# Cancer Prevention and Treatment with Resveratrol: From Rodent Studies to Clinical Trials

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**Abstract** Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) is a dietary polyphenol derived from grapes, berries, peanuts, and other plant sources. During the last decade, resveratrol has been shown to possess a fascinating spectrum of pharmacologic properties. Multiple biochemical and molecular actions seem to contribute to resveratrol effects against precancerous or cancer cells. Resveratrol affects all three discrete stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis. The anticancer property of resveratrol has been supported by its ability to inhibit proliferation of a wide variety of human tumor cells *in vitro*. These *in vitro* data have led to numerous preclinical animal studies to evaluate the potential of this drug for cancer chemoprevention and chemotherapy. This review provides concise, comprehensive data from preclinical *in vivo* studies in various rodent models of human cancers, highlighting the related mechanisms of action. Bioavailability, pharmacokinetic, and potential toxicity studies of resveratrol in humans and ongoing interventional clinical trials are also presented. The conclusion describes directions for future resveratrol research to establish its activity and utility as a human cancer preventive and therapeutic drug.



The ability of natural agents to suppress carcinogenesis has attracted the widespread attention of cancer prevention and treatment researchers. The natural agent resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) has been shown to possess many biological activities relevant to human cancer prevention and treatment (1, 2). Resveratrol is a phytoalexin, or plant antibiotic, produced in large quantities in various plants in response to environmental stress and pathogenic attack and thus acts as a natural inhibitor of cell proliferation (3). Perhaps most widely known as a constituent of red wine, resveratrol has been detected in more than 70 plant species, including grapes, berries, plums, peanuts, and pines (3, 4). Epidemiologic studies have shown an inverse correlation between red wine consumption and the incidence of cardiovascular disease, a phenomenon called the "French paradox" and suggested to be due to resveratrol (5).

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**Note:** The author sincerely apologizes for not discussing and citing numerous important publications because of the limitation of space and of the number of references. This review is dedicated to the memory of Amiya K. Bishayee.

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Many preclinical and clinical studies have shown that resveratrol can prevent or slow the progression of a wide variety of age-associated illnesses, including cancer, diabetes, arthritis, and coronary, neurodegenerative, and pulmonary diseases (1–3). It also mimics caloric restriction, improves health, and interferes with the aging process, all linked to its ability to activate sirtuin proteins (6, 7). Sirtuins are a conserved family of $NAD^+$-dependent protein deacetylases that are involved in gene silencing processes related to aging, blockade of apoptosis, and promotion of cell survival. It has been speculated that the caloric restriction mimetic and antiaging mechanisms of resveratrol may contribute to its effects against cancer.

Extensive study over the past decade has shown both the chemopreventive and chemotherapeutic potential of resveratrol (8, 9). It suppresses the proliferation of a wide variety of human tumor cells *in vitro* (reviewed in ref. 9). The antitumor activities of resveratrol are mediated through several cell signaling pathways and include cell cycle arrest, suppression of tumor cell proliferation, induction of apoptosis and differentiation, reduction of inflammation and angiogenesis, and inhibition of adhesion, invasion, and metastasis (Fig. 1; reviewed in refs. 9–11). Although resveratrol anticarcinogenic potential has been linked with an impressive amount of data primarily from human cell culture systems, emerging results of cancer prevention and therapy studies in laboratory animal models provide convincing evidence that resveratrol can inhibit carcinogenesis in several organ sites. This evidence is summarized in this review, which also highlights underlying mechanisms

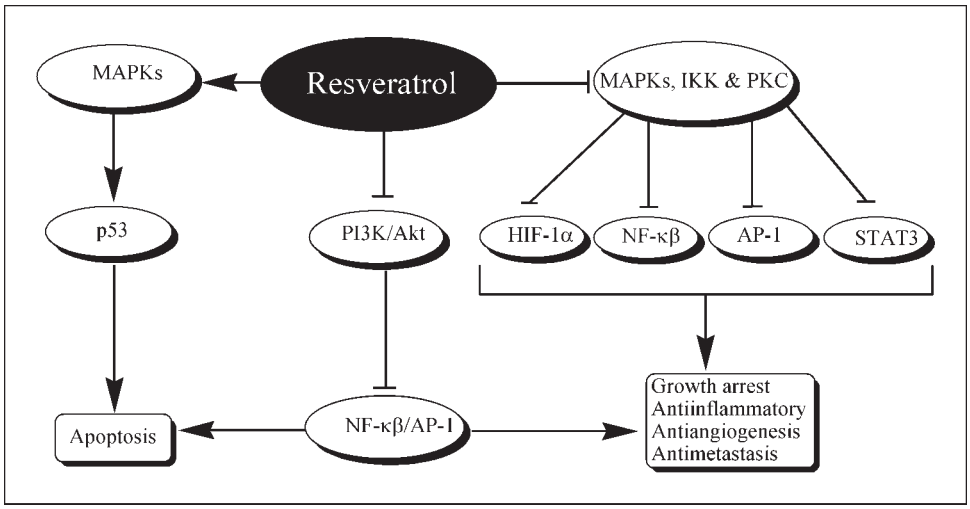


**Fig. 1.** Effect of resveratrol on intracellular signal transduction pathways involved in carcinogenesis [adapted from Kundu and Surh (11)]. AP-1, activator protein-1; HIF-1α, hypoxia-inducible factor-1α; IKK, IκB kinase; MAPKs, mitogen-activated protein kinases; NF-κB, nuclear factor-κB; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; STAT3, signal transducer and activator of transcription 3.

that provide a rationale for testing resveratrol clinically in human populations.

