

Resveratrol in prostate diseases – a short review

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Introduction. Resveratrol is a plant-derived polyphenol suggested to have many beneficial health effects, including antioxidant, anti-inflammatory, anti-proliferative, proapoptotic, and anti-angiogenic. It is even speculated that uptake of resveratrol by red wine consumption could be behind the so-called French paradox the lower incidence of cardiovascular diseases in the French population. These properties, together with good absorption and tolerance, would make it an attractive agent in prostatic diseases, especially in cancer prevention and treatment.

Material and methods. MEDLINE search (keywords “prostate res- veratrol”) resulted in 39 research papers published since 2007. It has been shown that resveratrol down-regulate androgen receptor expression, inhibit proliferation, and promote apoptosis in prostate cancer cell lines and enhance their sensitivity to ionizing radiation. Several studies on animal prostate cancer development also suggest that resveratrol is able do delay or prevent carcinogenesis in prostate. Despite these promising results, there is no proof of any therapeutic properties of resveratrol in prostate diseases from human clinical trials nor any information about ongoing trials in this field.

Conclusions. Resveratrol is produced and sold as a nutritional supplement, there is not enough clinical evidence to justify a recommendation for the administration of resveratrol in humans at present.

Key Words: resveratrol ◊ prostate ◊ cancer

INTRODUCTION

Resveratrol (trans-3, 4', 5-trihydroxystilbene, $C_{14}H_{12}O_3$) is a plant-derived polyphenolic phytoalexin produced in response to environmental stress such as vicissitudes in climate, exposure to ozone, sunlight and heavy metals, and infection by pathogenic microorganisms. Resveratrol exists in both cis- and trans- stereoisomeric forms, the predominant trans- isomer is the biologically active one [1, 2, 3]. Exposure to heat and ultraviolet radiation can cause trans-resveratrol to isomerize to the cis-resveratrol. It is primarily found in the skin of grapes as well as in other fruits and plants, such as raspberries, blueberries, mulberries, Scots pine, Eastern white pine, and knotweed [1, 4].

It is speculated that uptake of resveratrol by red wine consumption could be behind the so-called French

paradox – whereby the French population, in spite of a rather fatty diet, has a lower incidence of cardiovascular disease [1]. Resveratrol is also produced by chemical and biotechnological synthesis and sold as a nutritional supplement. It is well absorbed upon oral ingestion and metabolized to sulfate and glucuronate [1, 2].

Resveratrol has been reported do have a wide range of effects beneficial for health, including cardioprotective, neuroprotective, and immunomodulatory function as well as improving insulin sensitivity, but in relation to prostatic diseases, the following ones are the most interesting: anticancer – resveratrol has been reported to have antiproliferative and proapoptotic effects on prostate cancer cell lines LNCaP, DU-145, and PC-3; it also potentiates the effect of ionizing radiation and chemotherapeutic agents; potential chemopreventive properties; anti-inflammatory and antioxidant functions, which may

be useful in treatment of prostate inflammation; and also play a role in chemoprevention, as a positive correlation between prostatitis and prostate cancer risk has been reported [5, 6].

Prostate cancer (PCa), being one of the most common malignancies and a major cause of cancer-related death in men, is a considerable health problem, especially in ageing populations, since it is typically diagnosed in men over the age of 50 [6, 7]. All these, together with its long latency, make PCa an attractive target for chemopreventive interventions [4, 6]. There is also a considerable amount of epidemiological data suggesting that certain nutritional factors may influence PCa occurrence [6, 8]. Consequently, several PCa risk reduction studies were conducted, but only in two of them – PCPT (finasteride) and REDUCE (dutasteride) – a reduction of PCa incidence was observed. The most important endpoint – the reduction of mortality, however, was not reached in either of them [9]. This may be partially due to the slow natural course of the disease, which would require an ideal observation period of around 20 years. In this paper, recently published research articles on the application of resveratrol in prostate diseases have been reviewed in order to shed light on the evidence justifying its application in prevention and treatment of prostate diseases.

