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Resveratrol and cellular mechanisms of cancer prevention

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The use of novel and improved chemopreventive and chemotherapeutic agents for the prevention and treatment of cancer is on the rise. Natural products have always afforded a rich source of such agents. Epidemiological evidence suggests that a higher flavonoid intake is associated with low cancer risk. Accumulating data clearly indicate that the induction of apoptosis is an important component in the chemoprevention of cancer by naturally occurring dietary agents. Resveratrol, a naturally occurring polyphenol, demonstrates pleiotropic health benefits, including antioxidant, anti-inflammatory, antiaging, cardioprotective, and neuroprotective activities. Because of these properties and their wide distribution throughout the plant kingdom, resveratrol is envisioned as a potential chemopreventive/curative agent. Currently, a number of preclinical findings from our lab and elsewhere suggest resveratrol to be a promising natural weapon in the war against cancer. Remarkable progress in elucidating the molecular mechanisms underlying the anticancer properties of resveratrol has been achieved. Here, we focus on some of the myriad pathways that resveratrol targets to exert its chemopreventive role and advocate that resveratrol holds tremendous potential as an efficient anticancer drug of the future.

Keywords: resveratrol; cancer; apoptosis; miRNA; CD95; Wnt

Introduction

Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) is a dietary polyphenol derived from grapes, berries, peanuts, and other plant sources. During the last decade resveratrol has been shown to possess a fascinating wide spectrum of pharmacologic properties. Multiple biochemical and molecular actions seem to contribute to its effects against precancerous or cancer cells. Resveratrol affects all three discrete stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis, and hence is considered by some to be a promising anticancer therapy.[3] The anticancer property of resveratrol has been supported by studies indicating that it inhibits proliferation of a wide variety of human tumor cells *in vitro*; these data have led to numerous preclinical animal studies to evaluate the potential of resveratrol for cancer chemoprevention and chemotherapy. The polyphenolic phytoalexin and its analogues have attracted attention of researchers over the past couple of decades because of a number of reports highlighting its benefits *in vitro* and *in vivo* in a variety of human disease models, including cardio- and neuroprotection, immune regulation, and cancer chemoprevention.

Since its discovery resveratrol has been shown to exhibit a plethora of physiological properties that could be useful in human medicine. Even greater interest in resveratrol developed at the beginning of the 1990s, when it was first reported to be in red wine.[4] Resveratrol is present in many plants and fruits, including red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts, red wine, and grape skins.

The use of complementary and alternative medicine (CAM) is increasing rapidly in developed countries and is evident in the use of traditional medicines in various Asian countries, for example the Indian system of medicine called

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Ayurveda. Many plant products are in use as herbal medicines, as food supplements, or as spices in Indian cooking. Some of them have been studied in various experimental models of cancer and have been shown inhibit cell proliferation. Cancer patients are especially interested in exploring the use of CAM because of the high risk of mortality and long-term morbidity associated with surgical procedures of cancer management and high side effects of chemotherapy. Cancer is the second leading cause of death after cardiovascular disorders, and research shows that the chances of developing cancer can be reduced by lifestyle changes and dietary habits. People worldwide use dietary vegetables, medicinal herbs, and plant extracts to prevent or treat cancer.[5]

Cancer cells are known to have alterations in multiple cellular signaling pathways, and because of complexities in communication between multiple signaling networks, the treatment and the cure for most human malignancies remain challenging.[6] Because no set paradigm for the treatment of a particular malignancy can be easily designed due to species response variation, varying lifestyle, and dietary habits, research on such differences and responses is still underway. Nevertheless, in general, epidemiological data suggest that the consumption of fruits and vegetables is associated with reduced risk of several types of cancer.[7] Nutritional supplements, some based on chemicals found in fruits and vegetables, are currently being investigated for their use in preventing, inhibiting, and reversing the progression of cancer. There is also growing evidence for the use of natural products as adjunctive therapy alongside conventional cancer treatments.