## *In vivo* Preclinical Studies

### Skin

Conducted by Jang et al. (12), the first animal study of the chemopreventive effects of resveratrol was reported in a two-stage mouse skin carcinogenesis model. Topical resveratrol significantly reduced 7,12-dimethylbenz(*a*)anthracene (DMBA)–initiated and 12-*O*-tetradecanoylphorbol-13-acetate (TPA)–promoted skin tumors in mice (Table 1). Subsequent studies showed that pretreating mouse skin with resveratrol negated several TPA-induced effects, including increased expressions of cyclooxygenase (COX)-1, COX-2, c-myc, c-fos, c-Jun, transforming growth factor-β1, and tumor necrosis factor-α (13). In the DMBA-TPA mouse skin carcinogenesis model, resveratrol inhibited tumor promotion, possibly due at least partly to antioxidant effects (14). Soleas et al. (15) found that resveratrol was moderately effective in inhibiting the rate of tumor formation and reducing the number of animals developing DMBA-induced skin tumors. Resveratrol effectively prevented development of DMBA-TPA–induced mouse skin tumors through induction of apoptosis, characterized by induction of cytochrome *c* release, expression of p53, Bax, and apoptotic protease-activating factor-1, and inhibition of Bcl-2 (16). Afaq et al. (17) showed that resveratrol has the potential to ameliorate edema and inflammation caused by short-term UVB exposure in the skin of SKH-1 hairless mice, presumably due to inhibition of the photocarcinogen-mediated induction of COX, ornithine decarboxylase (ODC), and lipid peroxidation, and topical resveratrol inhibited skin hyperplasia induced by UVB radiation in the SKH-1 hairless mouse model. Mechanistic studies in this model revealed that resveratrol exerted antiproliferative effects mediated through decreased expression of cyclin-dependent kinase (CDK)-2, CDK-4, CDK-6, cyclin D1, cyclin D2, proliferative cell nuclear antigen, and mitogen-activated protein kinase and increased expression of p21WAF1/CIP1 (18). Further study revealed that resveratrol inhibited the expression of survivin and markers of tumor promotion, such as COX-2 and ODC, in the skin of mice (19). In an extension of these mechanistic studies, resveratrol treatment both before and after UVB exposure resulted in a significant reduction of mouse skin tumor incidence and delay in the onset of tumorigenesis involving up-regulated protein and mRNA levels of survivin and phospho-survivin protein and down-regulated proapoptotic Smac/DIABLO protein (20).

Resveratrol via i.p. injection inhibited the growth of highly metastatic B16-BL6 melanoma cells in mice (21). In contrast, oral resveratrol did not inhibit the growth of B16M melanoma cells injected into the footpad of mice; it did, however, reduce the metastatic invasion of intrasplenically injected melanoma cells into the liver (22). Moreover, resveratrol did not have a significant effect in reducing the growth of an A375 human melanoma xenograft in athymic mice, even stimulating this growth at higher dose levels (23). These collective melanoma data suggest that resveratrol effects on melanoma depend on dose, route of administration, and the specific model studied.

### Breast

Although having no effect on tumor incidence, resveratrol in the diet strikingly reduced the incidence and multiplicity of DMBA-induced mammary tumors, concurrently extending the latency period, in mice. These findings were associated with decreased COX-2 and matrix metalloproteinase-9 expression and suppression of nuclear factor-κB activation (24). Dietary resveratrol inhibited DMBA-induced mammary cancer in rats by enhancing maturation of the mammary gland, reducing cellular proliferation, and increasing apoptosis in mammary epithelial cells (25). Resveratrol combined with the soy isoflavone genistein was better than resveratrol alone in reducing tumor multiplicity and extending tumor latency in rats with DMBA-induced mammary tumors (26). Oral resveratrol also reduced *N*-methyl-*N*-nitrosourea–induced tumorigenesis in rats (27). However, a short-term prepubertal exposure to resveratrol resulted in endocrine disruption, or altered endocrine function indicated by a significant increase in the

