Anti-aging properties of resveratrol: Review and report of a potent new antioxidant skin care formulation

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Anti-aging properties of resveratrol: review and report of a potent new antioxidant skin care formulation

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Summary

Resveratrol, an antioxidant polyphenol from red wine, has been the subject of intense interest in recent years due to a range of unique anti-aging properties. These include cardiovascular benefits via increased nitric oxide production, down-regulation of vasoactive peptides, lowered levels of oxidized low-density lipoprotein, and cyclooxygenase inhibition; possible benefits on Alzheimer's disease by breakdown of beta-amyloid and direct effects on neural tissues; phytohormonal actions; anticancer properties via modulation of signal transduction, which translates into anti-initiation, antipromotion, and anti-progression effects; antimicrobial effects; and sirtuin activation, which is believed to be involved in the caloric restriction-longevity effect. Here we report a resveratrol-based skin care formulation, with 17 times greater antioxidant activity than idebenone. The role of resveratrol in prevention of photoaging is reviewed and compared with other antioxidants used in skin care products.

Keywords: antiaging, antioxidant, nutraceuticals, polyphenols, resveratrol

Introduction

The ideal anti-aging intervention should be applicable for both cosmetic maintenance of an age-appropriate healthful appearance, stemming the development of degenerative diseases, optimizing the function of the aging brain and other tissues, and acting on biologic systems known to prolong lifespan. Although there is continuing debate about defining anti-aging, and whether there is indeed any true anti-aging intervention,[1,2] there is more of a consensus about what factors contribute to biologic aging. The oxidative theory[3] has gained scientific acceptance and considerable traction in the public's mind, and antioxidants are a popular ingredient in dietary and skin care products. Genetic factors play another important but not overriding role,[4] and modulation of genetic expression is another front in the anti-aging battle.[5] Caloric restriction remains the only proven means of lifespan extension in the animal model and is believed to occur via up-regulation of an evolutionarily conserved class of enzymes known as sirtuins,[6] involved in mitochondrial metabolism. Reports in recent years that the caloric restriction effect could be elicited in progressively complex organisms via sirtuin activation by the polyphenolic phytoalexin resveratrol[7–9] has generated considerable interest. Resveratrol has been the subject of intensive investigation in recent years (Fig. 1) and is reported to be an extremely potent antioxidant, a modulator of genetic expression via signal transduction, an inhibitor of inflammatory mediators, and to have other actions including phyto-hormonal effects. This combination of biological properties and cosmetic effects makes resveratrol a unique candidate anti-aging agent.

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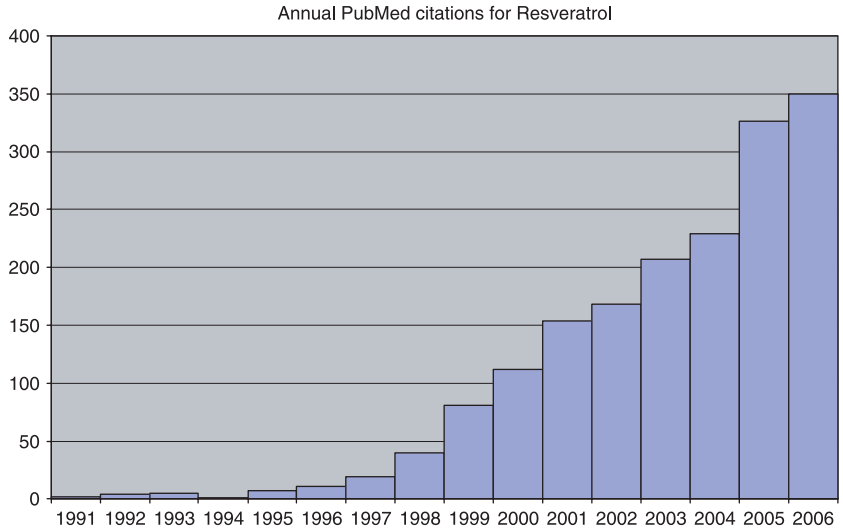

Figure 1 PubMed citations for resveratrol as a function of year.