Background

In 1997, Jang *et al*. first reported that topical resveratrol applications prevented skin cancer development in mice treated with a carcinogen.[8] There have since been dozens of studies of the anticancer activity of resveratrol in animal models.[9] However, no results of human clinical trials for cancer have been reported.[10] Clinical trials to investigate the effects of resveratrol on colon cancer and melanoma are currently recruiting patients.

In vitro data have shown that resveratrol interacts with multiple molecular targets and damaged cells of breast, skin, gastric, colon, esophageal, prostate, and pancreatic cancer, as well as leukemia.[9] However, the study of pharmacokinetics of resveratrol in humans concluded that even high doses of resveratrol might be insufficient to achieve resveratrol concentrations *in vivo* required for the systemic prevention of cancer.[11] This is consistent with the results from animal cancer models, which indicate that the *in vivo* effectiveness of resveratrol is limited by its poor systemic bioavailability.[10,12,13] The strongest evidence of anticancer action of resveratrol exists for tumors it can come into direct contact with, such as skin and gastrointestinal tract tumors. For other cancers, the evidence is uncertain, even if massive doses of resveratrol are used.[10]

Topical application of resveratrol in mice, both before and after the UVB exposure, inhibited skin damage and decreased skin cancer incidence; however, oral resveratrol was ineffective in treating mice inoculated with melanoma cells.[10] Resveratrol given orally also had no effect on leukemia and lung cancer;[10,14] however, injected intraperitoneally, 2.5 or 10 mg/kg of resveratrol slowed the growth of metastatic Lewis lung carcinomas in mice.[10,15] Resveratrol (1 mg/kg orally) reduced the number and size of the esophageal tumors in rats treated with a carcinogen.[16] In several studies, small doses (0.02–8 mg/kg) of resveratrol, given prophylactically, reduced or prevented the development of intestinal and colon tumors in rats given different carcinogens.[10]

Resveratrol treatment appeared to prevent the development of mammary tumors in animal models; however, it had no effect on the growth of existing tumors. Paradoxically, treatment of prepubertal mice with high doses of resveratrol enhanced formation of tumors. Yet, injected in high doses into mice, resveratrol slowed the growth of neuroblastomas.[10]

By regulating multiple important cellular signaling pathways, including NF-κB, Akt, MAPK, Wnt, etc., some natural products can activate cell death signals and induce apoptosis in precancerous or cancer cells without adversely modulating the activity of normal cells. Therefore, nontoxic "natural agents" harvested from the bounties of nature could be useful either alone or in combination with conventional therapeutics for the prevention of tumor progression and/or treatment of human malignancies.

A major challenge is to understand the biological processes and molecular pathways by which resveratrol induces beneficial effects. Below we will

summarize some of the studies on resveratrol's affects on key signaling pathways.

CD95 signaling pathway

The Fas receptor (FasR) is a death receptor on the surface of cells that leads to programmed cell death (PCD; also called apoptosis); it is one of two apoptosis pathways, the other being the mitochondrial pathway. FasR is also known as CD95, Apo-1, and tumor necrosis factor receptor superfamily member 6 (TNFRSf6). FasR is located on chromosome 10 in humans and 19 in mice. Similar sequences related by evolution (orthologs) are found in most mammals. Fas forms the death-inducing signaling complex (DISC) upon ligand binding. Membrane-anchored Fas ligand trimer on the surface of an adjacent cell causes trimerization of Fas receptor.[17] This event is also mimicked by binding of agonistic Fas antibody, though some evidence suggests that the apoptotic signal induced by the antibody is unreliable in the study of Fas signaling.

