

# The Effects of Resveratrol on the Skin



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## Studies Regarding Topical Benefits of Resveratrol

### Chemoprevention of skin cancer by grape constituent resveratrol: relevance to human disease?

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Erratum in:  
FASEB J. 2005 Jul;19(9):1 p following 1195.

#### Abstract

According to the World Cancer Report, skin cancer constitutes approximately 30% of all newly diagnosed cancers in the world, and solar ultraviolet (UV) radiation (particularly, its UVB component; 290-320 nm) is an established cause of approximately 90% of skin cancers. The available options have proven to be inadequate for the management of skin cancers. Therefore, there is an urgent need to develop mechanism-based novel approaches for prevention/therapy of skin cancer. In this study, we evaluated the chemopreventive effects of resveratrol against UVB radiation-mediated skin tumorigenesis in the SKH-1 hairless mouse model. For our studies, we used a UVB initiation-promotion protocol in which the control mice were subjected to chronic UVB exposure (180 mJ/cm<sup>2</sup>, twice weekly, for 28 weeks). The experimental animals received either a pretreatment (30 min before each UVB) or post-treatment (5 min after UVB) of resveratrol (25 or 50 micro mole/0.2 ml acetone/mouse). The mice were followed for skin tumorigenesis and were killed at 24 h after the last UVB exposure, for further studies. The topical application of skin with resveratrol (both pre- and post-treatment) resulted in a highly significant 1) inhibition in tumor incidence, and 2) delay in the onset of tumorigenesis. Interestingly, the post-treatment of resveratrol was found to impart equal protection than the pretreatment; suggesting that resveratrol-mediated responses may not be sunscreen effects. Because Survivin is a critical regulator of survival/death of cells, and its overexpression has been implicated in several cancers, we evaluated its involvement in chemo-prevention of UVB-mediated skin carcinogenesis by resveratrol. Our data demonstrated a significant 1) up-regulation of Survivin (both at protein- and mRNA- levels), 2) up-regulation of phospho-Survivin protein, and 3) down-regulation of proapoptotic Smac/DIABLO protein in skin tumors; whereas treatment with resveratrol resulted in the attenuation of these responses. Our study also suggests that resveratrol enhanced apoptosis in UVB-exposure-mediated skin tumors. Our study, for the first time, demonstrated that 1) resveratrol imparts strong chemopreventive effects against UVB exposure-mediated skin carcinogenesis (relevant to human skin cancers), and 2) the chemopreventive effects of resveratrol may, at least in part, be mediated via modulations in Survivin and other associated events. On the basis of our work, it is conceivable to design resveratrol-containing emollient or patch, as well as sunscreen and skin-care products for prevention of skin cancer and other conditions, which are believed to be caused by UV radiation.

### Delivery of resveratrol, a red wine polyphenol, from solutions and hydrogels via the skin.

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#### Abstract

Resveratrol, the main active polyphenol in red wine, has been demonstrated to show benefits against skin disorders. The bioavailability of orally administered resveratrol is insufficient to permit high enough drug concentrations for systemic therapy. In this study, we examined the feasibility of the topical/transdermal delivery of res-veratrol. The effects of vehicles on the in vitro permeation and skin deposition from saturated solutions such as aqueous buffers and soybean oil were investigated. The general trend for the delivery from solutions was: pH 6 buffer=pH 8 buffer>10% glycerol formal in pH 6 buffer>pH 9.9 buffer>pH 10.8 buffer>soybean oil. A linear relationship was established between the permeability coefficient (K(p)) and drug accumulation in the skin reservoir. Viable epidermis/dermis served as the predominant barrier for non-ionic resveratrol permeation. On the other hand, both the stratum corneum (SC) and viable skin acted as barriers to anionic resveratrol. Several prototype hydrogel systems were also studied as resveratrol vehicles. The viscosity but not the polarity of the hydrogels controlled resveratrol permeation/deposition. Piceatannol, a derivative of resveratrol with high pharmacological activity, showed 11.6-fold lower skin permeation compared to resveratrol. The safety profiles of resveratrol suggested that the hydrogel caused no SC disruption or skin erythema. It was concluded that delivery via a skin route may be a potent way to achieve the therapeutic effects of resveratrol. This is the first report to establish the permeation profiles for topically applied resveratrol.  
Cancer Prev Res (Phila Pa). 2010 Feb;3(2):170-8. Epub 2010 Jan 26.

