation of the tumor suppressor pRb was observed in Caco-2 cells (62) and in A431 epidermoid carcinoma cells after treatment with resveratrol. In A431 cells, this effect was accompanied by decreased protein levels of all E2F family members [1-5] and their binding partners DP-1 and DP-2 (64). Resveratrol arrested the cell cycle of nonandrogen-responsive prostate cancer cell lines in the S-phase, but did not modify the cell cycle distribution of the androgen-responsive cell line LNCaP (65). Stivala *et al.* demonstrated that the cell cycle effects of resveratrol are dependent on certain structural determinants. The *trans*-configuration in combination with the hydroxy group in the 4'-position are essential for the effects of resveratrol on the cell cycle (66).

Piceatannol is also a cell cycle inhibitor that acts preferably in the S-phase. It has been demonstrated to inhibit the growth of Caco-2 and HCT-116 colon cancer cell lines. Following piceatannol treatment, the number of Caco-2 cells in the S-phase increased and reduced levels of Cdk4, cyclin D1, cyclin B1 and $p27^{Kip1}$ were detected. At the same time, an increase in cyclin E and cyclin A expression were shown. Taken together, these effects were comparable to those observed after treatment with resveratrol (67).

Apoptosis

Apoptosis or programmed cell death is necessary for the maintenance of normal tissue homeostasis. Impaired apoptosis has been associated with hyperproliferation and tumorigenesis. Induction of apoptosis is accompanied by certain morphological and molecular changes in the cell such as DNA fragmentation, cleavage of caspases and caspase substrates and breakdown of mitochondrial transmembrane potential. Resveratrol was demonstrated to induce apoptosis in a number of cell types (62, 68). The polyphenol not only induced apoptosis in leukemic hematopoietic cells but also in normal activated peripheral blood lymphocytes; it had no apoptotic effect on nonactivated peripheral blood lymphocytes (69). In HL-60 promyelocytic leukemia cells resveratrol-induced apoptosis was prevented by caspase inhibitors (70). Resveratrol-induced apoptosis of CEM-C7H2 acute lymphoblastic leukemia cells was accompanied by cleavage of caspase-6, -3 and -2, but seemed to be independent of caspase-8 activation, since a caspase-8 deficient mutant Jurkat cell line was sensitive to resveratrol-induced cell death (44). Activation of these caspases was inhibited by overexpression of the oncogene Bcl-2 (71). In acute lymphoblastic leukemia cell lines, activation of caspase-9 and depolarization of mitochondrial membranes could be monitored after treatment with resveratrol (72). Resveratrol, but not stilbene or stilbene oxide, prevented H_2O_2-induced apoptosis of K562 erythroleukemia cells (40). Apoptosis can be induced by binding of proapoptotic proteins (TNF-α, Fas ligand) to their receptors. TNF-α-induced apoptosis, reactive oxygen species (ROS)-generation and lipid peroxidation were also inhibited by pretreatment with 5 μM resveratrol in U937 cells (42). Clément *et al.* detected Fas-dependent apoptosis-signaling in HL-60 and T47D cells (73), whereas Fas-independent apoptosis could be demonstrated in CEM-C7H2 (44) and THP-1 monocytic leukemia cells (74). Induction of apoptosis by resveratrol was also monitored in leukemia cell lines that are resistant to Fas-induced cell death (72). In CEM-C7H2 cells, resveratrol-induced breakdown of the mitochondrial transmembrane potential was independent of caspase-8 activation and Bid-cleavage, which are arguments against Fas involvement in this context (71).

In THP-1 cells, overexpression of $p16^{INK4}$ with subsequent cell cycle arrest in G0/G1-phase abrogated apoptosis (74). The same effect could be observed in the acute lymphoblastic leukemia cell line CEM-C7H2 demonstrating the dependence of resveratrol-induced apoptosis on the S-phase arrest (56). In CEM-C7H2 cells overexpression of the antiapoptotic protein Bcl-2 prevented resveratrol-induced apoptosis and mitochondrial transmembrane potential breakdown (71). Overexpression of Bcl-2 in U937 cells also attenuated apoptosis and prevented cleavage of caspase-3 and PARP (poly ADP-ribose polymerase) (75).