**Table 1.** *In vivo* effects of resveratrol on cancer development and growth and their possible mechanisms

| Target/effects | Mechanisms | Dose/duration | Route | References |
|---|---|---|---|---|
| Skin | | | | |
| Reduces the number of skin tumors initiated with DMBA and promoted by TPA in female CD-1 mice | ↓COX-1; ↓COX-2; ↓c-myc; ↓c-fos; ↓c-Jun; ↓TGF-β1; ↓TNF-α | 1, 5, 10, 25 μmol Twice/week for 18 wk | top. | Jang et al. (12); Jang and Pezzuto (13) |
| Suppresses the development of DMBA-initiated and TPA-promoted papillomas in female ICR mice | Free radical scavenging | 85 nmol/L 21 wk | top. | Kapadia et al. (14) |
| Reduces the onset of skin tumors with DMBA-TPA model in CD-1 mice | | 1, 5, 10, 25 μmol Twice/week, 18 wk | top. | Soleas et al. (15) |
| Inhibits the development of DMBA-TPA–induced skin tumors in male Swiss albino mice | ↑Apoptosis; ↑Bax; ↑p53; ↓ Bcl-2; ↑cytochrome *c* release; ↑APAF-1 | 50 μmol/mouse 3-24 week | top. | Kalra et al. (16) |
| Prevents UVB-mediated photocarcinogenesis in female SKH-1 mice | ↓COX; ↓ODC; ↓lipid peroxidation | 25 μmol/mouse | top. | Afaq et al. (17) |
| Decreases UVB-induced skin hyperplasia in female SKH-1 mice | ↑CDK-2, CDK-4, and CDK-6; ↑ cyclin D1 and cyclin D2; ↑ MAPK; ↑ p21; ↑p53; ↓COX-2; ↓ODC; ↓survivin mRNA and protein | 10 μmol/mouse 7 times, alternate days | top. | Reagan-Shaw et al. (18); Aziz et al. (19) |
| Prevents UV radiation-mediated skin tumorigenesis in female SKH-1 mice | ↑Survivin mRNA and protein; ↑ phospho-survivin; ↓Smac/DIABLO | 25, 50 μmol/mouse Twice/week, 28 wk | top. | Aziz et al. (20) |
| Delays tumor growth in female C57Bl/6N mice transplanted with B16-BL6 melanoma cells | | 50 mg/kg 19 d | i.p. | Caltagirone et al. (21) |
| Does not slow down the growth of B16M melanoma cells inoculated into the footpad of male C57Bl/6J mice | | 20 mg/kg 23 mg/mL 10 d | p.o. d.w. | Asensi et al. (22) |
| Does not inhibit the growth of A375 human melanoma cells xenografted in male *nu/nu* mice | | 0.005, 0.01% 0.0025, 0.006% 10, 25, 50, 100 mg | d.w. Diet s.p. | Niles et al. (23) |
| Breast | | | | |
| Suppresses DMBA-induced mammary carcinogenesis in female Sprague-Dawley rats | ↓NF-κB; ↓COX-2; ↓MMP-9 | 10 ppm 127 d | Diet | Banerjee et al. (24) |
| Suppresses DMBA-induced mammary cancer in Sprague-Dawley rats | ↓Proliferation; ↑apoptosis | 100 mg/kg 25 wk | Diet | Whitsett et al. (25) |
| In combination with genistein improves the tumor inhibitory action of resveratrol in DMBA-initiated rat mammary carcinogenesis | | 100, 333 mg/kg Lifetime | Diet | Whitsett and Lamartiniere (26) |
| Reduces MNU-induced mammary tumorigenesis in female Sprague-Dawley rats | Estrogen modulation | 100 mg/kg 127 d | p.o. | Bhat et al. (27) |
| Increases MNU-induced mammary carcinogenesis in female Sprague-Dawley rats | Endocrine disruption | 100 mg/kg 37 wk | s.c. | Sato et al. (28) |
| Inhibits the growth of MDA-MB-231 breast tumor explants in female athymic nude mice | ↑Apoptosis; ↓angiogenesis | 25 mg/kg 3 wk | i.p. | Garvin et al. (29) |

(*Continued to the following page*)

