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Review

Pro- and Anti-angiogenesis Effects of Resveratrol

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Abstract. *Resveratrol, a natural polyphenol, has a variety of effects including protection against ischemia-reperfusion injury, and antitumor and chemopreventive action against malignant tumors. In recent years, resveratrol has been found to exert pro- and anti-angiogenic effects, depending on the situation. For example, pro-angiogenic effects are noted in the peri-infarct myocardium, whereas resveratrol inhibits angiogenesis in tumors. In this article, a review of the literature concerning both pro-angiogenic and anti-angiogenic effects of resveratrol and the underlying mechanisms of its effects on angiogenesis is presented.*

Resveratrol (3,4,5'-trihydroxy-*trans*-stilbene, $C_{14}H_{12}O_3$) is a natural polyphenol primarily extracted from grape and mulberry (1). Resveratrol has been reported to have a variety of effects, such as an antioxidant effect, antiestrogenic activity, reduction of hepatic lipid synthesis, decreased synthesis of eicosanoids, inhibition of platelet aggregation and protection of vessels from arteriosclerosis (1-5). Resveratrol can also activate numerous systems including the expression of p53, the Fas-Fas ligand system and mitogen-activated protein kinase (MAPK); it can also inhibit p4501A1, ribonucleotide reductase, ornithine decarboxylase, protein kinase C (PKC), DNA polymerase, cyclooxygenase (COX) and cell cycle progression, and induce cellular apoptosis (6-16). Recently, resveratrol demonstrated antitumor and chemopreventive effects on malignant tumors, such as prostate, breast and colon cancer, neuroblastoma, and glioma, as well as leukemia (5, 7, 12, 17-25). Its action on tumor initiation, promotion and progression (20, 25) is a result of its effect on cellular proliferation.

Among the various functions attributed to resveratrol, its effects on angiogenesis are particularly interesting. Resveratrol has contrasting effects on angiogenesis that are situation-dependent. For example, pro-angiogenic effects are noted in the peri-infarct myocardium, whereas anti-angiogenic effects have been noted in other tissues, including tumors. In this article, a review of the literature describing the pro-angiogenic and anti-angiogenic effects of resveratrol and the underlying mechanisms of action on angiogenesis is presented.

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Angiogenesis

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is the driving force of organ development in ontogeny and is utilized in such conditions as cancer and atherosclerosis (26). Angiogenesis is stimulated by cytokines and growth factors whose expressions correlate with pathological neovascularization (27). Furthermore, these angiogenic factors are related not only to vascular cell proliferation, but also to the invasion and differentiation of vascular cells of the neovasculature (27). These cytokines and growth factors act on the specific receptors on the endothelial cells, induce gene expression and proliferation of endothelial cells, and stimulate these cells to produce proteolytic enzymes that destroy the matrix, resulting in endothelial cell migration and invasion into tissues (28-30).

Different types of angiogenic factors are recruited, depending on the circumstances. During the wound healing process, the basement membrane of the vessels will express several kinds of adhesive proteins, such as von Willebrand factor, fibronectin, and fibrin (31). Alternatively, cultured

smooth muscle cells and endothelial cells express adhesion receptors of the integrin family (32). In tumor angiogenesis, the tumor-secreted soluble factors such as basic fibroblast growth factor (bFGF), transforming growth factor-α (TGF-α), epidermal growth factor receptor, and vascular endothelial growth factor (VEGF) act on the specific receptors on the surface of endothelial cells (30, 33). This induction of angiogenesis promotes tumor growth and increases the number of channels for tumor cell metastases. Tumor angiogenesis is important since the number of vessels noted in cancers correlates with patient prognosis (34, 35).

Resveratrol Protects Against Ischemia-reperfusion Injury and Enhances Angiogenesis

Resveratrol can protect against ischemia-reperfusion (I/R) injury in the heart, kidney, ovary, spinal cord and brain (36-45). Resveratrol was found to exert protective effects against I/R-induced arrhythmia and mortality in rats, although it had no protective effects on ischemia-induced arrhythmias or mortality (39). In addition, 10 or 15 μM of resveratrol administered 15 min prior to I/R injury of isolated rat heart had cardioprotective effects shown as improved recovery of ventricular function and reduced infarct size (42, 43). Such cardioprotective effects of resveratrol were considered related to the antioxidant activity and upregulation of nitric oxide production (39, 42, 43). In contrast, administration of resveratrol (0.15 or 1.5 mg/kg) 30 min before I/R injury did not reduce the infarct size of the heart in rabbits (46). Moreover, resveratrol also has a protective effect on renal I/R injury (37, 47). In renal I/R injury induced by cross-clamping of both renal pedicles, pretreatment with 1 μM of resveratrol improved the renal function and reduced the mortality of I/R rats (47). Another study also found oral administration of 5 mg/kg of resveratrol 30 min prior to I/R injury of the kidney in rats attenuated the renal damage (37). Such renal protective effects induced by resveratrol were also considered through a nitric oxide-dependent mechanism (37, 47).