Mechanism of action

Resveratrol induces a broad range of effects on cell phenotype. Numerous studies have reported resveratrol to cause cell growth inhibition, modulation of cell cycle, induction of apoptosis in many different cell lines, including PCa ones [2, 10–45], and induction of differentiation in certain cell types [27, 46–49]. All these are important in cancer treatment and are exerted by modulating a complex range of cellular processes, including: receptor function, transduction pathways, and transcription factor activity. The detailed description of all the documented resveratrol mechanisms of action would exceed this paper.

Apart from these, resveratrol has been reported to exhibit other properties that may be useful in cancer treatment: inhibition of tumor invasion and angiogenesis as well as increase of radiosensitivity and chemosensitivity.

The expression of matrix metalloproteases (MMPs) correlates with tumor invasion and metastasis, which make them attractive pharmaceutical targets in cancer treatment [50]. Resveratrol reduced the expression of MMP–2 and MMP–9 in certain cell lines [51–55] and decreased the level of vascular epithelial growth factor (VEGF), a protein crucial for angiogenesis and maintaining tumor growth, thus inhibiting

angiogenesis [56–60].

Another interesting property of resveratrol is its ability to increase prostate cancer cell lines sensitivity to ionizing radiation, which has a potential for clinical application in combination with radiotherapy – an important treatment in PCa [17, 19, 20, 43].

Resveratrol has also been shown to sensitize human cancer cell lines, including prostate carcinoma, to such chemotherapeutic agents as doxorubicin, cytarabine, actinomycin D, taxol, and methotrexate by down-regulating survivin expression and increasing apoptosis [61]. Inflammation has been proven to be a significant factor in the initiation/progression stages of cancer development by inducing oxidative damage and promoting cell growth [62, 63]. Cyclooxygenase–2 (COX–2) catalyzes the conversion of free arachidonic acid to prostaglandins, which can stimulate cell proliferation, promote angiogenesis, and suppress apoptosis all of which promote malignancy [64–66]. Resveratrol expresses anti-inflammatory activity by directly inhibiting COX–2 activity and suppressing NF κ B by up-regulating MKP5 [44, 67].

Review of current studies

Resveratrol and its mechanisms of action have been intensively investigated and a large amount of evidence suggesting that it may be a promising molecule in both PCa treatment and prevention has been collected. MEDLINE search (keywords “prostate resveratrol”) resulted in 39 research papers published since 2007 – the results of which are presented in Table 1. Surprisingly, a considerable number of *in vitro* and a few animal model experiments have been performed, with lack of human clinical trials. There are currently no published demonstrations of therapeutic or protective effects of resveratrol in appropriately designed clinical trials [64]. Web page <http://www.clinicaltrials.org> reported five ongoing trials of resveratrol in cancer, but none in prostate disease. The results of several resveratrol pharmacokinetics and metabolism studies in humans, however, have already been published and despite good absorption upon oral administration, poor bioavailability of unchanged resveratrol indicates that it would be difficult to achieve concentrations proven to be effective in *in vitro* studies [68, 69]. Additionally, a study by Klink et al., indicates that resveratrol may actually worsen the survival in certain prostate cancer xenograft models [70].

Among 38 research papers on resveratrol in prostate diseases published between 2007 and 2012, 35 were performed on cell lines and nine on *in vivo* models (five transgenic models of PCa development and five PCa xenografts). Seven studies concentrated on the

Table 1. Studies on resveratrol in prostate diseases published in years 2007–2012

