Perspective

Resveratrol from Red Grapes - Pedestrian Polyphenol or Miraculous Anticancer Agent?

Andreas J Gescher

_____

Affiliation

Cancer Biomarkers and Prevention Group, Department of Cancer Studies and

Molecular Medicine, University of Leicester, Leicester LE2 7LX, UK

Key words

_____

Introduction

Phytochemicals with beneficial effects on health regularly make newspaper headlines.

Media awareness reflects the considerable interest of the general public in naturally

occurring remedies rooted in the assumptions that the plant kingdom harbours

remedies against all sorts of ills, and that many of these remedies have still to be

discovered. The realisation that fruits and vegetables can prevent diseases such as

cancer has engendered an intense search for the constituents which may be

responsible for these properties. Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) is an

example of a dietary constituent which has been shown over the last decade to possess

a fascinating spectrum of pharmacological properties. Resveratrol was first isolated

from the roots of white hellebore (*Vertarum grandiflorum O. Loes*) in 1940 and later

from the roots of *Polygonum cuspidatum*, a plant used in Chinese and Japanese medicine. In 1992 resveratrol was suggested to explain some of the cardioprotective effects of red wine [1]. Since then many reports have shown that resveratrol can prevent, or decelerate, the progression of illnesses such as cancer, cardiovascular disease and ischaemic injury, as well as enhance stress resistance and extend the lifespan of various organisms from yeast to vertebrates. In 1997 Jang *et al.* [2] published a paper, in which the ability of resveratrol to inhibit diverse cellular events associated with initiation, promotion and progression of cancer was described. This paper fired the imagination of the cancer chemoprevention research community. During the 11 years since its publication, literally hundreds of reports have appeared in the literature in which cellular and biochemical mechanisms of resveratrol have been described, and their potential role in the putative cancer chemopreventive activity of this agent has been discussed. As a triphenol resveratrol is exceedingly prone to undergo metabolic conjugation, so that its bioavailability is extremely low. Its intriguing efficacy in spite of low bioavailability constitutes a conundrum [3]. This perspective aims at exploring whether recent results of investigations of resveratrol, especially those in humans, may help resolve the conundrum. It focuses in particular on mechanisms and pharmacokinetics of resveratrol and describes resveratrol analogues designed to optimise its pharmacology. There have been several incisive and comprehensive reviews of the health effects [e.g. 4] and pharmacokinetics [e.g. 5] of resveratrol, yet information of the pharmacology of resveratrol in humans remains scarce.

How can resveratrol prevent cancer?

Prominent among the mechanisms, which may mediate the cancer chemopreventive efficacy of resveratrol, are inhibition of cyclooxygenase enzymes, inhibition of angiogenesis, modulation of drug metabolising enzymes, antioxidation and alterations in cell cycle and apoptotic machinery. Jang et al originally proposed that resveratrol inhibits the enzymatic activity of both cylooxygenase enzymes COX-1 and -2 [2]. Epidemiological evidence suggests that long-term inhibition of cyclooxygenase significantly reduces the risk of developing many cancers, and deletion of the gene that encodes COX-2 is protective in a mouse model of colorectal cancer [6](18 Oshima Cell). Resveratrol inhibited COX-1 in a somewhat selective fashion and reduced COX-2 at the mRNA level [7-10](21-24ev Baur). Resveratrol, delivered systemically, inhibited tumour-induced neovascularisation required to support solid tumour growth, illustrating its anti-angiogenic properties [11, 12] (31,32).

Resveratrol can modulate the expression and activity of multiple drug-metabolising enzymes. It inhibited various cytochrome P450s [13-16] (35-38) and induced expression of phase II drug detoxifying enzymes [17] (44). These activities suggest that resveratrol may reduce the exposure of cells to carcinogens by decreasing carcinogen formation and/or increasing their detoxification.

Reactive oxygen species (ROS) have been shown to be involved with the initiation and progression of cancer via damaging DNA and other biomolecules. Resveratrol has antioxidant capacity, as reflected by its ability to increase plasma antioxidant activity and to decrease lipid peroxidation [18-20](62-64).

