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Review

Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in carcinogenesis

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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 could be an explanation for the so-called 'French paradox' as it 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. 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. It has been shown that resveratrol and some of its analogs interfere with signal transduction pathways, modulate cell cycle-regulating proteins, and is a potent inducer of apoptosis in multiple carcinoma cell lines. This review summarizes the recent advances that have provided new insights into the molecular mechanisms underlying the promising properties of resveratrol.

Keywords: Apoptosis / Angiogenesis / Cancer / Cell cycle / Resveratrol / Signal transduction

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Contents

1 Introduction

In addition to cardiovascular diseases, cancer is one of the leading causes of death worldwide. Each year, the American Cancer Society estimates the number of new cancer cases and deaths expected in the United States in the current year, and compiles the most recent data on cancer incidence, mortality, and survival by using incidence data from the National Cancer Institute (NCI) and mortality data from the National Center for Health Statistics (NCHS). A total of 1 368 030 new cancer cases and 563 700 deaths were expected in the United States in 2004. The three leading cancer types for the estimated new cancer cases are at first cancers of the genital system, with 33% prostate cancers in male and 32% breast cancers in female, followed by about 13% cancers of lung and bronchus. Colorectal cancer is the third most common cancer. It affects both genders almost equally, with about 401 000 new cases in men annually and 381 000 in women [1]. It is estimated that 394 000 deaths from colorectal cancer still occur worldwide annually, and colorectal cancer is the second commonest cause of death from any cancer in men in the European Union [2]. Cancer is caused by both external (tobacco, chemicals, radiation, and infectious organisms) and internal factors (hormones, mutations, and immune conditions). One of the major risk factors is age as about 76% of cancers are diagnosed at age 55 and older. Other risk factors include smoking, alcohol consumption, obesity, physical inactivity, a high-fat diet, as well as inadequate intake of fruits and vegetables [1].

As conventional chemotherapy has no consistent benefit in overall survival, attention is focusing on preventative strate-

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Abbreviations: FGF-2, fibroblast growth factor 2; **MAPK**, mitogen-activated protein kinase; **MEK**, MAPK kinase; **NSAID**, nonsteroidal anti-inflammatory drug; **PMA**, phorbol ester myristate; **ROS**, reactive oxigen species; **TNF**, tumor necrosis factor

gies for multiple cancers [3 – 9]. Chemoprevention is defined as the employment of drugs or natural compounds to prevent malignant tumors [10]. Several epidemiological, clinical, and experimental studies established nonsteroidal anti-inflammatory drugs (NSAIDs) as promising cancer chemopreventive agents [11]. Long-term use of aspirin and other NSAIDs has been shown to reduce the risk of cancer of the colon and other gastrointestinal organs as well as of cancer of the breast, prostate, lung, and skin [12]. But also a large number of natural compounds have been linked to a possible decreased incidence of developing cancers [13 – 15]. Among others there is a special focus on polyphenols present in dietary and medicinal plants exhibiting anti-carcinogenic activities [16].

The plant polyphenol resveratrol (3,4′,5-trihydroxy-*trans*-stilbene; Fig. 1) has been classified as a phytoalexin, because it is synthesized in spermatophytes in response to certain types of stress, including injury, UV irradiation, or fungal attack [17, 18]. It was first described as a component in the root extracts of the weed *Polygonum cuspidatum*, which has been known in traditional Asian medicine under the name Ko-jo-kon [19]. Resveratrol naturally occurs in grapes [20 – 22], wine [23], and peanuts [24 – 26]. An important factor for resveratrol concentrations in wine is the fermentation time in contact with grape skins because resveratrol is produced by the skin but not by the fruit flesh [27]. This explains the low concentrations in white wine because the grape skins are not fermented in the production process [23]. Resveratrol came to scientific attention as a possible explanation for the "French paradox" as it has beneficial effects on the development of cardiovascular diseases [28]. It has been shown to inhibit platelet aggregation and eicosanoid synthesis [29], to interfere with arachidonate metabolism [30], to exert strong inhibitory effects on reactive oxygen species produced by human polymorphonuclear leukocytes [31], to be an antioxidant more powerful than vitamin E in preventing low-density lipoprotein (LDL) oxidation [32], and to exert vasorelaxing effects on endothelium-intact aorta rings of rats [33]. Further studies could show that resveratrol is an agonist for the estrogen receptor which may also be relevant to the reported cardiovascular benefits of drinking wine [34].