Ref. no.	Model used	Observed effects and mechanism
72	SV-40 Tag rats	suppressed prostate cancer development
73	TRAMP mice	suppressed tumor growth in vivo
12	PC-3, TRAMP-C2 cell lines TRAMP mice	reduced cell proliferation; reduced prostate cancer in vivo; inhibits Hedgehog signaling
13	PTEN-CaP8 cell line prostate-specific PTEN-KO mice	reduces cell proliferation, induces apoptosis; decreased prostatic adenocarcinoma in vivo
14	COS7, LNCaP cell lines TRAP rats	induces apoptosis through androgen receptor down-regulation; suppressed tumor growth in vivo
70	mouse xenograft model of prostate cancer (LNCaP and LAPC-4)	worsens survival with LAPC-4 tumors, no difference with LNCaP tumours
71	mouse xenograft model of prostate cancer	inhibited tumor growth, metastasis and angiogenesis
15	LNCaP cell line mouse xenograft model of prostate cancer	reduces cell proliferation <i>in vitro</i> ; delayed tumor growth in vivo
16	PC-3M-MM2 cell line mouse xenograft model of prostate cancer	reduced cell viability, migration and invasiveness inhibited the tumor growth, decreased the incidence and number of metastases
17	LAPC4, CWR22, LNCaP, PC-3, DU-145 cell lines mouse xenograft model of prostate cancer	reduces cell proliferation <i>in vitro</i> ; no effect observed in vivo
18	PC-3 cell line	enhanced irradiation-induced apoptosis
19	PC-3, DU-145 cell lines	enhanced irradiation-induced apoptosis by up-regulation of the expression of perforin and granzyme B
20	PC-3, 22RV1, PNT1A cell lines	enhanced irradiation-induced apoptosis, arrests cell cycle
21	DU-145 cell line	enhanced irradiation-induced apoptosis
22	LNCaP cell line	inhibits the function of the androgen receptor
23	LNCaP cell line	inhibition of androgen-promoted growth, inhibition of androgen receptor transcriptional activity, effect synergistic with flutamide
24	LNCaP cell line	inhibition of androgen receptor transcriptional activity
25	LNCaP, PC-3 cell lines	decreased the post-translational androgen receptor level
26	LNCaP, PC-3 cell lines	decreased androgen receptor and estrogen receptor alpha protein levels
27	C4-2, LNCaP cell lines	stimulates PTEN expression through androgen receptor inhibition, inhibits EGFR phosphorylation decreasing AKT phosphorylation
28	LNCaP cell line	reduces cell proliferation, induces apoptosis; inhibited the phosphorylation of PI3K, AKT and mTOR
29	LNCaP cell line	induced cell cycle arrest and apoptosis
30	LNCaP cell line	reduces cell proliferation, induces apoptosis; sensitized cells to TRAIL
31	LNCaP, DU-145 cell lines	down-regulated oncogenic microRNAs and up-regulated tumor suppressor microRNAs
32	LNCaP, DU-145 cell lines	induces apoptosis; restores p53-signaling pathways
33	LNCaP, PC-3 cell lines	reduces cell proliferation, induces apoptosis; inhibits NFkB specific binding to DNA
34	LNCaP, PC-3, DU-145 cell lines	induces apoptosis, SOCS-3 reduced apoptosis in resveratrol-treated cells
35	LAPC4, LNCaP, PC-3, DU-145 cell lines	anti-inflammatory activity by up-regulation of MKP5
36	PZ-HPV-7, LNCaP, PC-3 cell lines	induced cell cycle arrest, reduced cell proliferation
37	C4-2, LNCaP cell lines	induces apoptosis
38	PC-3 cell line	inhibition of cell proliferation, down-regulation of expression of CAV1, IGF2, NR2F1, and PLAU genes, suppressed secretion of the urokinase plasminogen activator
2	PC-3, DU-145 cell lines	reduces cell proliferation; trans- isoform more active than cis-
39	PC-3, DU-145 cell lines	sensitized cells to TRAIL, Fas, TNFalpha
40	PC-3, DU-145 cell lines	down-regulated the expression of Bcl-2, Bcl-X(L) and survivin and upregulated the expression of Bax, Bak, PUMA, Noxa, Bim, TRAIL-R1/DR4 and TRAIL-R2/DR5
41	C4-2B, PC-3, DU-145, LNCaP, RWPE-1 cell lines	reduces cell proliferation; modulation of SIRT1/S6K signaling
42	22Rv1, PC-3, DU-145 cell lines	synergistic with AdΔΔ adenovirus, increases apoptosis
43	CWR22Rv1 cell line	reduced cell proliferation
44	RWPE-1, WPE1-NA22, WPE1-NB14, WPE1-NB26 cell lines	induced cell cycle arrest
45	ALVA-41, PC-3 cell lines	reduces cell proliferation, induces apoptosis; synergy with casein kinase 2 inhibition