Huang *et al.* demonstrated that induction of apoptosis in JB6 mouse epidermal cells is dependent on the presence of the tumorsuppressor p53 (76). In thyroid cancer cells (BHP 2-7, BHP 18-21, FTC 236, and FTC 238), apoptosis induced by resveratrol was inhibited by *p53* antisense oligonucleotide transfection or by addition of the p53 inhibitor pifithrin-α (77). In DU145 prostate cancer cells resveratrol-induced apoptosis was also inhibited by pifithrin-α. In addition, it was demonstrated that overexpression of p53 led to a higher apoptotic response (78). In contrast to these results, induction of apoptosis by resveratrol has been seen in cell types deficient in functional p53 (34, 52, 79). In the colorectal cancer cell line HCT-116, which possesses wild-type p53, apoptosis occurred after incubation with resveratrol via a p53-independent mechanism (35). Stabilization of p53 by phosphorylation at Ser15 in mouse JB6 epidermal cells induced by resveratrol was shown to be dependent on activated ERKs and p38 kinase, but not on activated JNK (80). In thyroid cancer cells apoptosis, c-Fos and p53 induction induced by resveratrol were blocked by the MEK inhibitor PD-98059 (77). In DU145 cells, Ser15 phosphorylation of p53 by resveratrol was also blocked

by PD-98059 (78). Resveratrol induced nonsteroidal anti-inflammatory drug-activated gene (NAG)-1 which has been demonstrated to induce apoptosis in the colorectal cancer cell line HCT-116 and the osteosarcoma cell line U2OS. NAG-1 induction was dependent on the presence of wild-type p53 which has been shown to activate the promoter of NAG-1 (81).

The synthetic resveratrol analog 3,4,5,4'-tetrahydroxystilbene induced DNA fragmentation in SV40 transformed WI38 lung fibroblasts but not in normal WI38 cells. This induction of apoptosis was accompanied by an increase in p53 and Bax expression, enhanced p53-binding to the *bax* promoter and decreased Bcl-x_L, Bcl-x_S, Bcl-2 expression. In addition, mRNA levels of BRCA1, BRCA2 and COX-2 were reduced (82).

Angiogenesis and invasion

Neovascularization is essential for tumor growth. Endothelial cell migration and proliferation are required for the process as well as the breakdown of existing basal membranes by matrix metalloproteinases (MMP). These enzymes are also implicated in tumor cell invasion which is the first step in metastasis development. Resveratrol was found to inhibit growth of bovine aorta endothelial cells in a dose-dependent manner. In addition, it suppressed migration of these cells in a wound assay and endothelial tube formation in collagen matrix, which represents a marker for neoangiogenesis (83). Resveratrol inhibited invasion but not proliferation of the rat ascites hepatoma cell line AH109A pretreated with hypoxanthine and xanthine oxidase in a coculture model with mesothelial cells. Addition of sera from rats fed with resveratrol instead of calf serum also inhibited invasion but not proliferation of AH109A cells, indicating a role for resveratrol in ROS-induced cell invasion (84). Resveratrol also inhibited the growth of FGF-2-stimulated bovine capillary endothelial cells and induced avascular zones in developing chick chorioallantoic membranes in a dose-dependent manner. Corneal neovascularization induced by vascular endothelial growth factor (VEGF) and FGF-2 in mice was suppressed by oral administration of resveratrol. The inhibitory effects of resveratrol on angiogenesis were confirmed in a mouse skin model, where delayed wound healing could be demonstrated (24). Resveratrol inhibited capillary-like tube formation of human umbilical vein cells (HUVEC) and inhibited the binding of VEGF to HUVEC (30). In contrast to these findings, resveratrol did not inhibit invasion of the murine melanoma cell line B16-BL6 as determined in a Boyden chamber invasion assay (85). The direct effects of resveratrol on MMP-2 and MMP-9 were weak (86), whereas resveratrol decreased the secretion of MMP-2 by 40% and inhibited migration of liver myofibroblasts (45).