Additionally, we and others have examined that resveratrol and its analogs (Fig. 1) exhibit multiple properties including chemopreventive effects in several carcinogenesis models both *in vivo* and *in vitro* [35 – 41]. Several signal transduction pathways have been examined to explain these effects. One hypothesis is focusing on polyamine metabolism as a possible target of resveratrol activity [42]. Because many reviews regarding the preventive effect of resveratrol on cardiovascular diseases have been published [43, 44], this review will summarize our work on the mechanisms and activity of resveratrol and its derivatives in carcinogenesis.

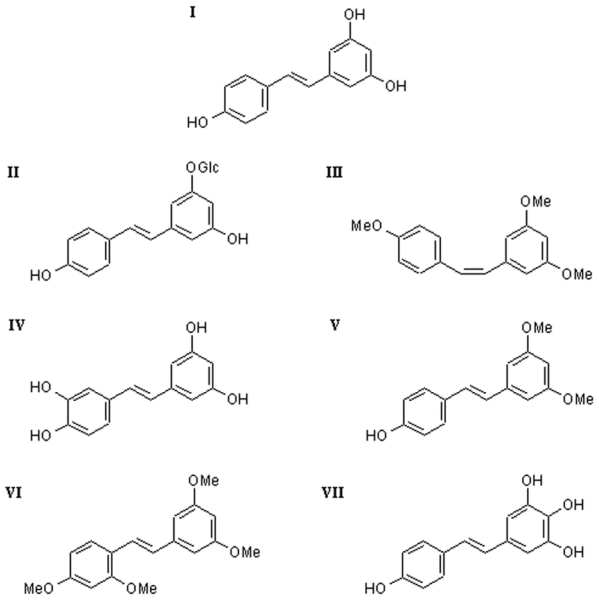

Figure 1. Chemical structures of stilbene compounds cited in this review. (I) 3,4′,5-trihydroxystilbene (resveratrol); (II) *trans*-resveratrol-3-*O*-D-glucoside (piceid); (III) *cis*-3,4′,5-trimethoxystilbene; (IV) 3,3′,4′,5-tetramethoxystilbene (piceatannol); (V) 3,5-dimethoxy-4′-hydroxystilbene (pterostilbene); (VI) 2′,3,4′,5-tetramethoxystilbene; (VII) 2,3,4′,5-tetrahydroxystilbene. Substituents are hydroxyl (OH) and methoxy (OCH_3) groups and *O*-β-D-glucose (OGlc).

2 Resveratrol and its analogs in carcinogenic *in vivo* models

Oral administration of resveratrol inhibited tumor growth of T241 fibrosarcoma in mice [45]. Rats inoculated with Yoshida AH-130 hepatoma cells and treated with resveratrol (intraperitoneal injection) had a decreased tumor cell number [46]. 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 [47, 48], whereas in Balb/c mice resveratrol protects the lung from DNA damage and apoptosis caused by benzo[*a*]pyrene [49]. Additionally administration of resveratrol *per os* reduced the number of aberrant crypt foci in azoxymethane-induced tumorigenesis in the rat colon and led to enhanced expression of the proapoptotic protein Bax in these crypt foci [50]. In a 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced mammary carcinogenesis model in Sprague Dawley rats dietary administration of resveratrol had indeed no effects on body weight gain and tumor volume but produced reductions in the incidence, multiplicity, and extended latency period of tumor development [51]. The mean survival time of mice inoculated with 32Dp210 leukemia cells and treated with up to 80 mg resveratrol/kg body weight was not significantly different from untreated controls, even though resveratrol