Resveratrol possesses antiproliferative and pro-apoptotic effects in tumour cell lines [65](50). These effects may be mechanistically linked to its abilities to downregulate cell cycle proteins [66-68](51-53) and increase apoptosis [69-71](54-56) in tumour

models *in vivo*. Resveratrol sensitized tumour cells to apoptosis induced by TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) [72](59), and this property may explain its pro- apoptotic effects *in vivo*.

At the end of 2006 two reports suggested that resveratrol is a caloric restriction mimetic in lower organisms and mice, associated with its ability to activate sirtuin proteins and to extend lifespan [73, 74]. Sirtuins are NAD-dependent deacetylases involved in gene silencing processes germane to aging, blockade of apoptosis and promotion of cell survival. So paradoxically, resveratrol can counteract radical oxygen species (ROS) production, induce apoptosis and inhibit cell growth, but it can also increase mitochondrial metabolism and, in turn, ROS production, thus enhancing cell survival. Scanning internet websites devoted to life enhancement shows that a surprisingly large number of healthy humans now ingest resveratrol at high doses with the objective to prolong their lives, without bearing in mind that the safety of high-dose resveratrol ingested for a long term is unknown.

Pharmacokinetics of resveratrol

In rodents resveratrol possesses a short initial half life, 8-14 min [75, 76] as it is metabolised extensively and rapidly. Results from clinical trials are essentially compatible with the rodent studies. Table 1 describes the widely varying situations in which resveratrol has been studied in humans, administered either as pure compound [77, 78] or as constituent of wine or grape fruit juice or grape extract [79-84](Zern, Meng, Vitaglione, Goldberg, Zamaroa, Lekakis). Walle et al [77] showed that the bulk of an iv dose of 25 mg per human resveratrol was converted to sulphate conjugates within 30 min. Serum peak levels of res were <22 nM. Five metabolites were identified in the urine, resveratrol mono sulphate, two isomeric

monoglucuronides, dihydroresveratrol monosulphate and dihydroresveratrol monoglucuronide. Total sulphate conjugates accounted for ~37% of the metabolites in the urine and total glucuronide conjugates ~19%, and there were only trace amounts of free res. Recently a study of the pharmacokinetics of single oral resveratrol administered at high doses (0.5, 1, 2.5 or 5g) was conducted in healthy human volunteers (10 per dose level) [78]. The doses were safe and resveratrol and six metabolites were recovered from plasma and urine. Peak plasma level of resveratrol at the highest dose (5g) was 2.4 μM, which occurred 1.5 h post-dose. Peak levels of two monoglucuronides and resveratrol-3-sulfate were 3-8 fold higher. The area under the plasma concentration curve values for resveratrol-3-sulfate and resveratrol monoglucuronides were up to 23 times greater than those of resveratrol. Urinary excretion of resveratrol and its metabolites was rapid, with 77% of all urinary agent-derived species excreted within 4 h after the lowest dose.

Conjugate formation typically reduces cell permeability and aids drug excretion, therefore the reported in vivo efficacy of resveratrol in spite of its low bioavailability has led to speculation that its metabolites could mediate at least in part the efficacy exerted by the parent molecule. Concentrations of resveratrol in red wine vary widely, but a reasonable estimate is about 5 mgL^{-1} (22 μM) [85](180). Assuming a consistent daily intake of two glasses of wine (~375 ml) a person weighing 70 kg would receive a dose of ~27 μg per kg body weight each day. The plasma concentrations after such a low dose are clearly vanishingly small, in the 1-10 nM range [86](178), certainly orders of magnitudes below those found to elicit most pharmacological effects reported *in vitro*. Therefore it seems prudent to explore the pharmacology of resveratrol from two separate standpoints, firstly considering it as diet constituent, and secondly as agent in its own right which just happens to be diet-derived. Russo [87]

surmised that the diet constituent resveratrol, ie resveratrol at low doses, may be useful as a caloric restriction mimic, whilst at high doses, it may be a promising chemotherapeutic agent, but in neither case useful as cancer chemopreventive agent. This interpretation is based on the findings that low doses generate concentrations capable of mimicking caloric restriction, but insufficient to engage anticarcinogenesis, whilst high doses, which are pharmaceutically unfeasible in the chemoprevention paradigm, engender levels exerting antiproliferative and pro-aptototic effects. Nevertheless in the light of the polymechanistic nature of the effect of resveratrol its seems premature to write off its potential chemopreventive activity. The maximum tolerated dose of resveratrol has not been properly established, but at 300 mg/kg it did not have detrimental effects in the rat [88](147).