role of androgen receptor and four on enhancement of radiosensitivity (Table 1). A short characteristic of PCa cell lines most commonly used in experiments listed in Table 1 – their androgen sensitivity, p53 and PTEN (proteins important in mechanism of action of resveratrol in PCa cells) are presented in Table 2. TRAMP, TRAP, and SV-40 Tag are transgenic animal models of PCa development – animals programmed to develop prostate cancer – were used to assess potential chemopreventive properties of resveratrol.

CONCLUSIONS

The anti-cancer potential of resveratrol has been well documented in many *in vitro* and *in vivo* studies. Down-regulation of androgen receptor and synergy with flutamide, as well as enhancement of radiosensitivity are the most interesting properties in treatment of prostate cancer. Resveratrol has displayed a potential as prostate

Table 2. A short characteristic of PCa cell lines

Cell line	androgen sensitivity	p53	PTEN
PC-3	AR-negative	mutant	mutant
DU-145	AR-negative	mutant	wild-type
C4-2B	androgen independent	wild-type	mutant
LNCaP	broad steroid specificity	wild-type	mutant
LAPC-4	wild-type	mutant	wild-type
CWR22rv1	androgen independent	mutant	wild-type

cancer chemoprevention in both *in vitro* and animal model studies.

Resveratrol is well-tolerated, but an optimal dose has not yet been determined.

There are no results from human clinical trials on therapeutic effects of resveratrol in prostate diseases. Despite promising results from many studies, published evidence is not strong enough to justify chronic administration of resveratrol to humans.