exerted antileukemic properties on 32Dp210 cells *in vitro* [52]. In mice bearing highly metastatic Lewis lung carcinoma tumors resveratrol inhibited the DNA synthesis of tumor cells with an IC_{50} value of 6.8 μM. No effect could be monitored on CD4+, CD8+, and natural killer cells, from which the authors concluded that these cells are not responsible for the effects of resveratrol on DNA synthesis [53]. The *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 [54]. In addition, resveratrol treatment of mice (40 mg/kg daily for 28 days) suppressed the growth rate of subcutaneous neuroblastomas, resulting in 70% long-term survival [55]. 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 [56]. In $Apc^{Min/+}$ mice, an animal model for familiar adenomatous polyposis, the number of adenomas was reduced by 70% (colons contained no polyps following treatment) by 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, mitogen-activated protein kinase (MAPK), TSG101 tumor susceptibility protein, and other targets [36]. In contrast to these results, resveratrol did not inhibit tumorigenesis in $Apc^{Min/+}$ mice in a study conducted by Ziegler *et al.* [57], even though reduced PGE_2 levels could be observed in tumor tissue. Also in 4T1 breast cancer cells resveratrol had no effects on growth inhibition *in vivo*, although it exhibits potent inhibitory effects *in vitro* [58]. These controversial results may be due to metabolic processes, as resveratrol is absorbed in the small intestine as resveratrol glucuronide. Glucuronides of phenolic compounds have been assumed to be rapidly excreted *in vivo* and to be pharmacologically inactive [59].

3 Effects of resveratrol and its analogs *in vitro*

3.1 Resveratrol and MAPKs

The MAPKs 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. Tumor necrosis factor (TNF-α)-induced AP-1, JNK, and MEK (MAPK kinase) activation were inhibited in U937 lymphoma cells by pretreatment with resveratrol [60]. Resveratrol inhibited phosphorylation of ERK1 and ERK2 induced by fibroblast growth factor 2 (FGF-2) in bovine capillary endothelial cells [45] and by human serum in liver myofibroblasts [61]. In the cervical squamous cancer cell line HeLa, pretreatment 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, wheras resveratrol had only a weak effect on epidermal growth factor (EGF)-induced ERK2-activation [62]. In undifferentiated SH-SY5Y neuroblastoma cells, treatment with resveratrol led to increased ERK1 and ERK2 phosphorylation. At a concentration of 50 μM and higher ERK phosphorylation was inhibited. Resveratrol treatment of SH-SY5Y cells caused to differentiate with retinoic acid decreased ERK phosphorylation at first, but then increased ERK phosphorylation markedly [63]. 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 [64]. In another report it is shown that growth-inhibitory concentrations of the phytochemical resveratrol suppress endothelial growth factor receptor (EGFR)-dependent ERK1/2 activation pathways stimulated by EGF and phorbol ester (12-*O*-tetradecanoyl phorbol 13-acetate, TPA) in human AI PrCa PC-3 cells *in vitro*. These effects are mediated by protein kinase C (PKC) inhibition by resveratrol, the major cellular receptor for phorbol esters. The results provide evidence that resveratrol may have value as an adjuvant cancer therapeutic in advanced prostate cancer [65].

Resveratrol inhibited the activity of recombinant PKC prepared from sonicated vesicles induced by 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 [66]. Resveratrol inhibited the PMA-induced redistribution of PKC from cytosol to membrane in mammary epithelial cells [67] and the autophosphorylation of isolated protein kinase D in a dose-dependent manner, whereas it had only negligible effects on PKC isozyme autophosphorylation [68].

The natural ocurring 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 [69]. In addition, piceatannol inhibits the tyrosine kinase activity of human placenta [70] and the focal adhesion kinase and Src in thrombocytes [71]. In MCF-7 human breast cancer cells cAMP levels increased

after addition of resveratrol. This effect was demonstrated to be dependent on protein kinase A and phospholipase A_2 activities and independent of the estrogen receptor [72].