Resveratrol analogues

Not surpisingly the diverse attractive pharmacological features of resveratrol in concert with its relatively simple chemical structure have inspired medicinal chemists to synthesize analogues with the aim to design novel agents with cancer chemopreventive/chemotherapeutic efficacy superior to that of parent resveratrol. Efforts have focussed on structure – activity relationships of substituted stilbene derivatives to optimise cytotoxic potency, ability to inhibit activation of NFkB, tyrosine kinase or cytochrome P450 or to exert antioxidation [89-93](12-15 JMEdChem. Heynekamp). For example a series of cis- and trans-stilbenes related to resveratrol with varying aryl, hydroxyl, methoxy and/or amine moieties have been synthesized and evaluated for ability to induce apoptosis in human leukaemia-derived HL60 cells [94] (Roberti). Among the analogues cis-3,4',5-trimethoxy-3'-aminostilbene and cis-3,4',5- trimethoxy-3'-hydroxystilbene (Fig. 1) were found to

possess potency superior to that of the lead compound resveratrol. Other workers have generated polyhydroxystilbenes, exemplified by 3,3',4',5-tetrahydroxystilbene (Fig. 1), to maximise the antioxidant activity of this type of molecule [95](Murias). A relatively subtle chemical change brought about by methylation of the stilbene hydroxy mioeties increased several pharmacological potencies of resveratrol. This increased potency may be, at least in part, due to the fact that methoxy moieties tend to be less vulnerable to attack by metabolising enzymes than hydroxy. Pertinent in this context is the finding that pterostilbene, bis-methylated resveratrol found in blueberries (Fig. 1), at 40 ppm in the diet potently suppressed aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis rat model and suppressed inducible nitric oxide synthase expression [96](Suh).

The recent realisation that resveratrol may extend lifespan, and the assumption that this property may ultimately be observed in humans, has engendered a flurry of medicinal chemistry projects in the pharmaceutical industry. These activities are primarily aimed at generating novel patentable molecules which activate sirtuins, possess life extending properties and mimic health effects of calorie restriction without requiring a change in eating habits, undoubtedly an attractive endeavour from a financial standpoint. It seems worthwhile to test these analogues, when they will be available, for cancer chemopreventive properties.

Future work

Are we any closer to resolve the conundrum posed by the undeniable efficacy of resveratrol in preclinical models in spite of its low systemic availability? Hardly. It still unclear whether metabolites can contribute to, or mediate, resveratrol efficacy. Experiments to explore this issue are afoot. The differential effects of dietary (ie low)

doses of resveratrol on the one hand and pharmacological (ie high) doses on the other

has sparked investigations of dose-dependent differences in metabolite profiles

obtained after consumption of either red wine or purified resveratrol. Results from

studies of this type will undoubtedly help explain dose-response issues related to

resveratrol pharmacology. Further chemical syntheses of resveratrol cogeners might

well generate molecules with biological activities superior to those of resveratrol. It

remains to be seen whether new synthetic caloric restriction mimetics modelled on

resveratrol will prolong human life and whether such molecules exert cancer

chemopreventive activity. Whilst studies in humans conducted hitherto support the

tentative notion that resveratrol is a safe molecule, it will take a long time to establish

whether chemically designed resveratrol analogues retain the safety of the parent

molecule. Lack of knowledge of their safety will for a long time confound

consideration of such novel molecules as potential cancer chemopreventive agents.