**Table 1.** *In vivo* effects of resveratrol on cancer development and growth and their possible mechanisms (Cont'd)

| Target/effects | Mechanisms | Dose/duration | Route | References |
|---|---|---|---|---|
| Does not influence the growth and metastasis of transplanted 4T1 mammary carcinoma cells in female BALB/c mice | | 1, 3, 5 mg/kg 23 d | i.p. | Bove et al. (30) |
| Delays the development and reduces the metastatic growth of spontaneous mammary tumors in female HER-2/*neu* transgenic mice | ↑Apoptosis; ↓HER-2/*neu*; mRNA and protein | 0.2 mg/kg 2 mo | d.w. | Provinciali et al. (31) |
| In combination with quercetin and catechin retards the growth of xenografts of MDA-MB-231 cells in female athymic *nu*/*nu* mice | | 5, 25 mg/kg Thrice/week, 117 d | p.o. | Schlachterman et al. (32) |
| Prostate | | | | |
| Suppresses prostate cancer progression in male TRAMP model | ↑ER-β; ↑IGF-I; ↓phospho-ERK-1and ERK-2 | 625 mg/kg 7-23 wk | Diet | Harper et al. (33) |
| Suppresses prostate cancer growth in male TRAP rats | ↑Apoptosis; ↓AR; ↓GK11 mRNA | 50, 100, 200 μg/mL 7 wk | d.w. | Seeni et al. (34) |
| Gastrointestinal tract | | | | |
| Inhibits AOM-induced colon carcinogenesis in male F344 rats | ↑Bax; ↑p21 | 200 μg/kg 100 d | d.w. | Tessitore et al. (35) |
| Suppresses DMH-induced colon carcinogenesis in male Wistar rats | Modulation of antioxidant defense and biotransformation enzymes | 8 mg/kg 15-29 wk | p.o. | Sengottuvelan et al. (36–38) |
| Prevents the formation of colon tumors and reduces small intestinal tumors in $Apc^{Min/+}$ mice | ↓Cyclin D1 and cyclin D2; ↓DP1; ↓YB1; ↑TGF-β; ↑TSG101 (all mRNA) | 0.01% 7 wk | d.w. | Schneider et al. (39) |
| Decreases intestinal adenoma formation in $Apc^{Min/+}$ mice | ↓COX-1; ↓COX-2; ↓$PGE_2$ | 240 mg/kg 10-14 wk | Diet | Sale et al. (40) |
| Does not affect intestinal tumorigenesis in male $Apc^{Min/+}$ mice | | 4, 20, 90 mg/kg 7 wk | Diet | Ziegler et al. (41) |
| Inhibits NMBA-induced esophageal tumorigenesis in male F344 rats | ↓COX-1 and COX-2 mRNA; ↓$PGE_2$ | 1, 2 mg/kg 16-20 wk | p.o. or i.p. | Li et al. (42) |
| Inhibits the growth of implanted human primary gastric carcinoma cells in female BALB/c nude mice | ↑Apoptosis; ↑Bax and ↓Bcl-2 (mRNA and protein) | 500, 1,000, 1,500 mg/kg 6 times in 11 d | i.t. | Zhou et al. (43) |
| Does not modify BOP-induced pancreatic carcinogenesis in male Syrian hamsters | | 10 ppm 3-14 wk | Diet | Kuroiwa et al. (44) |
| Decreases the growth of transplanted Yoshida AH-130 ascites hepatoma cells in male Wistar rats | ↑Cells in $G_2$-M phase; ↑apoptosis | 1 mg/kg 7 d | i.p. | Carbó et al. (45) |
| Suppresses tumor growth and metastasis in male Donryu rats implanted with AH-109A ascites hepatoma cells | ↓Serum TG; ↓VLDL; ↓LDL | 50 ppm 20 d | Diet | Miura et al. (46) |
| Inhibits the weight of tumors in BALB/c mice implanted with H22 hepatoma cells | Immunomodulation | 500, 1,000, 1500 mg/kg 10 d | abd | Liu et al. (47) |
| Reduces the volume of tumors in BALB/c mice implanted with H22 tumors | ↓Cyclin B1; ↓p34cdc2 | 5, 10, 15 mg/kg 10 d | abd | Yu et al. (48) |
| Enhances the antitumor effect of 5-fluorouracil in male BALB/c mice implanted with H22 tumors | ⊥S phase | 5, 10, 15 mg/kg 10 d | abd | Wu et al. (49) |

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**Table 1.** *In vivo* effects of resveratrol on cancer development and growth and their possible mechanisms (Cont'd)