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring molecule found in high concentrations in many red wines and is a member of a family of compounds known as wine polyphenols, which also includes flavonoids.[10] Other sources of resveratrol include some colored berries and the nonedible parts of the peanut plant. Of the two isoforms, the *trans*-resveratrol isomer is more stable and biologically active than the *cis*-resveratrol isomer.[11] Resveratrol has been reported to be a strong inhibitor of NADPH- and adenosine 5′-diphosphate (ADP)-Fe^{+}-lipid peroxidation and ultraviolet (UV) light–induced lipid peroxidation, and an efficient scavenger of 2,2′-azobis-(2-amidinopropane)-dihydrochloride peroxyl radicals.[12] Several studies have evaluated the structure-activity relationship of resveratrol and other stilbene derivatives. Olas and Wachowicz[13] evaluated the activities of resveratrol in platelets and determined that the hydroxyl group in ring B was important in the inhibition of the production of reactive oxygen species, reduction of lipid peroxidation, and protection against peroxynitrate-induced platelet lipid and protein oxidation. Stojanovic *et al.*[14] also found resveratrol to be an extremely efficient free radical scavenger in a model employing gamma-irradiation of liposomes, with the para-hydroxyl configuration the most effective. Resveratrol was 95% efficient at preventing lipid peroxidation, compared with ~65% for vitamin E and ~37% for vitamin C. Flavonoid polyphenols are more ubiquitous. Silymarin, derived from the milk thistle plant, has been found to share some properties with resveratrol, including an antiapoptotic effect following UV radiation, modulation of signal transduction, and sirtuin activation.[15] Topical and systemic administration of silymarin was shown to attenuate burn-induced oxidative tissue injury in rats[16] and is being evaluated for chemoprevention of prostate and skin cancers.[17] Direct comparisons of silymarin's antioxidant capacity with other polyphenols has not been reported, however, and this compound has not been extensively studied.

Cardiovascular

The inverse relationship between wine consumption and heart disease ('French paradox') has been known for some time and well documented.[18–20] Resveratrol and other wine phenolics are believed to be largely responsible for this correlation via increased nitric oxide production,[21] down-regulation of vasoactive peptides known as endothelins,[22] reduction of oxidized low-density lipoprotein,[23] and anti-inflammatory effects via cyclooxygenase (COX) inhibition and down-regulation of eicosanoid synthesis.[24]

Brain function

Population studies reveal a consistent inverse relationship of moderate wine consumption and Alzheimer's/senile dementia as well as overall better maintenance of cognitive ability with advancing age.[25] Resveratrol has been shown to facilitate the breakdown of beta-amyloid, which is associated with Alzheimer's disease, via specific mechanisms unrelated to antioxidant effects,[26] and to protect against beta-amyloid toxicity *in vitro*.[27] Mitogen-activated protein enzymes (MAP kinases), which are active in learning and memory centers of the brain, are up-regulated by resveratrol in neural tissues.[28] Neuronal AMP kinases are also activated by resveratrol.[29]

Resveratrol has also been shown to protect the brain against the effects of traumatic injury in a rat model.[30] In a gerbil stroke model, resveratrol administered either during or after carotid artery occlusion significantly decreased cerebral ischemic injury.[31] This same study documented the ability of resveratrol to traverse the blood–brain barrier.

Phyto-hormonal effects

Resveratrol is known to bind the estrogen receptor,[32] and evidence suggests that regular wine consumption attenuates perimenopausal symptoms[33] and protects against osteoporosis. A report from China Medical University in Taiwan[34] concluded that resveratrol's bone-protective effects were similar to hormone replacement therapy (HRT), without increased risk of breast cancer, via signal-transduction mediated effects resulting in activation of forkhead proteins, which were also involved in anticancer effects. Given current controversies about HRT following the Women's Health Initiative report,[35] this may prove extremely valuable, but remains to be clinically documented in prospective trials.