Resveratrol can protect the nervous system from I/R injury (41, 44, 48, 49). Hypoxia/hypoglycemia followed by reoxygenation in cortical mixed glial cells had increased interleukin-6 (IL-6) expression, which was reduced by resveratrol; thus, resveratrol was considered to be useful in treating ischemia-induced inflammatory processes in stroke (49). In gerbils, transient global cerebral ischemia was induced by occlusion of both carotid arteries (CCA) for 5 min and then treated with intraperitoneal injection of 30 mg/kg resveratrol during or shortly after CCA occlusion, and again at 24 h after ischemia (44). The brain of the gerbils treated with resveratrol showed significantly decreased neuronal death and glial cell activation, which indicated that resveratrol can cross the blood brain barrier to exert cerebral protection (44). In addition to the brain, resveratrol also has protective effects against I/R injury of the spinal cord (41). Administration of 10 mg/kg of resveratrol 30 min before I/R injury of the spinal cord induced by occlusion of infrarenal artery in rabbits showed enhanced neuronal survival in the spinal cord and improved neurological functions; however, 1 mg/kg of resveratrol had no protective effects (41). The mechanisms of the neuroprotective effects of resveratrol, similar to those of the cardioprotective effects, were considered to be related to the decreased oxidative stress and increased nitric oxide release (41). In addition to the use of resveratrol in the treatment of stroke, the beneficial effects of chronic use of resveratrol in cerebral protection was tested by adding resveratrol to the drinking water of rats; however only partial neuroprotection against systemic injection of excitotoxin kanic acid-induced brain damage was noted (48).

From the literature, we found that resveratrol has protective effects on the ischemia-reperfusion injury; however, the mechanisms by which resveratrol protects against I/R injury seem to be multifactorial. In addition to the mechanisms mentioned above (antioxidant effects, increased nitric oxide, and suppressed cytokine secretion such as IL-6), other mechanisms such as suppression of platelet aggregation, anti-inflammatory effects (*e.g.* the prevention of leukocyte recruitment and modulation of endothelial cell function) and prevention of endothelial barrier disruption, increased heme oxygenase (HO) activity and increased adenosine release may also contribute to the protective effects of resveratrol against ischemia-reperfusion injury (1, 3, 4, 36, 37, 39-41, 45, 47, 49-54).

On the other hand, resveratrol also has pro-angiogenic effects, which are primarily noted in myocardial infarcts (40, 55). Following arterial occlusion, blood vessels respond by growing and remodeling pre-existing arterioles into physiologically relevant arteries (arteriogenesis) (56). Human coronary arteriolar endothelial cells exposed to resveratrol on Matrigel showed significantly accelerated tubular morphogenesis with induction of HO-1 and VEGF expression (40). Such angiogenic response was repressed by HO-1 inhibitor, along with down-regulation of VEGF expression (40). In addition, rat neonatal cardiomyocytes treated with resveratrol significantly expressed thioredoxin (Trx)-1, HO-1 and VEGF (40). Pretreatment with resveratrol (1 mg/kg/day) for 2 weeks reduced infarct size 24 h after myocardial infarction and increased capillary density in the peri-infarct myocardium in rats (40). Furthermore, resveratrol-treated myocardium after myocardial infarction significantly induced Trx-1, HO-1 and VEGF expression (40). These data suggest that resveratrol mediates cardioprotection and neovascularization through the Trx-1-HO-1-VEGF pathway (40). As a whole, resveratrol enhances myocardial angiogenesis both *in vitro*

and *in vivo*, manisfested as accelerated tubular morphogenesis of human coronary arteriolar endothelial cells and increased capillary density in the peri-infarct myocardium (40, 55). The mechanisms by which resveratrol induces pro-angiogenesis are not well known. In addition to the Trx-1-HO-1-VEGF pathway, several factors such as nitric oxide, nitric oxide synthase, nuclear factor (NF)-κB and specificity protein (SP)-1 are also considered as likely to play a significant role in the pro-angiogenic effects of resveratrol because they are up-regulated in the myocardium after infarction (37, 40, 55-57).