| Target/effects | Mechanisms | Dose/duration | Route | References |
|---|---|---|---|---|
| Inhibits DENA-initiated hepatocarcinogenesis in female Sprague-Dawley rats | ↓Proliferation; ↑apoptosis; ↑Bax; ↓Bcl-2 | 50, 100, 300 mg/kg 20 wk | Diet | Bishayee and Dhir (50) |
| Lung | | | | |
| Does not influence lung tumorigenesis induced by B[*a*]P and NNK in female A/J mice | | 500 ppm 25 wk | Diet | Hecht et al. (51) |
| Does not reduce the number or size of B[*a*]P-induced lung tumors in female A/J mice | | 6-8 mg/kg ~5 mo | Diet | Berge et al. (52) |
| Inhibits tumor growth and lung metastasis in female C57Bl/6 mice transplanted with Lewis lung carcinoma cells | ↑Apoptosis; ↓DNA synthesis; ↓angiogenesis | 2.5, 10 mg/kg 21 d | i.p. | Kimura and Okuda (53) |
| Decreases metastasis of implanted Lewis lung carcinoma cells in C57Bl/6 mice | ↓Angiogenesis | 5, 25 mg/kg 15 d | i.p. | Busquets et al. (54) |
| Inhibits tumor growth in female C57Bl/6 mice inoculated with Lewis lung carcinoma cells; an analogue is found more potent | ↑Apoptosis; ↓angiogenesis | 20 mg/kg 17 d | i.p. | Lee et al. (55) |
| Other systems | | | | |
| Suppresses the growth of implanted neuro-2a neuroblastoma cells in male A/J mice | ↑Apoptosis; ⊥S phase; ↓p21; ↑cyclin E | 40 mg/kg 28 d | i.p. | Chen et al. (56) |
| Inhibits the growth of implanted RT-2 glioma cells in F344 rats | ↑Apoptosis; ↓angiogenesis | 40 or 100 mg/kg 4 wk | i.p. | Tseng et al. (57) |
| Represses tumor growth in Fischer rats inoculated with RT-2 glioma cells | ↓Angiogenesis; ↓CD31 | 40 mg/kg 4 wk | i.p. | Chen et al. (58) |
| Diminishes the growth of NGP and SK-N-AS neuroblastoma cells in athymic mice | ↑Apoptosis; mitochondrial dysfunction; ↑cytochrome *c* release; ↑Smac/DIABLO release; ↑caspases | 2, 10, 50 mg/kg 5 wk | p.o. | van Ginkel et al. (59) |
| Exhibits weak antileukemic effects in male C3H (H-2$^k$) mice with 32Dp210 cells | ↑Apoptosis; ↑caspase-3 | 80 mg/kg 5 times/week; 14-60 d | p.o. | Gao et al. (60) |
| Enhances antitumor immune activity in male BALB/c mice bearing L1210 lymphocytic leukemic cells | ↑Apoptosis; ↓Bcl-2; ↓IL-6 mRNA and protein | 12.5, 25, 50 mg/kg 3 wk | i.g. | Li et al. (61) |
| Inhibits the growth of implanted T241 fibrosarcoma cells in C57Bl6/J mice | ↓Angiogenesis | 1 mg/kg ~23 d | d.w. | Bråkenhielm et al. (62) |
| Retards the growth of inoculated C918 and Mum2b cells in athymic mice | ↑Apoptosis; mitochondrial dysfunction; ↑cytochrome *c* release; ↑Smac/DIABLO release; ↑caspase-3 | 0.4-50 mg/kg 3-5 wk | p.o. | van Ginkel et al. (63) |

Abbreviations: TGF, transforming growth factor; TNF, tumor necrosis factor; APAF-1, apoptotic protease-activating factor-1; MAPK, mitogen-activated protein kinase; MMP-9, matrix metalloproteinase-9; MNU, *N*-methyl-*N*-nitrosourea; IGF-I, insulin-like growth factor-I; TRAMP, transgenic adenocarcinoma mouse prostate; TRAP, transgenic rat for adenocarcinoma of prostate; AR, androgen receptor; GK11, glandular kallikrein 11; AOM, azoxymethane; DMH, 1,2-dimethylhydrazine; NMBA, *N*-nitrosomethylbenzylamine; BOP, *N*-nitroso-bis(2-oxopropyl)amine; TG, triglyceride; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; DENA, diethylnitrosamine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; IL-6, interleukin-6; top., topical; p.o., per os; d.w., drinking water; s.p., slow-release pellet; abd, abdominal injection; i.t., intratumoral.

incidence of irregular estrous cycle with a prolonged estrus phase, which culminated in increased incidence and multiplicity of mammary tumors in rats (28).

In a xenograft animal model, resveratrol inhibited the growth of estrogen receptor (ER)-α–negative and ER-β–positive MDA-MB-231 tumor explants, increased apoptosis, and decreased angiogenesis in nude mice (29). Resveratrol had no effect on the *in vivo* growth and metastasis of transplanted ER-α–negative 4T1 murine mammary cancer cells in nude mice (30). It has been shown that resveratrol, believed to be a phytoestrogen, functions as a mixed agonist/antagonist on the ER and exhibits higher transcriptional activity when bound to ER-β than when bound to ER-α. In addition, resveratrol seems to have antagonist activity with ER-α but not with ER-β. Therefore, the growth-inhibitory effects of resveratrol in these models may be mediated by ER-β or may be ER independent. Resveratrol supplementation in drinking water delayed the development of spontaneous mammary tumors in HER-2/*neu* transgenic mice and reduced the mean number and size of mammary tumors by down-regulating *HER-2/neu* gene expression and increasing apoptosis in the mammary glands of these mice (31). Recently, the combined polyphenols resveratrol, quercetin, and catechin administered by gavage reduced the primary growth of xenografts of MDA-MB-231 breast cancer cells in nude mice, as monitored by *in situ* fluorescence image analysis of fluorescently tagged tumor cells (32).

### Prostate

Dietary resveratrol significantly reduced the incidence of prostatic adenocarcinoma in the transgenic adenocarcinoma mouse prostate model. The decrease in cell proliferation and insulin-like growth factor-I, down-regulation of phospho-extracellular signal-regulated kinase (ERK)-1 and ERK-2, and increase in ER-β provided a biochemical basis for resveratrol-mediated suppression of prostate cancer development (33). Resveratrol in the drinking water suppressed prostate cancer growth in the transgenic rat for adenocarcinoma of prostate model with induction of apoptosis. Moreover, resveratrol not only down-regulated the androgen receptor expression but also suppressed the androgen-responsive glandular kallikrein 11 at the mRNA level (34).