References

- Catalgol B, Batirel S, Taga Y, Ozer NK. Resveratrol: French paradox revisited. *Front Pharmacol.* 2012; 3: 141.
- [No authors listed] Resveratrol. *Monograph. Altern Med Rev.* 2010; 15: 152–158.
- Anisimova NY, Kiselevsky MV, Sosnov AV, Sadovnikov SV, Stankov IN, Gakh AA. Trans-, cis- and dihydro-resveratrol: a comparative study. *Chem Cent J.* 2011; 5: 88.
- Van Poppel H, Tombal B. Chemoprevention of prostate cancer with nutrients and supplements. *Cancer Manag Res.* 2011; 3: 91–100.
- Athar M, Back JH, Kopelovich L, Bickers DR, Kim AL. Multiple molecular targets of resveratrol: Anti-carcinogenic mechanisms. *Arch Biochem Biophys.* 2009; 486: 95–102.
- Cimino S, Sortino G, Favilla V, Castelli T, Madonia M, Sansalone S, et al. Polyphenols: key issues involved in chemoprevention of prostate cancer. *Oxid Med Cell Longev.* 2012; 2012: 632–959.
- Siegel R, Ward E, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; 61: 212–236.
- Szliszka E, Bronikowska J, Czuba ZP, Krol W. Isoflavones augment the effect of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on prostate cancer cells. *Centr Eur J Urol.* 2010; 63: 182–186.
- Pinsky PF, Black A, Grubb R, Crawford ED, Andriole G, Thompson I, Parnes H. Projecting prostate cancer mortality in the PCPT and REDUCE chemoprevention trials. *Cancer.* 2013; 119: 593–601.
- Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada RY. Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. *Anticancer Res* 2004; 24: 2783–2840.
- Pezzuto JM. In Aggarwal BB, Shishodia S, eds. *Resveratrol as an Inhibitor of Carcinogenesis.* Boca Raton, London, New York: Resveratrol in Health and Disease CRC Press Edited by Taylor and Francis, 2006; pp. 233–384.
- Slusarz A, Shenouda NS, Sakla MS, Drenkhahn SK, Narula AS, MacDonald RS, Besch-Williford CL, Lubahn DB. Common botanical compounds inhibit the hedgehog signaling pathway in prostate cancer. *Cancer Res.* 2010; 70: 3382–3390.
- Narayanan NK, Nargi D, Randolph C, Narayanan BA. Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer incidence in PTEN knockout mice. *Int J Cancer.* 2009; 125: 1–8.
- Seeni A, Takahashi S, Takeshita K, Tang M, Sugiura S, Sato SY, Shirai T. Suppression of prostate cancer growth by resveratrol in the transgenic rat for adenocarcinoma of prostate (TRAP) model. *Asian Pac J Cancer Prev.* 2008; 9: 7–14.
- Wang TT, Hudson TS, Wang TC, Remsberg CM, Davies NM, Takahashi Y, et al. Differential effects of resveratrol on androgen-responsive LNCaP human prostate cancer cells *in vitro* and *in vivo*. *Carcinogenesis.* 2008; 29: 2001–2010.
- Sheth S, Jajoo S, Kaur T, Mukherjea D, Sheehan K, Rybak LP, Ramkumar V. Resveratrol Reduces Prostate Cancer Growth and Metastasis by Inhibiting the Akt/MicroRNA-21 Pathway. *PLoS One.* 2012; 7: e51655.
- Osmond GW, Masko EM, Tyler DS, Freedland SJ, Pizzo S. *In vitro* and *in vivo* evaluation of resveratrol and 3,5-dihydroxy-4'-acetoxy-trans-stilbene in the treatment of human prostate carcinoma and melanoma. *J Surg Res.* 2013; 179: e141–148.
- Fang Y, DeMarco VG, Nicholl MB. Resveratrol enhances radiation sensitivity in prostate cancer by inhibiting cell proliferation and promoting cell senescence and apoptosis. *Cancer Sci.* 2011; 103: 1090–1098.
- Fang Y, Herrick EJ, Nicholl MB. A possible role for perforin and granzyme B in resveratrol-enhanced radiosensitivity of prostate cancer. *J Androl.* 2012; 33: 752–760.
- Rashid A, Liu C, Sanli T, Tsiani E, Singh G, Bristow RG, et al. Resveratrol enhances