### Synergistic effects of combined phytochemicals and skin cancer prevention in SENCAR mice.

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#### Abstract

The purpose of our study was to determine the inhibitory effect of combined phytochemicals on chemically induced murine skin tumorigenesis. Our hypothesis was that concurrent topical and dietary treatment with selected compounds would lead to more efficient prevention of skin cancer. We tested ellagic acid and calcium D-glucarate as components of diets, while resveratrol was applied topically; grape seed extract was applied topically or in the diet. The 4-week inflammatory-hyperplasia assay based on the 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin carcinogenesis model in SENCAR mice was used. We have found that all the selected combinations caused a marked decrease of epidermal thickness compared with the DMBA-treated group and also with groups treated with a single compound and DMBA. All combinations of resveratrol with other compounds showed a synergistic effect on hyperplasia and Ha-ras mutations. Skin tissue of mice receiving the combinations showed decreased cell proliferation and Bcl2 expression; decreased p21, a regulator of cell cycle; and decreased marker of inflammation cyclooxygenase-2. All the selected combinations diminished the DMBA-induced mRNA expression of the CYP1B1 level, and also caused a marked decrease of protooncogenes c-jun and c-fos, components of transcription factor activator protein. In conclusion, all combinations showed either additive or synergistic effects and their joint actions allowed for decreasing the doses of the compounds. Especially, resveratrol combinations with ellagic acid, grape seed extract, and other phytochemicals are very potent inhibitors of skin tumorigenesis, based on the suppression of epidermal hyperplasia as well as on the modulation of intermediate biomarkers of cell proliferation, cell survival, inflammation, oncogene mutation, and apoptosis.  
Ann N Y Acad Sci. 2006 May;1067:337-42.

### Dermal wound healing properties of redox-active grape seed proanthocyanidins.

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#### Abstract

Angiogenesis plays a central role in wound healing. Among many known growth factors, vascular endothelial growth factor (VEGF) is believed to be the most prevalent, efficacious, and long-term signal that is known to stimulate angiogenesis in wounds. The wound site is rich in oxidants, such as hydrogen peroxide, mostly contributed by neutrophils and macrophages. We proposed that oxidants in the wound microenvironment support the repair process. Proanthocyanidins or condensed tannins are a group of biologically active polyphenolic bioflavonoids that are synthesized by many plants. Previously we have reported that a grape seed proanthocyanidin extract containing 5000 ppm resveratrol (GSPE) potently upregulates oxidant and tumor necrosis factor-alpha inducible VEGF expression in human keratinocytes (Free Radic. Biol. Med. 31:38-42, 2001). Our current objective was to follow up on that finding and test whether GSPE influences dermal wound healing in vivo. First, using a VEGF promoter-driven luciferase reporter construct we observed that the potentiating effect of GSPE on inducible VEGF expression is at the transcriptional level. The reporter assay showed that GSPE alone is able to drive VEGF transcription. Next, two dermal excisional wounds were inflicted on the back of mice and the wounds were left to heal by secondary intention. Topical application of GSPE accelerated wound contraction and closure. GSPE treatment was associated with a more well-defined hyperproliferative epithelial region, higher cell density, enhanced deposition of connective tissue, and improved histological architecture. GSPE treatment also increased VEGF and tenascin expression in the wound edge tissue. Tissue glutathione oxidation and 4-hydroxynonenal immunostaining results supported that GSPE application enhanced the oxidizing environment at the wound site. Oxidants are known to promote both VEGF as well as tenascin expression. In summary, our current study provides firm evidence to support that topical application of GSPE represents a feasible and productive approach to support dermal wound healing.  
Pharm Res. 2009 Jan;26(1):211-7. Epub 2008 Sep 13.

### Chemopreventive potential of resveratrol in mouse skin tumors through regulation of mitochondrial and PI3K/AKT signaling pathways.

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#### Abstract

**PURPOSE:** To investigate the chemopreventive potential of resveratrol, a phytoalexin found in seeds and skin of grapes, berries and peanuts in 7,12 dimethyl benz(a)anthracene (DMBA) induced mouse skin tumorigenesis. **METHODS:** Topical treatment of resveratrol was given to the animals 1 h prior to DMBA for 28 weeks. At the end of the study period, the skin tumors were dissected out and western blotting was carried out to examine the regulation of proteins involved in anti-tumorigenesis in response to resveratrol. **RESULTS:** Chemo-preventive properties of resveratrol were reflected by delay in onset of tumorigenesis, reduced cumulative number of tumors, and reduction in tumor volume. Results of the western blotting showed that resveratrol treatment increased the DMBA suppressed p53 and Bax while decreased the expression of Bcl-2 and Survivin. Further, resveratrol supplementation resulted in release of cytochrome C, caspases activation, increase in apoptotic protease-activating factor-1 (Apaf-1) as mechanism of apoptosis induction. Resveratrol was also found to inhibit skin tumorigenesis through regulation of Phosphatidylinositol-3-kinase (PI3K)/ and AKT proteins which are implicated in cancer progression because it stimulates proliferation and suppresses apoptosis. **CONCLUSIONS:** Based on the results we can conclude that resveratrol regulates apoptosis and cell survival in mouse skin tumors as mechanism of chemoprevention hence deserve to be a chemopreventive agent.  
Biol Pharm Bull. 2008 May;31(5):955-62.

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