### Gastrointestinal tract

Oral resveratrol inhibited the number and multiplicity of azoxymethane-induced aberrant crypt foci, completely abolishing large aberrant crypt foci, in the colon of rats, and these effects were linked to mechanisms involving changes in Bax and p21 expression (35). In rats, resveratrol markedly reduced the number of 1,2-dimethylhydrazine–induced aberrant crypt foci and incidence and size of 1,2-dimethylhydrazine–induced tumors, possibly through the modulation of antioxidant defense status and activities of carcinogen-detoxifying enzymes (36–38). Resveratrol in drinking water administered to $Apc^{Min/+}$ mice prevented the formation of colon and small intestine tumors by down-regulating genes that are directly involved in cell cycle progression or cell proliferation (39). Resveratrol and its synthetic analogue *trans* 3,4,5,4′-tetramethoxystilbene (DMU-212) decreased the adenoma load in $Apc^{Min/+}$ mice, with resveratrol showing slightly greater potency. This chemopreventive effect of resveratrol in $Apc^{Min/+}$ mice has been associated with inhibition of COX enzymes and interference with prostaglandin $E_2$ ($PGE_2$) generation (40). In contrast, a powdered admixture of resveratrol in the diet did not affect intestinal tumorigenesis or COX-2 expression in $Apc^{Min/+}$ mice (41). Although poor bioavailability may explain the lack of effect of the resveratrol powder (41), additional experiments are required to better understand this finding mechanistically.

Oral or i.p. resveratrol reduced the number and size of esophageal tumors induced by *N*-nitrosomethylbenzylamine in rats (42). Increased expressions of COX-1, COX-2, and $PGE_2$ in this *N*-nitrosomethylbenzylamine–induced system were significantly decreased by resveratrol. High doses of resveratrol injected directly next to tumors resulting from implanted human primary gastric cancer cells inhibited tumor growth in nude mice (43). Resveratrol also induced apoptosis in these tumors by down-regulating the expression of *Bcl-2* and up-regulating the expression of *Bax*. Dietary resveratrol had no anticarcinogenic effect against *N*-nitrosobis(2-oxopropyl)amine–induced pancreatic carcinogenesis in hamsters (44).

Resveratrol caused a significant decrease in the cell count of a fast-growing tumor (Yoshida AH-130 ascites hepatoma) injected into rats, inducing apoptosis in the tumor cell population (45). Resveratrol in the diet suppressed (in a modest dose-dependent fashion) the growth and metastasis of ascites hepatomas arising from implanted AH-109A cells in rats (46). Resveratrol also suppressed the serum levels of triglyceride, very low-density lipoprotein cholesterol, and low-density lipoprotein cholesterol in these hepatoma-bearing rats. Resveratrol (500-1,500 mg/kg) inhibited the growth of transplanted H22 murine tumors by nonspecific host immunomodulatory activity (47). Resveratrol was able to exhibit tumor growth-inhibitory effects even at lower doses (5-15 mg/kg), which might involve the inhibition of the cell cycle progression through decreased expression of cyclin B1 and p34cdc2 (48). Finally, resveratrol was found to enhance the antitumor effect of 5-fluorouracil on H22 murine hepatoma and markedly antagonize its toxicity (49).

Resveratrol has been well studied and shown to be effective for treating but not preventing liver cancer in animals. Therefore, our laboratory is conducting studies of resveratrol for prevention in a rat model of chemically-induced liver carcinogenesis. We recently reported the first published study showing that dietary resveratrol exerts a significant chemopreventive effect on diethylnitrosamine-initiated and phenobarbital-promoted hepatocarcinogenesis in rats through inhibition of cell proliferation and induction of apoptosis (50). According to our study, resveratrol-induced apoptogenic signal during rat liver carcinogenesis may be mediated through the down-regulation of Bcl-2 and up-regulation of Bax expression.

### Lung

A study in A/J mice (51) showed that resveratrol in the diet during the post-tumor initiation phase had no effect on the multiplicity of lung tumors induced by benzo[*a*]pyrene (B[*a*]P) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; *ad libitum* access to a diet containing resveratrol (0.4%) had no effect on B[*a*]P-induced lung tumorigenesis, and that resveratrol did not change the expression of B[*a*]P metabolizing genes such as *cytochrome P450 1A1* (*CYP1A1*) and *CYP1B1* or the level of B[*a*]P-protein adducts in lung tissue (52). The lack

of chemopreventive activity seems to be related to insufficient concentrations or nonreactive forms of resveratrol in the lungs of experimental animals (52).