- prostate cancer cell response to ionizing radiation. Modulation of the AMPK, Akt and mTOR pathways. *Radiat Oncol.* 2011; 6: 144.
21. Scarlatti F, Sala G, Ricci C, Maioli C, Milani F, Minella M, et al. Resveratrol sensitization of DU145 prostate cancer cells to ionizing radiation is associated to ceramide increase. *Cancer Lett.* 2007; 8: 124–130.
 22. Iguchi K, Toyama T, Ito T, Shakui T, Usui S, Oyama M, Iinuma M, Hirano K. Antiandrogenic Activity of Resveratrol Analogs in Prostate Cancer LNCaP Cells. *J Androl.* 2012; 33: 1208–1215.
 23. Kai L, Levenson AS. Combination of resveratrol and antiandrogen flutamide has synergistic effect on androgen receptor inhibition in prostate cancer cells. *Anticancer Res.* 2011; 31: 3323–3330.
 24. Shi WF, Leong M, Cho E, Farrell J, Chen HC, Tian J, Zhang D. Repressive effects of resveratrol on androgen receptor transcriptional activity. *PLoS One.* 2009; 4: e7398.
 25. Harada N, Murata Y, Yamaji R, Miura T, Inui H, Nakano Y. Resveratrol down-regulates the androgen receptor at the post-translational level in prostate cancer cells. *J Nutr Sci Vitaminol (Tokyo).* 2007; 53: 556–560.
 26. Benitez DA, Pozo-Guisado E, Clementi M, Castellón E, Fernández-Salguero PM. Non-genomic action of resveratrol on androgen and oestrogen receptors in prostate cancer: modulation of the phosphoinositide 3-kinase pathway. *Br J Cancer.* 2007; 96: 1595–1604.
 27. Wang Y, Romigh T, He X, Orloff MS, Silverman RH, Heston WD, Eng C. Resveratrol regulates the PTEN/AKT pathway through androgen receptor-dependent and -independent mechanisms in prostate cancer cell lines. *Hum Mol Genet.* 2010; 19: 4319–4329.
 28. Chen Q, Ganapathy S, Singh KP, Shankar S, Srivastava RK. Resveratrol induces growth arrest and apoptosis through activation of FOXO transcription factors in prostate cancer cells. *PLoS One.* 2010; 5: e15288.
 29. Wang TT, Schoene NW, Kim YS, Mizuno CS, Rimando AM. Differential effects of resveratrol and its naturally occurring methylether analogs on cell cycle and apoptosis in human androgen-responsive LNCaP cancer cells. *Mol Nutr Food Res.* 2010; 54: 335–344.
 30. Shankar S, Chen Q, Siddiqui I, Sarva K, Srivastava RK. Sensitization of TRAIL-resistant LNCaP cells by resveratrol (3, 4', 5 tri-hydroxystilbene): molecular mechanisms and therapeutic potential. *J Mol Signal.* 2007; 2: 7.
 31. Dhar S, Hicks C, Levenson AS. Resveratrol and prostate cancer: promising role for microRNAs. *Mol Nutr Food Res.* 2011; 8: 1219–1229.
 32. Kai L, Samuel SK, Levenson AS. Resveratrol enhances p53 acetylation and apoptosis in prostate cancer by inhibiting MTA1/NuRD complex. *Int J Cancer.* 2010; 126: 1538–1548.
 33. Benitez DA, Hermoso MA, Pozo-Guisado E, Fernández-Salguero PM, Castellón EA. Regulation of cell survival by resveratrol involves inhibition of NF kappa B-regulated gene expression in prostate cancer cells. *Prostate.* 2009; 69: 1045–1054.
 34. Horndasch M, Culig Z. SOCS-3 antagonizes pro-apoptotic effects of TRAIL and resveratrol in prostate cancer cells. *Prostate.* 2011; 71: 1357–1366.
 35. Nonn L, Duong D, Peehl DM. Chemopreventive anti-inflammatory activities of curcumin and other phytochemicals mediated by MAP kinase phosphatase-5 in prostate cells. *Carcinogenesis.* 2007; 28: 1188–1196.