3.2 Cell cycle

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 regulated by their expression levels and by cell cycle-inhibiting proteins ($p21^{Waf1/Cip1}$, $p27^{Kip1}$, and members of the INK family of proteins) (Fig. 2). The effect of resveratrol on the cell cycle distribution of tumor cells seems to focus on the S-phase. A cell cycle arrest in the S-phase has been reported for different cell types [37, 73 – 81], except from HepG2 cells in which a G1 phase arrest could be observed [82]. An increased cyclin E and cyclin A expression was observed in HL-60 leukemia cells [83], U937 lymphoma cells [78], HCT-116, and Caco-2 colon cancer cells [37]. Ragione *et al.* [83] identified inactivation of Cdc2 by phosphorylation at tyrosine residue 15 as a possible pathway by which this S-phase arrest is mediated. A concentration-dependent decrease of the $p27^{Kip1}$ expression level was observed in LNCaP, U937, and Caco-2 cells [37, 77, 78]. In bovine pulmonary artery endothelial cells [75], HL-60 cells [83], A431 cells [80], and U937 cells [78] 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 [37] and decreased in LNCaP cells [77] and neuroblastoma cells [55]. In the human prostate carcinoma cell line the antiproliferative effect of resveratrol was associated with the inhibition of D-type cyclins and Cdk 4 expression, and the induction of tumor suppressor p53 and Cdk inhibitor p21. Moreover, the kinase activities of cyclin E and Cdk2 were inhibited by resveratrol without alteration of their protein levels [84]. 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 tumorsuppressor pRb was observed in Caco-2 cells [37] 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 [85]. Resveratrol arrested the cell cycle of non-androgen responsive prostate cancer cell lines in the S-phase, but did not modify the cell cycle distribution of the androgen-responsive cell line LNCaP [86]. Stivala *et al.* [87] 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 is essential for the effects of resveratrol on the cell cycle.

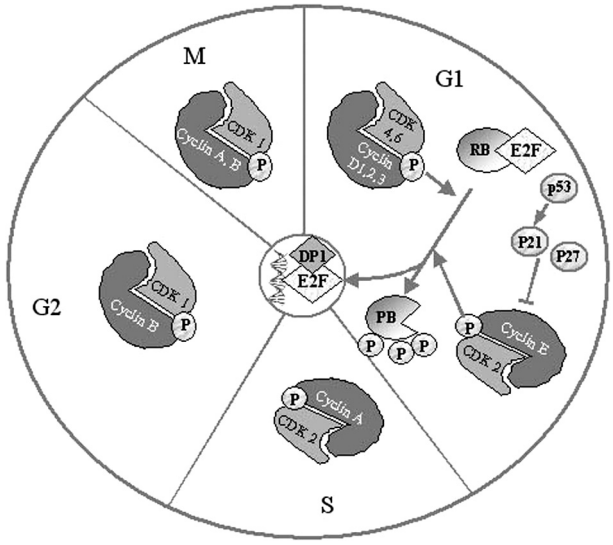

Figure 2. Cell cycle and possible modulation by resveratrol. The polyphenol resveratrol has been shown to inhibit the activity of cdc2 and cdk4. Additionally there is an accumulation of cyclins E and A, accompagnied by a decrease of D-type cyclins as well as an increase of p21 expression. Furthermore, resveratrol promotes dephosphorylation and thus activation of the tumor suppressor pRb. These activities contribute to the ability of resveratrol to inhibit cell progression at S-phase.

Cell cycle regulation was also observed in a few *in vivo* studies. In H22-bearing mice, resveratrol inhibited the growth of transplantable liver cancer by decreasing the expression of cyclin B and cdc2 protein [88]. In another study, resveratrol downregulated UVB-induced expression of Cdk2, 4, 6 and cyclin D1 and D2 in SKH-1 hairless mouse skin, which was accompanied by an upregulated UV-mediated increase in the expression of the Cdk inhibitor WAF1/p21 and the tumor supressor protein p53 [89]. In addition to the regulation of cell cycle proteins, the negative effect of resveratrol on proliferation has in part been attributed to inhibition of ribonucleotide reductase and DNA synthesis [90].

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 could be shown. Taken together, these effects were comparable to those observed after treatment with resveratrol [38]. The methylated resveratrol analog *cis*-3,5,4′-trimethoxystilbene (0.3 μM) induces accumulation of Caco-2 cells in the G_2/M-phase with a diminished G_0/G_1-phase population. These effects were caused by depolymerization of the microtubule network [91].