Contrary to reports cited above, Kimura and Okuda (53) found that resveratrol significantly reduced tumor volume, tumor weight, and metastasis to the lung in mice bearing highly metastatic Lewis lung carcinoma. Resveratrol also inhibited DNA synthesis, increased apoptosis, and suppressed tumor-induced neovascularization (53). In another study, resveratrol had no effect on the growth of implanted Lewis lung carcinoma in mice, but it exhibited a clear antimetastatic effect, decreasing both the number and weight of lung metastases (54). Furthermore, resveratrol and its tetramer heyneanol decreased tumor growth in mouse Lewis lung carcinoma. The tumor inhibitory effect was accompanied by a marked increase in tumor cell apoptosis as detected by cleaved caspase-3, decreased tumor cell proliferation index, and diminished tumor microvessel density; these findings support the involvement of apoptotic and antiangiogenic activities in the anticancer effects of resveratrol (55).

### Other systems

Resveratrol treatment (40 mg/kg for 28 days) efficiently suppressed the growth rate of neuroblastomas and increased apoptosis, which was accompanied by down-regulation of p21 and up-regulation of cyclin E (56). Resveratrol significantly inhibited cerebral tumors via induction of apoptosis and inhibition of glioma-induced angiogenesis (57). Rats treated with resveratrol (40 mg/kg, i.p.) had slower glioma growth rates, which correlated with tumor blood flow (indicated by the color Doppler vascularity index) and microvessel density (marked by the expression of CD31; ref. 58). Recently, it has been shown that resveratrol significantly diminished tumor growth through apoptosis induction, which involved direct activation of the mitochondrial intrinsic apoptotic pathway, in the SK-N-AS and NGP xenograft models of human neuroblastoma (59).

Although producing a weak antileukemic effect, oral resveratrol did not affect the survival of mice injected with 32Dp210 leukemia cells (60). However, oral resveratrol significantly improved the survival of mice bearing lymphocytic leukemia L1210 cells, producing a normalization of CD4/CD8 ratios and an enhancement of natural killer cell activities and anti-sheep RBC titers. Furthermore, resveratrol suppressed interleukin-6 cellular content, release, and mRNA expression (61). The antiangiogenic effect of resveratrol led researchers to investigate whether it could inhibit the growth of a murine fibrosarcoma, and resveratrol-supplemented water significantly inhibited the growth of T241 fibrosarcoma in mice through suppression of angiogenesis (62). Oral resveratrol treatment effectively inhibited tumor growth in two xenograft models of human uveal melanoma in mice. The underlying antitumor mechanisms of resveratrol in these models might have involved activation of the intrinsic mitochondrial pathway leading to release of cytochrome *c* and Smac/DIABLO, activation of caspase-9 and caspase-3, and tumor cell death by apoptosis (63).

## Clinical Studies

Although several reports have described the pharmacokinetics of resveratrol in animal model systems (reviewed in

**Table 2.** Clinical studies of resveratrol as a pure compound or given in beverages

| Human subjects | Objectives | Findings | Dose | Route | References |
|---|---|---|---|---|---|
| Healthy humans (10)* | Bioavailability | Plasma-free and conjugates peak in 30 min; ~25% recovered in urine over 24 h | 25 mg/person | Oral | Soleas et al. (64) |
| Healthy males (12) | Bioavailability | Peak glucuronide and sulfate conjugates appear in serum in 30 min; urinary 24-h excretion is 16-17% of the dose | 25 mg/70 kg | Oral | Goldberg et al. (65) |
| Healthy males (3)/ females (3) | Bioavailability | Absorption is 70% with plasma half-life of 9.2 h; mostly excreted in urine | 25 mg/person | Oral; i.v | Walle et al. (66) |
| Healthy males (3) | Bioavailability | Pure and derivatives are detectable in plasma and urine; 25-50% resveratrol is recovered in urine during 24 h | 0.03, 0.5, 1 mg/kg | Oral | Meng et al. (67) |
| Healthy humans (4) | Bioavailability | Six major conjugate metabolites are detected in and separated from serum and urine | 1 g/person | Oral | Boocock et al. (68) |
| Healthy humans (40) | Phase I dose escalation pharmacokinetics | Does not exhibit adverse effects; peak plasma levels occur in 1.5 h; 77% of all urinary species excreted in 24 h | 0.5, 1, 2.5, 5 g/person | Oral | Boocock et al. (69) |
| Healthy males (14)/ females (11) | Bioavailability | Pure or glucuronide conjugate is found in serum; meal does not affect bioavailability | 3.4, 7.5, 33 μg/kg | Oral | Vitaglione et al. (70) |
| Healthy males (10)/ females (10) | Urinary excretion | Increase in total metabolites, which could be used as biomarkers for clinical studies | 0.36, 0.4, 2.6 mg/person | Oral | Zamora-Ross et al. (71) |

*The number of human subjects is indicated in the parenthesis.