The findings briefly highlighted here show that resveratrol is certainly not a

pedestrian polyphenol. On the other hands, it is unlikely to turn out to be a miraculous

anticancer remedy, even though it constitutes undoubtedly a molecule which will

intrigue cancer pharmacologists for a long time to come.

_____

Table 1. Clinical trials of resveratrol

Study cohort	*Intervention*	*Dose and route of resveratrol*	*Reference*
Healthy volunteers (44)	Lyophilized grape powder	58μg pd x 4 weeks *po*	[80]
Healthy volunteers (6)	Resveratrol in whisky/grape juice	0.32 – 70mg single dose *po*	[79]
Healthy volunteers (25)	Red wine	0.25, 0.48 or 1.9mg single dose *po*	[81]
Healthy volunteers (12)	Red wine, fruit or vegetable juice	25mg single dose *po*	[82]
Healthy volunteers (20)	Red wine	0.4 – 2.6mg pd x 4 weeks *po*	[83]
Coronary heart disease patients (30)	Grape extract	0.9mg single dose *po*	[84]
Healthy volunteers (6)	Pure resveratrol	25mg single dose *iv/po*	[77]
Healthy volunteers (40)	Pure resveratrol	0.5, 1, 2.5 or 5g single dose *po*	[78]

References

[1] Siemann EH, Creasy LL. Concentration of the phytoalexin resveratrol in wine. Am J Eno Vitic 1992; 43: 49-52.

[2] Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997; 275:218-20.

[3] Gescher AJ, Steward WP. Relationship between mechanisms, bioavailibility, and preclinical chemopreventive efficacy of resveratrol: A conundrum. Cancer Epidemiol. Biomarkers & Prev 2003; 12: 953-7.

[4] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nature Rev Drug Discov 2006;5: 493-506.

[5] Wenzel E, Somoza V. Metabolism and bioavailability of trans-resveratrol. Molec Nutr Food Res 2005;49: 472-81.

[6] Oshima, M. *et al*. Suppression of intestinal polyposis in Apcδ716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). Cell 1996; 87: 803-9 (1996).

[7] Li ZG. *et al*. Suppression of *N*-nitroso-methylbenzylamine (NMBA)-induced esophagael tumourigenesis in F344 rats by resveratrol. Carcinogenesis 2002; 23: 1531-6.

[8] Aziz M, Afaq F, Ahmad N. Prevention of ultraviolet-B radiation damage by resveratrol in mouse skin is mediated via modulation in survivin. Photochem Photobiol 2004; 81: 25-31.

[9] Subbaramaiah K *et al*. Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. J Biol Chem 1998; 273: 21875-82.

[10] Martin AR, Villegas I, La Casa C, de la Lastra CA. Resveratrol, a polyphenol found in grapes, suppresses oxidative damage and stimulates apoptosis during early colonic inflammation in rats. Biochem Pharmacol 2004; 67: 1399-1410 (2004).

[11] Kimura Y, Okuda H. Resveratrol isolated from *Polygonuum cuspidatum* root prevents tumor growth and metastasis to lung and tumor-induced neovascularisation in Lewis lung carcinoma-bearing mice. J. Nutr 2001;131: 1844-9.

[12] Tseng SH *et al*. Resveratrol suppresses the angiogenesis and tumor growth of gliomas in rats. Clin Cancer Res 2004; 10: 2190-2.

[13] Yu C, Shin YG, Kosmeder JW, Pezzuto JM, van Breemen RB. Liquid chromatography/tandem mass spectrometric determination of inhibition of human cytochrome P450 isozymes by resveratrol and resveratrol-3-sulfate. Rapid Commun Mass Spectrom 2003; 17: 307-13.

[14] Piver B, Berthou F, Dreano Y, Lucas D. Inhibition of CYP3A, CYP1A and CYP2E1 activities by resveratrol and other non volatile red wine components. Toxicol Lett 2001; 125: 83-91.

[15] Chang TK, Lee WB, Ko HH. *Trans*-resveratrol modulates the catalytic activity and mRNA expression of the procarcinogen-activating human cytochrome P450 1B1. Can J Physiol Pharmacol 2000; 78: 874-81.