Anti-angiogenesis Effects of Resveratrol

In recent years, resveratrol has demonstrated anti-angiogenic effects, mainly observed in tumors such as lung cancer, gliomas and breast cancer (24, 58-63). Resveratrol was demonstrated to inhibit proliferation and induce apoptosis of bovine aortic smooth muscle cell proliferation in a dose-dependent manner and block the G1-S phase transition of smooth muscle cells (64). Resveratrol suppressed cultured bovine pulmonary artery endothelial cell proliferation by inducing the accumulation of p53 and p21, and perturbing the cell cycle progression through the S and G2 phases (61). Resveratrol can inhibit bFGF- and VEGF receptor-mediated capillary endothelial cell growth and chemotaxis (58). In addition, resveratrol promotes apoptosis in bFGF-stimulated endothelial cells by increasing p53 protein production and inhibits bFGF-induced angiogenesis in the chick chorioallantoic membrane model (65). Resveratrol can inhibit the capillary-like tube formation from human umbilical vein endothelial cells (HUVECs) and the binding of VEGF to HUVECs at concentrations of 10-100 μM, but not at concentrations of 1 and 5 μM (63).

In addition to the direct effects of resveratrol on endothelial cells, resveratrol also showed *in vivo* anti-angiogenic effects, especially on tumor-induced angiogenesis (24, 58, 59, 63, 66, 67). Mice which drank the resveratrol-containing fluid showed inhibited VEGF-induced corneal neovascularization (58). Resveratrol also inhibits human ovarian cancer progression and angiogenesis by inhibiting the expression of hypoxia-inducible factor-1α and VEGF (66), and the tumor-induced neovascularization in Lewis lung carcinoma-bearing mice (63). In addition, resveratrol suppresses the angiogenesis in gliomas by inducing the apoptosis of endothelial cells, inhibiting VEGF expression in glioma cells, and suppressing microscopic angiogenesis manifested as decreased microvessel density (24, 67). A higher dose of resveratrol (40 mg/kg/day) was demonstrated to significantly suppress the angiogenesis in gliomas than a lower dose of resveratrol (10 mg/kg/day) did (24). Furthermore, color Doppler ultrasound examination demonstrated resveratrol suppression of macroscopic angiogenesis in gliomas, which correlated with suppressed microscopic angiogenesis (decreased microvessel density) by resveratrol (59).

Both *in vitro* and *in vivo* studies demonstrated that resveratrol inhibits several key events of the angiogenic process, such as proliferation and migration of endothelial cells and vascular smooth muscle cells, capillary-like tube formation, and even macroscopic angiogenesis (24, 58, 59, 61-63, 68, 69). The mechanisms of the anti-angiogenic effects of resveratrol are considered to be related to many factors including: increased p53 and p21 expression and perturbed cell cycle progression of endothelial cells or smooth muscle cells (61, 64), inhibition of VEGF expression (17, 24, 60, 66, 68, 69), binding of VEGF to endothelial cells (63) and binding of bFGF to its receptor (65,67); inhibition of endothelial attachment to the basement membrane components fibronectin and laminin (68); and inhibition of COX-2, matrix metalloproteinase-2 (MMP-2), MMP-9, urokinase-type plasminogen activator, adhesion molecules, cyclin D1, and hypoxia-inducible factor-1α (17, 66, 68, 69).

Differential Effects of Resveratrol on Angiogenesis (Pro-angiogenic or Anti-angiogenic Effects)

While the underlying explanation of why resveratrol exerts both pro-angiogenic and anti-angiogenic effects in different situations remains unclear, the dosage and pharmacokinetics of resveratrol, events, and cell types are all considered to be important factors.