Phytoestrogens are being investigated as possible selective cytoplasmic and membrane surface estrogen receptor agonists to slow skin aging without the potential risks of estrogen.[36] Estrogen is known to enhance dermal water-holding capacity, increase glycosaminoglycan content, maintain skin elasticity and collagen content, and diminish wrinkling, although specific data on stilbene phytestrogens such as resveratrol are lacking.[37]

Antioxidant

Wine polyphenols as a class are the most potent dietary antioxidants, generally many times greater than vitamins A, C, and E. Large trials of vitamin supplementation have consistently found no reduction in the incidence of degenerative diseases.[38–40] Dietary intervention studies have documented a reduction of serum oxidative damage markers to a greater degree with the addition of red wine compared with vegetables rich in antioxidant vitamins. A representative study from the Catholic University of Chile in Santiago compared total plasma antioxidant capacity, levels of leukocyte DNA 8-OHdeoxyguanosine (8OHdG, a marker for DNA oxidation), and plasma 7C-hydroxycholesterol, in groups of volunteers given an occidental (high-fat) diet, a Mediterranean diet, or a Mediterranean diet supplemented isocalorically with either red wine or additional fruits and vegetables, for 3 months.[41] The wine-supplemented diet was more than twice as effective at reducing serum markers of oxidative stress than the vegetable added diet. A consensus is emerging that polyphenols, rather than antioxidant vitamins alone, are responsible for the anti-aging benefits of the Mediterranean diet.

Polyphenols from tea, primarily catechins and theaflavins, are also known to be potent antioxidants, although comparison data are sparse. A few *in vivo* studies document direct antioxidant activity through free radical scavenging and chelation of redox-active transition metal ions, and indirect actions including induction of the phase II antioxidant enzymes superoxide dismutases and glutathione *S*-transferases.[42] Photoprotection has also been seen with topical application or oral ingestion of the tea polyphenol (–)-epigallocatechin-3-gallate, with inhibition of carcinogen chemical- or UV radiation–induced skin carcinogenesis in various *in vivo* models.[43] Catechins, epicatechins, and gallic acids also occur in substantial amounts in red wine, along with ellagic acid, the primary antioxidant polyphenol in pomegranates. Peroxyl radical scavenging activities of these various compounds have been compared, with results in decreasing order found to be resveratrol > catechin > epicatechin = gallocatechin > gallic acid = ellagic acid.[44]

The synthetic coenzyme Q analog idebenone has been reported to be the strongest topical antioxidant.[45] Although all antioxidants ultimately function by scavenging reactive oxygen species, a variety of tests are employed including direct chemical measurements of free radical neutralization and biological *in vitro* and *in vivo* assays. A new product with 1% resveratrol (FAMAR, Athens, Greece) developed for Calidora Skin Clinics (Seattle, WA) was tested against 1% idebenone (Prevage MD, Allergan, Inc., Irvine, CA) using the ORAC test (Oxygen Radical Absorbance Capacity, Brunswick Laboratories, Norton, MA), an industry standard for cosmetics and nutrition. The resveratrol product yielded 4845 μmole VE/g (vitamin E equivalent per gram) compared with 279 for the 1% idebenone, approximately a 17-fold increase in antioxidant potency. Clinical testing is underway for this promising formulation.