[16] Chan WK, Delucchi AB. Resveratrol, a red wine constituent, is a mechanism-based inactivator of cytochrome P450 3A4. Life Sci 2000; 67: 3103-12.

[17] Cao Z, Li Y. Potent induction of cellular antioxidants and phase 2 enzymes by resveratrol in cardiomyocytes: protection against oxidative and electrophilic injury. Eur J Pharmacol 2004; 489: 39-48.

[18] Sengottuvelan M, Viswanathan P, Nalini N. Chemopreventive effect of *trans*-resveratrol – a phytoalexin against colonic aberrant crypt foci and cell proliferation in 1,2-dimethylhydrazine induced colon carcinogenesis. Carcinogenesis 2005; 27: 1038-46.

[19] Miura D, Miura Y, Yagasaki K. Hypolipidemic action of dietary resveratrol, a phytoalexin in grapes and red wine, in hepatoma-bearing rats. Life Sci 2003; 73: 1393-1400.

[20] Wenzel E, Soldo T, Erbersdobler H, Somoza V. Bioactivity and metabolism of *trans*-resveratrol orally administered to Wistar rats. Mol Nutr Food Res 2005; 49: 482-94.

[21] Aggarwal BB. *et al*. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer Res 2004; 24: 2783-40.

[22] Yu L, Sun ZJ, Wu SK, Pan CE. Effect of resveratrol on cell cycle proteins in murine transplantable liver cancer. World J Gastroenterol 2003; 9: 2341-3.

[23] Schneider Y. *et al*. Resveratrol inhibits intestinal tumourigenesis and modulates host-defense-related gene expression in an animal model of human familial adenomatous polyposis. Nutr Cancer 2001; 39: 102-7.

[24] Reagan-Shaw S, Afaq F, Aziz MH, Ahmad N. Modulation of critical cell cycle regulatory events during chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin. Oncogene 2004; 23: 5151-60.

[25] Garvin S, Ollinger K, Dabrosin C. Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts *in vivo*. Cancer Lett 2006; 231: 113-22.

[26] Provinciali M. *et al*. Effect of resveratrol on the development of spontaneous mammary tumors in HER-2/neu transgenic mice. Int J Cancer 2005; 115: 36-45.

[27] Zhou HB, Chen JJ, Wang WX, Cai JT, Du Q. Anticancer activity of resveratrol on implanted human primary gastric carcinoma cells in nude mice. World J Gastroenterol 2005; 11**:** 280-4.

[28] Fulda S, Debatin KM. Sensitization for tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis by the chemopreventive agent resveratrol. Cancer Res 2004; 64: 337-46.
[29] Baur JA, Pearson KJ, Price NL, Jamieson H A, Lerin C, Kalra A,
 et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006;444:337-42.

[30] Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al.

Resveratrol improves mitochondrial function and protects against metabolic disease

by activating SIRT1 and PGC-1 alpha. Cell 2006;127:1109-22.

[31] Marier JF. *et al*. Metabolism and disposition of resveratrol in rats: extent of absorption, glucuronidation, and enterohepatic recirculation evidenced by a linked-rat model. J Pharmacol Exp Ther 2002; 320: 369-73.

[32] Asensi M. *et al*. Inhibition of cancer growth by resveratrol is related to its low bioavailability. Free Radic Biol Med 2002; 33: 387-98.

[33] Walle T, Hsieh F, DeLegge MH, Oatis JE, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Disp 2004;32:1377-82.

[34] Boocock DJ, Faust GES, Patel KR, Schinas AM, Brown VA, Ducharme MP, et

al (2007) Phase I dose escalation pharmacokinetic study in healthy volunteers of

resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol Biomarkers & Prev 16, 1246-52.

[35] Meng XF, Maliakal P, Lu H, Lee MJ, Yang CS. Urinary and plasma levels of resveratrol and quercetin in humans, mice, and rats after ingestion of pure compounds and grape juice. J Agric Food Chem 2004;52:935-42.