Resveratrol, like other anticancer drugs, induces tumor cell death by targeting pathways through modulating the levels of Fas and FasL.[10–13,18] A recent study on resveratrol-induced apoptosis in multiple myeloma and T cell leukemia cells highlighted the role of recruitment of Fas/CD95 signaling in lipid rafts in antimyeloma and antileukemia chemotherapy through coclustering of Fas/CD95 death receptor and lipid rafts, whereas normal lymphocytes were spared.[10] Earlier reports have also documented this effect in leukemia cell lines,[11,12] colon,[13] and breast carcinoma cells.[18]

Apoptotic pathway

Apoptosis is the process of PCD that occurs in multicellular organisms. Biochemical events lead to characteristic cell changes and death; these changes include blebbing, loss of cell membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. Apoptosis may be mediated by either death receptors or signals arising from within the cell, that is, by a mitochondrial mechanism or by generation of reactive oxygen species.[3]

Data amassed from several laboratories point to the fact that resveratrol exerts its antiproliferative effect by targeting members of the apoptotic family in cancers of various tissues, such as prostate, breast, colon, brain, endometrium, blood, rectum, pancreas, skin, lung, liver, ovary, and bladder.[19–21]

Table 1. Potential of resveratrol as an anticancer agent

Site	Pathway involved	Reference
Lymphocytes	CD95	10
Colon	CD95	13
Breast	CD95	14
Skin	Apoptosis	18
Skin	NF-κB	20
Prostate	NF-κB	21
Lung	NF-κB	22
Endometrium	PI3K/Akt	24
Lung	SIRT1	30
Colon	Wnt	34–36

Nuclear factor κB pathway

Naturally occurring polyphenolic compounds, such as curcumin and resveratrol, are potent agents for modulating inflammation. Recently, both compounds were shown to mediate some of their effects by targeting the NF-κB (a protein complex that controls the transcription of DNA) signaling pathway. It was shown that resveratrol modulates the NF-κB pathway by inhibiting the proteasome in human articular chondrocytes. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens.[23] NF-κB plays a key role in regulating the immune response to infection. Conversely, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κB has also been implicated in processes of synaptic plasticity and memory. NF-κB is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival.[24] As such, many different types of human tumors have misregulated NF-κB. Active NF-κB turns on the expression of genes that keep the cell proliferating and protect the cell from conditions that would otherwise cause it to die via apoptosis.

Defects in NF-κB result in increased apoptosis because NF-κB regulates antiapoptotic genes, for example TRAF1 and TRAF2, and thereby alters the

activities of the caspase family of enzymes that are central to most apoptotic processes.[25]

Resveratrol suppressed NF-κB–regulated gene products involved in inflammation (cyclooxygenase-2, matrix metalloproteinase [MMP]-3, MMP-9, and vascular endothelial growth factor), inhibited apoptosis (Bcl-2, Bcl-xL, and TNF-α receptor-associated factor 1), and prevented activation of caspase-3.[26] In our laboratory, resveratrol and UVB treatment was shown to decrease the phosphorylation of tyrosine 701 of the important transcription factor signal transducer and activator of transcription (STAT1), which in turn inhibited translocation of phospho-STAT1 to the nucleus and metastatic protein LIMK1.[27] Likewise, in another study, NF-κB–mediated transcriptional activity induced by EGF and TNF-α were inhibited by resveratrol in prostate cancer cell lines.[28] The suppression of MMP-2 expression by resveratrol led to an inhibition of A549 cell invasion by inactivating phosphorylation of SAPK/c-Jun N-terminal kinase (JNK) and p38 MAPK signaling pathways. A time-dependent inhibition of protein levels for p65, c-Jun, and c-Fos in the nucleus by MR-3 treatment was also observed.[29] In addition, NF-κB promotes liver regeneration by upregulating IL-6 and other molecules such as hepatocyte growth factor. We observed that resveratrol inhibited IL-1β–induced apoptosis, caspase-3 activation, and PARP cleavage in human articular chondrocytes.[30]

Phosphoinositol 3 kinase/Akt pathway

Phosphatidylinositol 3-kinases (PI3-kinases or PI3Ks) are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking, which in turn are involved in cancer. They have also been linked to an extraordinarily diverse group of cellular functions, including cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking. PI3Ks phosphorylate the 3 position hydroxyl group of the inositol ring of phosphatidylinositol. The pathway, including oncogene PIK3CA and tumor suppressor PTEN (gene), is implicated in insensitivity of cancer tumors to insulin and IGF1 in calorie restriction.[31]