Prevention of photoaging

Botanical antioxidant compounds as a key ingredient in skin care products have received recent attention and validation of efficacy. The use of resveratrol and other botanical antioxidants has been reviewed by Afaq and Mukhtar[46] and Baliga and Katiyar.[47] Resveratrol has been demonstrated to act on cellular signaling mechanisms related to UV-mediated photoaging, including MAP kinases, nuclear factor kappa B (NF-κB), and matrix metalloproteinases. Topical application of resveratrol in a

SKH-1 hairless mouse model prior to UV-B radiation results in significant inhibition of cellular proliferation, mRNA survivin expression, and survivin phosphorylation. Resveratrol lowers levels of reactive oxygen species in UVA-exposed HaCaT keratinocytes in a dose-dependent manner, and electron microscopy confirmed that ultrastructural changes could be prevented.[48]

Anticancer

Several lines of evidence point to a role for resveratrol and other wine phenolics in chemoprevention of cancer as well as possible therapeutic roles.[49,50] Mechanisms at each step in carcinogenesis have been mapped in detail, with resveratrol acting as an anti-initiation, antipromotion, and antiprogression agent.[51] At the initiation level, antioxidant capabilities are believed to be important, whereas induction of apoptosis, decreased expression of antiapoptotic proteins, and down-regulation of cell activation pathways are involved in antipromotion effects. Antiprogression actions include suppression of growth factor signaling pathways, suppression of cancer cell growth, and inhibition of angiogenesis.[52] Direct suppression of breast cancer cells,[53] melanoma,[54] and many others by resveratrol has been reported. These effects are mediated through up-regulation of p12Cip1/WAF1, p53, and Bax; down-regulation of survivin, cyclin E, Bcl-2, Bcl-xL, and clAPS; activation of caspases; and suppression of transcription factors including NF-κB, AP-1, and Egr-1, and JAK-STAT.[55] Inhibition of several protein kinases and COX-2 is also believed to be important.

Resveratrol has also been demonstrated to enhance the effectiveness of cisplatin and doxorubicin in human ovarian (OVCAR-3) and uterine (Ishikawa) cancer cell lines, attenuating the cardiotoxic effects in rodent ventricular myocytes.[56] Resveratrol and other wine polyphenols act as chemosensitizers and radiosensitizers by blocking pathways that lead to treatment resistance.[57]

Infectious diseases

Resveratrol is produced in the skin of wine grapes in response to environmental stress, and is known to have antifungal, antibacterial, and antiviral properties.[58] Influenza virus replication has been shown to be inhibited by resveratrol[59] via blockade of the nuclear-cytoplasmic translocation of viral proteins, most likely related to protein kinase C activity, and mice infected with the influenza virus showed significantly better survival when treated with resveratrol. Antimicrobial effects on dermatophytes and bacterial pathogens of the skin have also been documented.[60]

Resveratrol as a sirtuin mimetic

Caloric restriction promotes longevity through activation of histone deacetylase enzymes known as sirtuins,[6] a phenomenon documented across animal species from simple organisms to vertebrates.[7,8] It is believed to be based upon a survival response to nutritional or other environmental stress, with altered mitochondrial metabolism, increased insulin sensitivity, lowered levels of insulin-like growth factor-1, increased AMP-activated protein kinase, and other downstream effects. Wine polyphenols are the only known sirtuin mimetics capable of replicating the calorie restriction effect by up-regulating sirtuin activity. The adverse effects of a high-calorie diet on mice were reversed with resveratrol,[9] and studies in primates are ongoing. The effects in humans have not yet been reported, though at least two biotechnology companies are developing resveratrol formulations for prescription use in diabetes and degenerative diseases.

Outlook for clinical use

Pending reports of prospective clinical trials in humans for specific conditions, the benefits of oral supplementation of resveratrol remain speculative. Questions about bioavailability, metabolism, and dosing remain largely unanswered as yet. Resveratrol seems to be rapidly absorbed after oral ingestion but quickly conjugated by glucuronic acid, although it may accumulate in epithelial tissues.[61,62] In pigs, resveratrol has been demonstrated to absorb well through the stratum corneum though not as well as a phosphorylated conjugate.[63] Topical use therefore seems to pose little theoretical risk and potentially large benefits. Synthetic resveratrol derivatives may allow for more targeted applications, although the native form is many times more potent in free radical absorption capacity than antioxidant vitamins and derivatives currently in use.