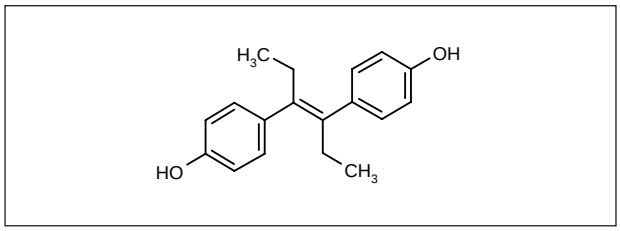


Fig. 2. Chemical structure of diethylstilbestrol.

Estrogenic/antiestrogenic properties

The stilbene structure of resveratrol is related to the synthetic estrogen diethylstilbestrol (Fig. 2). Therefore, the effect of resveratrol on estrogen receptors (ER) has been evaluated although the results obtained are inconsistent. Resveratrol bound to the human ER, inhibited receptor binding of estradiol and initiated transcriptional activity of a reporter gene construct in MCF-7 mammary carcinoma cells containing an ER-responsive element. The proliferation of T47D, an estrogen-dependent breast cancer cell line, was stimulated by resveratrol, but the stilbene was shown to possess proestrogenic activity that was weaker than that of estradiol (87). In MCF-7 cells, resveratrol inhibited growth and antagonized 17β-estradiol-induced growth, thus acting as an antiestrogen (88). In rat uterine cytosol, resveratrol acted as a weak ER ligand and transactivated the ER in ER-α and luteinizing hormone-beta cotransfected Cos-1 cells (89). Resveratrol has been shown to bind ER-α as well as ER-β, but with 7000-fold lower affinity than estradiol. Resveratrol exhibited growth inhibiting properties in CHO-K1 Chinese hamster ovary cells transfected with either ER-α or ER-β. In addition, resveratrol induced reporter gene activity of ER-responsive elements with ER-α and ER-β with equal potency. Resveratrol-liganded ER-β had a higher transcriptional activity than estradiol-liganded ER-β (90).

A study has shown that resveratrol also has effects on the androgen receptor. Treatment of the androgen-stimulated prostate cancer cell line LNCaP with resveratrol led to reduced levels of the androgen-inducible proteins $p21^{Waf1/Cip1}$, prostate specific antigen (PSA) and hK2. Experiments with a reporter gene construct revealed that resveratrol abolished activation of the PSA promoter and the androgen receptor binding site as well as activation of the androgen receptor promoter (68).

Allergies

Resveratrol and the stilbene analog rhapontigenin exhibited a potent inhibitory effect on β-hexoaminidase release from RBL-2H3 mast cells (91). Piceatannol inhibited the IgE-mediated histamine release in human basophils with an IC_{50} value of 3-5 μM (92).

Neuroprotection

Administration of resveratrol to rats protected the olfactory cortex and hippocampus from kainic acid-induced excitotoxic damage (93). Cultured hippocampal cells from rats treated with sodium nitroprusside, an NO-donor, were protected from NO-induced damage by cotreatment and posttreatment with resveratrol (94).

Antioxidant properties

Preincubation of murine peritoneal macrophages with resveratrol prevented LPS-induced production of ROS (39). Resveratrol inhibited iron and UV irradiation-catalyzed lipid peroxidation in microsomes prepared from rat liver. In addition, resveratrol scavenged 2,2'-diphenyl-*p*-picrylhydrazyl radicals whereas *trans*-stilbene did not induce any of these effects (95). Incubation of thrombocytes with 2 μM resveratrol led to reduced intracellular ROS levels. This effect was more pronounced than that observed after addition of 3 mM ascorbic acid (96). Pterostilbene was shown to possess antioxidant properties with a higher total reactive antioxidant potential than trolox, but with less potential than resveratrol (31).