3.3 Apoptosis

Apoptosis, also termed 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, like DNA fragmentation, cleavage of caspases and caspase substrates, and breakdown of mitochondrial transmembrane potential (Fig. 3). Resveratrol has been demonstrated to induce apoptosis in a number of cell types [37, 75–77, 80, 82, 84–86, 92, 93]. 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 [94]. In HL-60 promyelocytic leukemia cells resveratrol-induced apoptosis was prevented by caspase inhibitors [95]. 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, because a caspase-8-deficient mutant Jurkat cell line was sensitive to resveratrol-induced cell death [96]. Activation of these caspases was inhibited by overexpression of the oncogene Bcl-2 [97]. Overexpression of Bcl-2 in U937 cells also attenuated apoptosis and prevented cleavage of caspase-3 and PARP (poly ADP-ribose polymerase) [98]. These findings could be confirmed by Zhou *et al.* [99] demonstrating an upregulation of Bax as well as a downregulation of Bcl-2 during resveratrol-induced apoptosis. Another study could show that resveratrol-induced apoptosis is accompanied by induction of p53, upregulation of Bax, activation of caspase 9, and decrease in Bcl-2 levels [100].

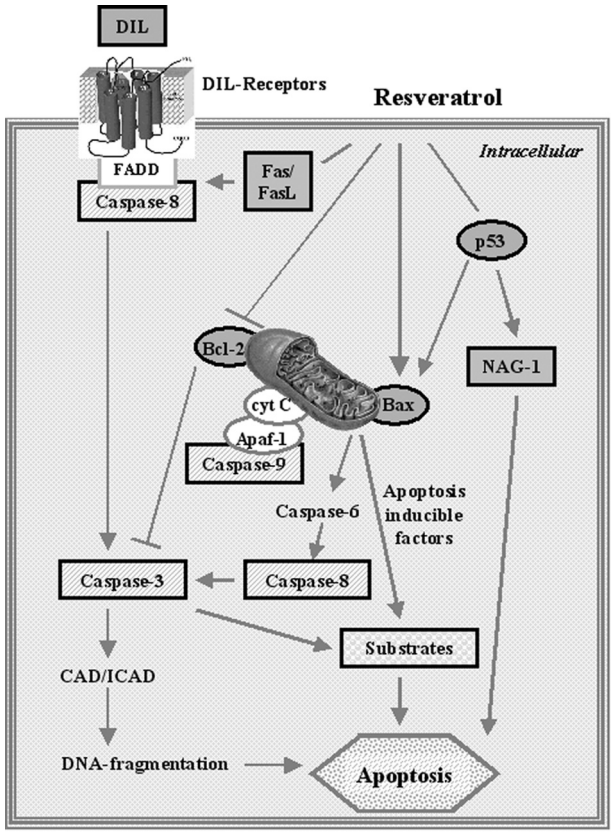

Figure 3. Apoptosis and possible stimulatory pathways by resveratrol. Resveratrol was shown to activate pro-apoptotic caspases-6, -3, and -9 but seems to be partly independent of caspase-8 activation. It also leads to an induction of tumor suppressor p53 and Bax as well as an inhibition of Bcl-2. Additionally, resveratrol leads to an upregulation of pro-apoptotic NAG-1. DIL, death-inducible ligands; NAG-1, NSAID-activated gene; CAD, caspase-activated Dnase; ICAD, inhibitor of CAD.