References

1 Draelos ZD. What is anti-aging? *J Cosmetic Dermatol* 2007; **6**: 73–4.
2 de Gray AD. The foreseeability of real anti-aging medicine: focusing the debate. *Exp Gerontol* 2003; **38**: 927–34.
3 Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. *Proc Nat Acad Sci USA* 1993; **90**: 7915–22.
4 National Institute on Aging. *Aging Under the Microscope*. NIH publication no. 02-2756. Bethesda, MD: NIH; 2002.
5 Burzynski SR. Aging: gene silencing or gene activation? *Med Hypotheses* 2005; **64**: 201–8.

6 Sauve AA, Schramm VL. SIR2: the biological mechanism of NAD(+)-dependent protein deacetylation and ADP-ribosyl enzyme intermediates. *Curr Med Chem* 2004; **11**: 807–26.
7 Howitz KT, Bitterman KJ, Cohen HY *et al*. Small molecule *activators* of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 2003; **425**: 191–6.
8 Valenzano DR, Terzibasi E, Genade T, Cattaneo A, Domeneci L, Cellerino A. Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate. *Curr Biol*, 2006; **16** (3): 296–300.
9 Baur JA, Pearson KJ, Price NL *et al*. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 2006; **144**: 337–42.
10 Siemann E, Creasy L. Concentration of the phytoalexin resveratrol in wine. *Am J Enol Vitic* 1992; **43**: 49–52.
11 Orallo F. Comparative studies of the antioxidant effects of *cis*- and *trans*-resveratrol. *Curr Med Chem* 2006; **13**: 87–98.
12 Miura T, Muraoka S, Ikeda N, Watanabe M, Fujimoto Y. Antioxidative and prooxidative action of stilbene derivatives. *Pharmacol Toxicol* 2000; **86**: 203–8.
13 Olas B, Wachowicz B. Resveratrol, a phenolic antioxidant with effects on blood platelet functions. *Platelets* 2005; **16**: 251–60.
14 Stojanovic S, Sprinz H, Brede O. Efficiency and mechanism of the antioxidant action of *trans*-resveratrol and its analogues in the radical liposome oxidation. *Arch Biochem Biophys* 2001; **391**: 79–89.
15 Li LH, Wu LJ, Tashiro SI, Onodera S, Uchiumi F, Ikejima T. Activation of the SIRT1 pathway and modulation of the cell cycle were involved in silymarin's protection against UV-induced A375-S2 cell apoptosis. *J Asian Nat Prod Res* 2007; **9**: 245–52.
16 Toklu HZ, Tunah-Akbay T, Erkanh G, Yüksel M, Ercan F, Şener G. Silymarin, the antioxidant component of *Silybum mairianum*, protects against burn-induced oxidative skin injury. *Burns* 2007; **33**: 908–16.
17 Deep G, Aggarwal R. Chemopreventive efficacy of silymarin in skin and prostate cancer. *Integr Cancer Ther* 2007; **6**: 130–45.
18 Cordova A, Jackson L, Berke-Schlessel D, Sumpio B. The cardiovascular protective effect of red wine. *J Am Coll Surg* 2005; **200**: 428–39.
19 Grønbaek M. Alcohol, type of alcohol, and all-cause and coronary heart disease mortality. *Ann N Y Acad Sci* 2002; **957**: 16–20.
20 Renaud S, Guéguen R, Siest G, Salamon R. Wine, beer, and mortality in middleaged men from eastern France. *Arch Intern Med* 1999; **159**: 1865–70.