[36] Zern TL, Wood RJ, Greene C, West KL, Liu YZ, Aggarwal D, et al. Grape polyphenols exert a cardioprotective effect in pre- and postmenopausal women by lowering plasma lipids and reducing oxidative stress. J Nutr 2005;135:1911-7.

[37] Vitaglione P, Sforza S, Galaverna G, Ghidini C, Caporaso N, Vescovi PP, et al. Bioavailability of trans-resveratrol from red wine in humans. Molec Nutr Food Res 2005;49:495-504.

[38] Goldberg DA, Yan J, Soleas GJ. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. Clin Biochem 2003;36:79-87.

[39] Zamora-Ros R, Urpi-Sarda M, Lamuela-Raventos RM, Estruch R, Vazquez-Agell M, Serrano-Martinez M, et al. Diagnostic performance of urinary resveratrol metabolites as a biomarker of moderate wine consumption. Clin Chem 2006;52:1373-80.

[40] Lekakis J, Rallidis LS, Andreadou I, Vamvakou G, Kazantzoglou G, Magiatis P, et al. Polyphenolic compunds from red grapes acutely improve endothelial function in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil 2005; 12: 596-600.

Crowell, J.A., Korytko, P.J., Morrissey, R.L., Booth, T.D. & Levine, B.S. Resveratrol-associated renal toxicity. *Toxicol. Sci.* **82**, 614-619 (2004).

Pettit GR, Grealish MP, Jung MK, Hamel E, Pettit RK, Chapuis JC, Schmidt JM. Antineoplastic agents. 465. Structural modification of resveratrol: sodium resveratrin phosphate. J Med Chem 2002; 45: 2534-42.

Kim S, Ko H, Park JE, Jung S, Lee SK, Chun YJ. Design, synthesis and discovery of novel *trans*-stilbene analogues as potent and selective human cytochrome P450 1B1 inhibitors. J Med Chem 2002; 45: 160-4.

Thakkar K, Geahlen RL, Cushman M. Synthesis and Protein − tyrosine kinase inhibitory activity of polyhydroxylated stilbene analogues of piceatannol. J Med Chem 1993; 36: 2950-5.

Cushman M, Nagarathnam D, Gopal D, He, HM, Lin CM, Hamel E. Synthesis and evaluation of analogues of (*Z*)-1-(4-methoxyphenyl)-2-(3,4,5-

trimethoxyphenyl)ethene as potential cytotoxic and antimitotic agents. J Med Chem 1992; 35: 2293-306.

 [87] Russo GL. Ins and outs of dietary phytochemicals in cancer chemoprevention. Biochem Pharmacol 2007;74:533-44.

[93] Heynekamp JJ, Weber WM, Hunsaker LA, Gonzales AM, Orlando RA, Deck

LM, Jagt DLV. Substituted trans-stilbenes, including analogues of the natural product

resveratrol , inhibit the human tumor necrosis factor alpha-induced activation of

transcription factor nuclear factor kappaB. J Med Chem 2006, 49: 7182-9.

[94] Roberti M, Pizzirani D, Simoni D, Rondanin R, Baruchello R, Bonora C, et al. Synthesis and biological evaluation of resveratrol and analogues as apoptosis-inducing agents. J Med Chem 2003;46:3546-54.

[95] Murias M, Jager W, Handler N, Erker T, Horvath Z, Szekeres T, et al.

Antioxidant prooxidant and cytotoxic activity of hydroxylated resveratrol analogues:

structure-activity relationship. Biochem Pharmacol 2005; 69: 903-12.

[96] Suh N, Paul S, Hao XP, Simi B, Xiao H, Rimando AM, et al. Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats. Clin Cancer Res 2007;13:350-5.

Figure legend

Fig. 1. Structures of resveratrol (I) and resveratrol analogues discussed in the text, cis-3,4',5-trimethoxy-3'-aminostilbene (II), cis-3,4',5- trimethoxy-3'-hydroxystilbene (III), 3,3',4',5-tetrahydroxystilbene (IV) and pterostilbene (V).