In human prostate carcinoma cells (DU145) resveratrol upregulated the Bax protein and mRNA expression in a dose-dependent manner, whereas Bcl-2 and Bcl-xL levels were not significantly affected. These results correlated with an activation of caspase-3 and caspase-9 [84]. Otherwise resveratrol-treated human liver cancer cells HepG2 and Hep3B had enhanced Bax expression but they were not involved in the Fas/Apo-1 apoptotic signal pathway [82]. In acute lymphoblastic leukemia cell lines, activation of caspase-9 and depolarization of mitochondrial membranes could be monitored after treatment with resveratrol [101]. 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 [60]. Clément *et al.* [102] detected Fas-dependent apoptosis-signaling in HL-60 and T47D cells, whereas Fas-independent apoptosis could be demonstrated in CEM-C7H2 [96] and THP-1 monocytic leukemia cells [103]. In a human colon cancer cell line (SW480) resveratrol-induced apoptosis was also not mediated directly through modulation of Fas/FasL interaction, but was attributable to caspase activation and increased accumulation of Bax and Bak [104]. High levels of p53 expression in cells with fractional DNA content, *i. e.*, in apoptotic cells, strongly suggests that their apoptosis may be associated with upregulation of p53 [75]. Furthermore, Huang *et al.* [105] demonstrated that induction of apoptosis in JB6 mouse epidermal cells is dependent on the presence of the tumor suppressor p53. In HepG2 cells also a p53-dependent pathway involving an increased expression of Bax and upregulation of p21 was suggested [82]. In thyroid cancer cells (BHP 2–7, BHP 18–21, FTC 236, and FTC 238) the apoptosis induced by resveratrol was inhibited by p53 antisense oligonucleotide transfection or by addition of the p53 inhibitor pifithrin-α [106]. In DU 145 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 [107]. In contradiction to these results induction of apoptosis by resveratrol has been shown in cell types deficient of func-

tional p53 [37, 108]. In the colorectal cancer cell line HCT-116, which possesses wild-type p53, apoptosis occurs after incubation with resveratrol *via* a p53-independent mechanism [109]. The MAPK activation by resveratrol was found to upregulate p53 in mouse epidermal JB6 cells [110, 111]. In thyroid cancer cells, apoptosis, c-Fos, and p53 induction induced by resveratrol were blocked by the MEK inhibitor PD98059 [106]. In DU 145 cells, Ser15 phosphorylation of p53 by resveratrol was also blocked by PD98059 [107]. Resveratrol induced NAG-1 (NSAID-activated gene), 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 [112]. Further studies suggest that an involvement of the pRb-E2F/DP pathway is suggested as an important contributor of resveratrol-mediated cell cycle arrest and apoptosis [85].

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 apoptosis induction was accompanied by increased p53 and Bax expression, enhanced p53-binding to the bax promoter, and decreased Bcl-xL, Bcl-xS, Bcl-2 expression. In addition, mRNA levels of BRCA1, BRCA2, and COX-2 were diminished [113]. Another analog, 3,5,2′,4′-tetramethoxy-*trans*-stilbene, was shown to induce the accumulation of cellular DNA contents in the sub-G0 phase of the cell cycle in a time-dependent manner, wheras the morphological changes were consistent with an apoptotic process [114]. The natural occuring resveratrol analog piceatannol (3,5,3′,4′-tetrahydroxy-*trans*-stilbene; PICE) was also shown to be a potent inducer of apoptosis in human SK-Mel-28 melanoma cells [115].

3.4 Angiogenesis and invasion

Neovascularization and thus supply of tumors with nutrients is essential for their growth. Endothelial cell migration and proliferation are as necessary for this process as the breakdown of existing basal membranes by matrix metalloproteinases (MMPs). These enzymes are also implicated in tumor cell invasion, which is the first step of 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 a collagen matrix, which is considered to represent a marker for neoangiogenesis [116]. 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, demonstrating a role for resveratrol in ROS-induced cell invasion [117]. 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 inhibiting effects of resveratrol on angiogenesis were confirmed in a mouse skin model, where delayed wound healing could be demonstrated [45]. Resveratrol inhibited capillary-like tube formation of human umbilical vein cells (HUVEC) and inhibited the binding of VEGF to HUVEC [53]. VEGF expression did not significantly change when rat RT-2 glioma cells were treated with low-dose resveratrol, but it was suppressed when they were treated with 10, 25, or 100 μM resveratrol [118]. Although resveratrol did not affect HIF-1α mRNA levels in human ovarian cancer cells, it did dramatically inhibit both basal-level and growth factor-induced HIF-1α protein expression in the cells as well as VEGF expression [119]. Furthermore, resveratrol abolished VEGF-induced VE-cadherin tyrosine phosphorylation and redistribution and Src activity in HUVEC [120]. 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 [121].

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Dedicated to the 65th Birthday of Prof. Dr. W. F. Caspary.

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