21 Wallerath T, Deckert G, Ternes T *et al*. Resveratrol, a polyphenolic phytoalexin present in red wine, enhances expression and activity of endothelial nitric oxide synthase. *Circulation* 2002; **106**: 1652–8.
22 Corder R, Douthwaite JA, Lees DM *et al*. Endothelin-1 synthesis reduced by red wine. *Nature* 2001; **414**: 863–4.
23 Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 1993; **341**: 454–7.
24 Pace-Asciak CR, Hahn S, Diamandis EP, Soleas G, Goldberg DM. The red wine phenolic *trans*-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis. *Clin Chim Acta* 1995; **235**: 207–14.
25 Anekonda TS. Resveratrol–a boon for treating Alzheimer's disease? *Brain Res Rev* 2006; **52**: 316–26.
26 Marambaudl P, Zhao H, Davies P. Resveratrol promotes clearance of Alzheimer's disease amyloid C-peptides. *J Biol Chem* 2005; **280**: 37377–82.
27 Savaskan E, Olivieri G, Meier F, Seifritz E, Wirz-Justice A, Müller-Spahn F. Red wine ingredient resveratrol protects from β-amyloid neurotoxicity. *Gerontology* 2003; **49**: 380–3.
28 Tredici G, Miloso M, Nicolini G, Galbiati S, Cavaletti G, Bertelli A. Resveratrol, MAP kinases and neuronal cells: might wine be a neuroprotectant? *Drugs Exptl Clin Res* 1999; **25**: 99–103.
29 Dasgupta B, Milbrandt J. Resveratrol stimulates AMP kinase activity in neurons. *Proc Nat Acad Sci USA* 2007; **104**: 7217–22.
30 Ates O, Cayli S, Altinoz E *et al*. Neuroprotection by resveratrol against traumatic brain injury in rats. *Mol Cell Biochem* 2007; **294**: 137–44.
31 Wang Q, Xu J, Rottinghaus GE *et al*. Resveratrol protects gainst global ischemic injury in gerbils. *Brain Res* 2002; **958**: 439–47.
32 Gehm BD, McAndrews JM, Chien PY, Jameson JL. Resveratrol, a polyphenolic compound found in grapes and red wine, is an agonist for the estrogen receptor. *Proc Nat Acad Sci USA* 1997; **94**: 14138–43.
33 Calabrese G. Nonalcoholic compounds of wine: the phytoestrogen resveratrol and moderate red wine consumption during menopause. *Drugs Exp Clin Res* 1999; **25**: 111–4.
34 Su JL, Yang CY, Zhao M, Kuo ML, Yen ML. Forkhead proteins is critical for BMP-2 regulation and anti-tumor activity of resveratrol. *J Biol Chem* 2007; **282**: 19385–98.
35 Nabel EG. The women's health initiative. *Science* 2006; **313**: 1703.
36 Verdier-Sevrain S. Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators. *Climacteric* 2007; **10**: 289–97.
37 Verdier-Sevrain S, Bonte F, Gilchrest B. Biology of estrogens in skin: implications for skin aging. *Exp Dermatol* 2006; **15**: 83–94.
38 Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet* 2003; **361**: 2017–23.
39 Huang HY, Caballero B, Chang S *et al*. The efficacy and safety of multivitamin and mineral supplement use to prevent cancer and chronic disease in adults: a systematic review for a National Institutes of Health state-of-the-science conference. *Ann Intern Med* 2006; **145**: 372–85.