 36. Benitez DA, Pozo-Guisado E, Alvarez-Barrientos A, Fernandez-Salguero PM, Castellón EA. Mechanisms involved in resveratrol-induced apoptosis and cell cycle arrest in prostate cancer-derived cell lines. *J Androl.* 2007; 28: 282–293.
 37. Freeman MR, Kim J, Lisanti MP, Di Vizio D. A metabolic perturbation by U0126 identifies a role for glutamine in resveratrol-induced cell death. *Cancer Biol Ther.* 2011; 12: 966–977.
 38. Jiang J, Eliaz I, Sliva D. Suppression of growth and invasive behavior of human prostate cancer cells by ProstaCaid™: mechanism of activity. *Int J Oncol.* 2011; 38: 1675–1682.
 39. Gill C, Walsh SE, Morrissey C, Fitzpatrick JM, Watson RW. Resveratrol sensitizes androgen independent prostate cancer cells to death-receptor mediated apoptosis through multiple mechanisms. *Prostate.* 2007; 67: 1641–1653.
 40. Shankar S, Siddiqui I, Srivastava RK. Molecular mechanisms of resveratrol (3,4,5-trihydroxy-trans-stilbene) and its interaction with TNF-related apoptosis inducing ligand (TRAIL) in androgen-insensitive prostate cancer cells. *Mol Cell Biochem.* 2007; 304: 273–285.
 41. Li G, Rivas P, Bedolla R, Thapa D, Reddick RL, Ghosh R, Kumar AP. Dietary Resveratrol Prevents Development of High-Grade Prostatic Intraepithelial Neoplastic Lesions: Involvement of SIRT1/S6K Axis. *Cancer Prev Res (Phila).* 2013; 6: 27–39.
 42. Adam V, Ekblad M, Sweeney K, Müller H, Busch KH, Johnsen CT, et al. Synergistic and Selective Cancer Cell Killing Mediated by the Oncolytic Adenoviral Mutant AdΔΔ and Dietary Phytochemicals in Prostate Cancer Models. *Hum Gene Ther.* 2012; 23: 1003–1015.
 43. Hsieh TC. Antiproliferative effects of resveratrol and the mediating role of resveratrol targeting protein NQO2 in androgen receptor-positive, hormone-non-responsive CWR22Rv1 cells. *Anticancer Res.* 2009; 29: 3011–3017.
 44. Hudson TS, Hartle DK, Hursting SD, Nunez NP, Wang TT, Young HA, et al. Inhibition of prostate cancer growth by muscadine grape skin extract and resveratrol through distinct mechanisms. *Cancer Res.* 2007; 67: 8396–8405.
 45. Ahmad KA, Harris NH, Johnson AD, Lindvall HC, Wang G, Ahmed K. Protein kinase CK2 modulates apoptosis induced by resveratrol and epigallocatechin-3-gallate in prostate cancer cells. *Mol Cancer Ther.* 2007; 6: 1006–1012.
 46. Wang Q, Li H, Wang XW, Wu DC, Chen XY, Liu J. Resveratrol promotes differentiation and induces Fas independent apoptosis of human medulloblastoma cells. *Neurosci Lett.* 2003; 351: 83–86.
 47. Gehm BD, McAndrews JM, Chien PY, Jameson JL. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. *Proc Natl Acad Sci USA.* 1997; 94: 14138–14143.
 48. Turner RT, Evans GL, Zhang M, Maran A, Sibonga JD. Is resveratrol an estrogen agonist in growing rats? *Endocrinology.* 1999; 140: 50–54.
 49. Della Ragione F, Cucciolla V, Borriello A, Della Pietra V, Racioppi L, Soldati G, et al. Resveratrol arrests the cell division cycle at S/G2 phase transition. *Biochem Biophys Res Commun.* 1998; 250: 53–58.
 50. Chambers AF, Matrisian LM. Changing views of the role of matrix metalloproteinases in metastasis. *J Natl Cancer Inst.* 1997; 89: 1260–1270.
 51. Cao Y, Fu ZD, Wang F, Liu HY, Han R. Anti-angiogenic activity of resveratrol, a natural compound from medicinal plants. *J Asian Nat Prod Res.* 2005; 7: 205–213.
 52. Igura K, Ohta T, Kuroda Y, Kaji K. Resveratrol and quercetin inhibit angiogenesis in vitro. *Cancer Letters.* 2001; 171: 11–16.