HIV

Resveratrol has been shown to synergistically enhance the anti-HIV activity of the nucleoside analogs zidovudine, zalcitabine and didanosine. In infected cells with decreased susceptibility to didanosine, combination treatment with resveratrol and didanosine decreased viral replication by 80%. When administered alone, resveratrol reduced viral replication in monocyte-derived macrophages by 30% (97).

P450 and aryl hydrocarbon receptor

Whereas Frötschl *et al.* demonstrated that resveratrol is a potent inducer of cytochrome P450 1A1-mRNA in HeLa cells (98), Chun *et al.* demonstrated that resveratrol is a selective inhibitor of P450 1A1, but not of P450 1A2 and NADPH-P450 reductase (99). Aryl hydrocarbon-induced P450 1A1 and P450 1A2 activities were inhibited dose-dependently in microsomes and HepG2 hepatoma cells. Expression of the *cyp1A1* gene was also inhibited in HepG2 and MCF-7 mammary carcinoma cells. Resveratrol abolished binding of the activated aryl hydrocarbon receptor to the xenobiotic-responsive element of the *cyp1A1* promoter (100). Recombinant CYP1B1 activity was inhibited in a dose-dependent fashion when treated with resveratrol. Expression of *cyp1B1*-mRNA was also inhibited in MCF-7 cells (101). Interestingly, Potter *et al.* showed that microsomal CYP1B1 converts resveratrol to piceatannol (102). Resveratrol inhibited dioxin-mediated transactivation in an aryl hydrocarbon receptor-positive breast cancer cell line (T-47D) transfected with a dioxin response element (103).

Liver

Resveratrol downregulates smooth muscle alpha-actin in human liver myofibroblasts but not in skin fibroblasts or vascular smooth muscle cells, indicating possible activity for the management of chronic liver diseases. Neither piceatannol nor piceid induced these effects. Resveratrol also inhibited the expression of type I collagen mRNA which is a sign of antifibrogenic activity (45). In rat hepatic stellate cells, resveratrol inhibited proliferation and also suppressed the expression of smooth muscle α-actin as well as that of cyclin D1 (104). Piceatannol inhibited proliferation of liver myofibroblasts but was cytotoxic at concentrations exceeding 25 μM. On the other hand, piceid had no inhibitory effect on proliferation up to concentration of 100 μM. (45).

Conclusions

Resveratrol could be valuable in improving cancer therapies as well as chemopreventive strategies. The compound has been demonstrated to be a potent inhibitor of cancer cell growth and might therefore be useful in cancer treatment. Beneficial effects might be achieved in combination with other chemopreventive substances for new chemopreventive strategies or with chemotherapeutic drugs to improve cancer therapy. Because resveratrol reversibly inhibits the cell cycle in the S-phase, it is possible that it could enhance the effect of chemotherapeutic drugs that act specifically in the S-phase. Zoberi *et al.* have demonstrated that resveratrol sensitizes cervical cancer cell lines against ionizing radiation, which leads to a decreased cell survival following radiation (105). Resveratrol also enhances the chemopreventive effects of the short-chain fatty acid butyrate. Butyrate, a product of microbial fermentation of fibers in the colon, serves as an energy source for untransformed colonocytes but inhibits growth and induces differentiation and apoptosis of colon cancer cells. Resveratrol enhances the differentiation-inducing effect of butyrate (34). These data support the use of combinatorial strategies including resveratrol. Animal studies have shown that oral supplementation with resveratrol is nontoxic. Clinical trials are needed to evaluate the anticarcinogenic potential of resveratrol *in vivo*.

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