40 Boothby LA, Doering PL. Vitamin C and vitamin E for Alzheimer's disease. *Ann Pharmacother* 2005; **39**: 2073–80.

41 Leighton F, Cuevas A, Guasch V *et al*. Plasma polyphenols and antioxidants, oxidative DNA damage, and endothelial function in a diet and wine intervention study. *Drugs Exp Clin Res* 1999; **25**: 133–41.

42 Frei B, Higdon JV. Antioxidant activities of tea polyphenols *in vivo*: evidence from animal studies. *J Nutr* 2003; **133**: 3275S–84S.

43 Katiyar SK. Skin photoprotection by green tea: antioxidant and immunomodulatory effects. *Curr Drug Targets Immune Endocr Metab Disord* 2003; **3**: 234–42.

44 Yilmaz Y, Toledo RT. Major flavonoids in grape seeds and skins. antioxidant capacity of catechin, epicatechin, and gallic acid. *J Agric Food Chem* 2004; **52**: 255–60.

45 McDaniel DH, Neudecker BA, Dinardo JC, Lewis JA, Maibach HI. Idebenone: a new antioxidant – part 1. Relative assessment of oxidative stress protection capacity compared to commonly known antioxidants. *J Cosmet Dermatol* 2005; **4**: 10–7.

46 Afaq F, Mukhtar H. Botanical antioxidants in the prevention of photocarcinogenesis and photoaging. *Exp Dermatol* 2006; **15**: 678–84.

47 Baliga MS, Katiyar SK. Chemoprevention of photocarcinogenesis by selected dietary botanicals. *Photochem Photobiol Sci* 2006; **5**: 243–53.

48 Chen ML, Li J, Xiao WR *et al*. Protective effect of resveratrol against oxidative damage of UVA irradiated HaCaT cells. *Jhong Nan Da Xue Xue Bao Yi Ban* 2006; **31**: 635–9.

49 Joe AK, Liu H, Suzui M, Vural ME, Xiao D, Weinstein IB. Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. *Clin Cancer Res* 2002; **8**: 893–303.

50 Delmas D, Lancon A, Colin D, Jannin B, Latruffe N. Resveratrol as a chemopreventive agent: a promising molecule for fighting cancer. *Curr Drug Targets* 2006; **7**: 423–42.

51 Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. *Anticancer Res* 2004; **25**: 2783–840.

52 Fulda S, Debatin KM. Resveratrol modulation of signal transduction in apoptosis and cell survival: a mini-review. *Cancer Detect Prev* 2006; **30**: 217–23.

53 Lanzilli G, Fuggetta MP, Tricarico M *et al*. Resveratrol down-regulates the growth and telomerase activity of breast cancer cells *in vitro*. *Int J Oncol* 2006; **28**: 641–8.

54 Niles RM, McFarland M, Weimer WB, Redkar A, Fu WM, Meadows GG. Resveratrol is a potent inducer of apoptosis in human melanoma cells. *Cancer Lett* 2003; **190**: 157–63.

55 Ulrich S, Wolter F, Stein JM. Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in carcinogenesis. *Mol Nutr Food Res* 2005; **49**: 452–61.

56 Rezk YA, Balulad SS, Keller RS, Bennett JA. Use of resveratrol to improve the effectiveness of cisplatin and doxorubicin. study in human gynecologic cancer cell lines and rodent heart. *Am J Obstet Gynecol* 2006; **194**: e23–6 epub 2006 April 21.

57 Garg AK, Buchholtz TA, Aggarwal BB. Chemosensitization and radiosensitization of tumors by plant polyphenols. *Antioxid Redox Signal* 2005; **7**: 1630–47.

58 Langcake P, Pryce RJ. The production of resveratrol by *Vitis vinifera* and other members of the Vitaceae as a response to infection and injury. *Physiol Plant Pathol* 1976; **9**: 77–86.

59 Palamara AT, Nencioni L, Aquilano K *et al.* Inhibition of influenza A virus replication by resveratrol. *J Infect Dis* 2005; **191**: 1719–29.

60 Chan MM. Antimicrobial effect of resveratrol on dermatophytes and bacterial pathogens of the skin. *Biochem Pharmacol* 2002; **63**: 99–104.

61 Vitaglione P, Sforza S, Galaverna G *et al*. Bioavailability of *trans*-resveratrol from red wine in humans. *Mol Nutr Food Res* 2005; **49**: 495–504.

62 Walle T, Hsieh F, DeLegge MH, Oatis JE Jr, Walle UK. High absorption but low bioavailability of oral resveratrol in humans. *Drug Metab Dispos* 2004; **32**: 1377–82.

63 Zhang G, Flach CR, Mendelsohn R. Tracking the dephosphorylation of resveratrol triphosphate in skin by confocal Raman microscopy. *J Control Release* 2007; [epub ahead of print].