ref. 1), there are few similar studies in humans to date. Table 2 summarizes the widely varying circumstances under which resveratrol, as a pure compound or in wine and/or other beverages, has been investigated in human subjects (64–71). It is clear from the tabular clinical observations that resveratrol is rapidly absorbed following oral administration; levels are detectable in both plasma and urine, with the maximum plasma concentrations being reached between 30 and 60 min after administration. Circulating levels of this polyphenol are low, partly explained, perhaps, by its rapid and extensive phase II metabolism, which generates glucuronide and sulfate conjugates. The preclinical *in vivo* studies described above show great promise for resveratrol in human cancer prevention and treatment. An extension of these *in vivo* data is a recently concluded 10-year epidemiologic study showing a 50% or greater reductions in breast cancer risk in women with resveratrol consumption from grapes, but not from wine (72). The inverse relationship between resveratrol and breast cancer risk could not be explained by several potential confounding factors, including alcohol intake, nor was it attributable to a nonspecific favorable effect of fruit on breast cancer risk (72). Several phase I/II clinical trials of oral resveratrol as a pure compound or in resveratrol-rich products (grapes and grape juice) are under way.[1] A phase I study will define the effect of grape-derived low-dose resveratrol on biomarkers related to the Wnt pathway, a key signaling pathway activated in >85% of colon cancers, and will evaluate the utility of this approach for colon cancer prevention. A phase II study in lymphoma patients will assess the ability of resveratrol in grape juice to induce apoptosis, inhibit cell proliferation, and modulate tumor cell infiltrate. A phase I/II clinical trial will examine the effects of resveratrol directly on colon cancer and surrounding normal colonic mucosa. A National Cancer Institute–sponsored phase I trial is studying the side effects and best regimen of resveratrol in patients with colorectal cancer that can be removed by surgery. Results of these trials may provide a foundation for designing future large-scale clinical trials to ascertain the full chemopreventive and chemotherapeutic efficacy of resveratrol.

## Future Directions and Conclusion

From the studies described in this review, it is clear that resveratrol holds great potential not only in the prevention but also in the therapy of a wide variety of cancers. Tumor cells use multiple survival pathways to prevail over normal cells. Therefore, agents such as resveratrol that can suppress multiple cellular pathways may have a strong potential for cancer prevention and treatment. It may be speculated that the anticancer effects of resveratrol cannot be explained by a unique mechanism of action but likely stem from various complementary actions of several molecular, biochemical, and physiologic pathways involved in carcinogenesis.

Several reports suggest that resveratrol could be ineffective in inhibiting tumor growth in certain animal models despite its *in vitro* antitumor action in related cells. For example, resveratrol had no effect on the *in vivo* growth and metastasis of transplanted 4T1 breast cancer cells in mice, whereas it inhibited the *in vitro* growth of the same cancer cells (30). Again, based on reports presented here, resveratrol could be more effective in inhibiting the growth of established tumors in a particular organ (e.g., the lung) than in preventing tumors in the same site. However, an opposite trend has also been observed (e.g., for skin and breast tumors). There is an obvious need for further studies to address the tissue specificity of resveratrol so as to determine where resveratrol may have the strongest preventive potential.

The conundrum posed by the undeniable efficacy of resveratrol in preclinical models in spite of its low bioavailability has not been resolved yet. Likewise, the question of whether resveratrol itself can accumulate to bioactive levels in target organs remains unanswered. To enhance the bioavailability of resveratrol, active research should examine resveratrol delivery routes and formulations and modulation of resveratrol metabolism, as well as possible interactions of resveratrol with other food components.

Developing novel resveratrol derivatives is another possible approach for enhancing bioavailability. A series of *cis*-stilbenes and *trans*-stilbenes related to resveratrol with varying functional groups have been synthesized, and some of these compounds are more potent than is resveratrol in suppressing the growth of human cancer cells *in vitro* (reviewed in ref. 2). Researchers have started to explore the anticancer effects of resveratrol derivatives *in vivo* (40, 55, 73–75), and at least one study indicated that a tetramer of resveratrol (heyneanol) had comparable or better anticancer efficacy than did resveratrol in a mouse lung cancer model (55). However, more *in vivo* studies of head-to-head comparisons between resveratrol and its analogues are ongoing and no doubt will help elucidate the anticancer potential of specific compounds.

Since the first report on the biological activity of resveratrol, an enormous body of work has revealed many important biological properties (e.g., anti-inflammatory, antioxidant, caloric restriction mimetic, and antiaging effects) of this naturally occurring polyphenol. Much more study is needed, however, including studies to identify resveratrol-binding proteins and the pathways through which resveratrol functions and thus may exert clinical effects, and to develop mechanism-based markers for evaluating clinical outcome. Long-term epidemiologic studies and controlled clinical trials are also necessary for developing resveratrol to become a standard clinical agent. The preclinical and clinical data examined in this review strongly suggest that resveratrol is a promising candidate in chemopreventive and chemotherapeutic strategies and a potential weapon in the effort to alleviate the burden of human cancer.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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[1] http://clinicaltrials.gov/ct2/home (accessed 2008 July 12).

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