The dosage of resveratrol might play an important role in determining whether resveratrol will exert a pro- or anti-angiogenic effect. As to the doses required to exert protective effects against ischemia-reperfusion injury or pro-angiogenic effects, resveratrol administered at 10-20 mg/kg or 10 μM is usually effective to protect the tissues from ischemia-reperfusion injury (36, 41, 43); however, the data from trials evaluating low doses of resveratrol are inconsistent (40, 41, 46). For example, neither 0.15 mg/kg nor 1.5 mg/kg of resveratrol demonstrated any cardioprotective effects in rabbits when administered 15 minutes prior to the onset of ischemia (46). In contrast, a low dose of 0.23 μg/kg of resveratrol did reduce the mortality of rats with renal ischemia reperfusion injury from 50% to 10%, with a reduction in renal damage (47). Rats treated with an oral administration of resveratrol (1 mg/kg/day) for 14 days demonstrated pro-angiogenic effects on the occluded coronary artery (40). On the other hand, an *in vitro* study revealed that resveratrol inhibited the growth of bovine aorta endothelial cells in a concentration-dependent manner (6-100 μM) (62). Resveratrol at 2.5 and 10 mg/kg inhibited tumor-induced neovascularization in Lewis lung carcinoma-bearing mice (63). In contrast, 40 mg/kg/day of resveratrol treatment was found to significantly decrease microscopic and macroscopic angiogenesis and inhibit tumor growth in gliomas;

however, 10 mg/kg/day did not suppress the glioma-induced angiogenesis (59). Therefore, the doses of resveratrol required to induce pro-angiogenic effects do not appear substantially different from those doses required to induce anti-angiogenic effects.

Another important factor is the pharmacokinetics of resveratrol (70). In the literature, the concentrations and doses used to achieve the various effects reported for resveratrol were quite variable (~32 nM-100 μM *in vitro* and ~100 ng-1500 mg/kg *in vivo*) (70). Furthermore, resveratrol has a short initial half life (8-14 min for the primary molecule) and most of the resveratrol molecules are metabolized extensively in the body into five metabolites: resveratrol monosulphate, two isomeric forms of resveratrol monoglucuronide, dihydroresveratrol monosulphate, and dihydroresveratrol monoglucuronide (70, 71). In the urine, the metabolites of resveratrol were found to consist of sulphate conjugates for 37%, glucuronide conjugates for 19%, with the remainder being unknown metabolites and a trace amount of free resveratrol (70). The serum half life of total resveratrol metabolites is about 9.2 h, indicating that the body was more significantly exposed to the modified forms of resveratrol than to the unchanged parent molecule (70, 72). After the administration of 100 mg/kg resveratrol to a rodent, the peak serum concentration is estimated to be 9 μM unchanged resveratrol and 680 μM total resveratrol (70). In addition, a 30-fold enrichment of resveratrol over serum concentrations was observed in intestinal mucosa, with significant accumulation of resveratrol in the bile, stomach, liver and kidneys noted too (73, 74). Although modifications such as glucuronidation and sulphation reduce the cell permeability of drugs and aid in their excretion, the resveratrol metabolites might retain some activity of the parent molecule (70). We believe the metabolism of resveratrol may vary widely among individuals, races and species. In addition, the distribution of the parent and modified forms of resveratrol in the serum and tissues may be quite variable. Moreover, the potency of the parent molecule and the various modified forms of resveratrol is unclear and may be markedly different. Therefore, we consider all these factors may contribute to the variability of resveratrol effects and partially explain why resveratrol exerts both pro-angiogenic and anti-angiogenic effects in different situations.

In addition to the doses and pharmacokinetics of resveratrol, the differential effects on angiogenesis caused by resveratrol might also be situation-dependent or cell type-related, since the pro-angiogenic effects usually occur in tissues having ischemia-reperfusion injury and the anti-angiogenic effects often manifest during tumor growth. To clarify the mechanisms of the resveratrol-induced opposite effects on angiogenesis, more studies are needed.

Conclusion

In the literature, increasing evidence shows that resveratrol might be used as an antitumor agent for malignant tumors. Angiogenesis is important for tissues with ischemia-reperfusion injury, tumor growth and tumor cell metastases. In order to use resveratrol clinically for the treatment of malignant tumors in the future, it is important to know that resveratrol can induce opposite effects on angiogenesis, either pro- or anti-angiogenic effects, and understand more of the underlying mechanisms why resveratrol exerts both pro-angiogenic and anti-angiogenic effects in different situations. A review of the literature reveals that the pharmacokinetics of resveratrol might be responsible for its variable effects on angiogenesis, which might then partially explain why the doses of resveratrol required to induce pro-angiogenic effects are not different from the doses required to induce anti-angiogenesis. In addition, the effects of resveratrol on angiogenesis might be situation-dependent or cell type-related.

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