53. Sun CY, Hu Y, Guo T, Wang HF, Zhang XP, He WJ, Tan H. Resveratrol as a novel agent for treatment of multiple myeloma with matrix metalloproteinase inhibitory activity. *Acta Pharmacologica Sinica*. 2006; 27: 1447–1452.
54. Banerjee S, Bueso-Ramos C, Aggarwal BB. Suppression of 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in rats by resveratrol: role of nuclear factor- κ B, cyclooxygenase 2, and matrix metalloproteinase 9. *Cancer Res*. 2002; 62: 4945–4954.
55. Li YT, Shen F, Liu BH, Cheng GF. Resveratrol inhibits matrix metalloproteinase-9 transcription in U937 cells. *Acta Pharmacol Sin*. 2003; 24: 1167–1171.
56. Garvin S, Ollinger K, Dabrosin C. Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts in vivo. *Cancer Lett*. 2006; 231: 113–122.
57. Zhang Q, Tang X, Lu QY, Zhang ZF, Brown J, Le AD. Resveratrol inhibits hypoxia-induced accumulation of hypoxia-inducible factor-1 α and VEGF expression in human tongue squamous cell carcinoma and hepatoma cells. *Mol Cancer Ther*. 2005; 4: 1465–1474.
58. Cao Z, Fang J, Xia C, Shi X, Jiang BH. trans-3,4,5'-Trihydroxystibene inhibits hypoxia-inducible factor 1 α and vascular endothelial growth factor expression in human ovarian cancer cells. *Clin Cancer Res*. 2004; 10: 5253–5263.
59. Nawroth R, Poell G, Ranft A, Kloop S, Samulowitz U, Fachinger G, et al. VE-PTP and VE-cadherin ectodomains interact to facilitate regulation of phosphorylation and cell contacts. *EMBO J*. 2002; 21: 4885–4895.
60. Lin MT, Yen ML, Lin CY, Kuo ML. Inhibition of vascular endothelial growth factor-induced angiogenesis by resveratrol through interruption of Src-dependent vascular endothelial cadherin tyrosine phosphorylation. *Mol Pharmacol*. 2003; 64: 1029–1036.
61. Gupta SC, Kannappan R, Reuter S, Kim JH, Aggarwal BB. Chemosensitization of tumors by resveratrol. *Ann N Y Acad Sci*. 2011; 1215: 150–160.
62. Goldstraw MA, Fitzpatrick JM, Kirby RS. What is the role of inflammation in the pathogenesis of prostate cancer? *BJU Int*. 2007; 99: 966–968.
63. Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. *J Urol*. 2004; 172 (5 Pt 2): S6–11.
64. de la Lastra CA, Villegas I. Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications. *Mol Nutr Food Res*. 2005; 49: 405–430.
65. Tsujii M, DuBois RN. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. *Cell*. 1995; 83: 493–501.
66. Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. *Cell*. 1998; 93: 705–716.
67. Bishayee A, Dhir N. Resveratrol-mediated chemoprevention of diethylnitrosamine-initiated hepatocarcinogenesis: inhibition of cell proliferation and induction of apoptosis. *Chem Biol Interact*. 2009; 179: 131–144.
68. Patel KR, Scott E, Brown VA, Gescher AJ, Steward WP, Brown K. Clinical trials of resveratrol. *Ann N Y Acad Sci*. 2011; 1215: 161–169.
69. Vang O, Ahmad N, Baile CA, Baur JA, Brown K, Csiszar A, et al. What is new for an old molecule? Systematic review and recommendations on the use of resveratrol. *PLoS One*. 2011; 6: e19881.
70. Klink JC, Tewari AK, Masko EM, Antonelli J, Febbo PG, Cohen P, et al. Resveratrol worsens survival in SCID mice with prostate cancer xenografts in a cell-line specific manner, through paradoxical effects on oncogenic pathways. *Prostate*. 2013; 73: 754–762.
71. Ganapathy S, Chen Q, Singh KP, Shankar S, Srivastava RK. Resveratrol enhances antitumor activity of TRAIL in prostate cancer xenografts through activation of FOXO transcription factor. *PLoS One*. 2010; 285: e15627.
72. Harper CE, Cook LM, Patel BB, Wang J, Eltoun IA, Arabshahi A, Shirai T, Lamartiniere CA. Genistein and resveratrol, alone and in combination, suppress prostate cancer in SV-40 tag rats. *Prostate*. 2009; 69: 1668–1682.
73. Harper CE, Patel BB, Wang J, Arabshahi A, Eltoun IA, Lamartiniere CA. Resveratrol suppresses prostate cancer progression in transgenic mice. *Carcinogenesis*. 2007; 28: 1946–1953. ■