Inhibition of beta-arrestin 2 increases the number of apoptotic cells and caspase-3 activation by reducing Akt/GSK3-β levels in endometrial cancer cells.[32] Resveratrol downregulated cell cycle-related proteins, including the expression of cyclin-dependent kinase (CDK) 2, cyclin E, CDK4, cyclin D1, retinoblastoma (Rb), and proliferative cell nuclear antigen (PCNA), thereby blocking the Akt pathway in rat aortic vascular smooth muscle cell,[33] bladder cancer,[34] and liver cancer cells.[35]

The SIRT1-regulated pathway

It has been established that genes control almost every aspect of human physiology, including longevity and aging processes on the cellular level, which in turn affects the lifespan and aging of the individual. One of the genes that may be associated with cellular longevity and ability to slow down the aging process is sirtuin 1 (SIRT1).[36]

SIRT1 is known to deacetylate histones and nonhistone proteins, including transcription factors, thereby regulating metabolism, stress resistance, cellular survival, cellular senescence, inflammation-immune function, endothelial functions, and circadian rhythms.[37] Resveratrol has been shown to activate SIRT1 directly or indirectly in a variety of models. Activation of SIRT1 by resveratrol may be beneficial for regulation of calorie restriction, oxidative stress, inflammation, cellular senescence, autophagy/apoptosis, autoimmunity, metabolism, adipogenesis, circadian rhythm, skeletal muscle function, mitochondria biogenesis, and endothelial dysfunction.[37] Resveratrol mimics the effects of calorie restriction in lower organisms, and mice fed a high-fat diet demonstrate reduced insulin resistance.[38] SIRT1 also plays an important role in regulating autophagy in response to cigarette smoke.[39] SIRT1 activation by resveratrol may also play a role in treatment strategies for stroke and other neurodegenerative disorders. The goal here is to provide a better understanding of the mode of action of resveratrol and its possible use as a potential therapeutic agent to ameliorate stroke damage as well as other age-related neurodegenerative disorders. Similarly, research on elucidating the beneficial effects of resveratrol during colitis revealed that it may be mediated through several mechanisms.[40] One mechanism may involve the negative regulation of NF-κB activity by SIRT1, as the NF-κB pathway has been shown to contribute to colitis and colon cancer associated with colitis Thus, downregulation of SIRT1 during colitis may induce inflammatory cytokines through activation of NF-κB, which is reversed by resveratrol.[41]

Table 2. Resveratrol health claims: animals versus humans

In vivo studies	Human cell lines	Human
√ Increased longetivity (C57BL/6NIA mice)	√ Inhibition of proliferation in many cancer cell lines	√ None
√ Increased mitochondria and endurance (Sprague-Dawley rats)	√ Improves cardiac muscle cells	
√ Impedes cancer cell growth(BALB/cAnNCr-nu/nu mice)	√ Improves insulin sensitivity	
√ Improves insulin sensitivity(db/db mice)		

miRNAs as molecular targets of resveratrol

In recent years, microRNAs have received greater attention in cancer research. MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression post-transcriptionally. About 3% of human genes encode for miRNAs, and up to 30% of human protein coding genes may be regulated by miRNAs. MiRNAs play a key role in diverse biological processes, including development, cell proliferation, differentiation, and apoptosis. These small, noncoding RNAs inhibit target gene expression by binding to the 3′ untranslated region of target mRNAs, resulting in either mRNA degradation or inhibition of translation. MiRNAs play important roles in many normal biological processes; however, studies have also shown that aberrant miRNA expression is correlated with the development and progression of some cancers.[42] Thus some miRNAs could have oncogenic or tumor suppressor activities. Moreover, specific miRNAs may regulate formation of cancer stem cells and epithelial-mesenchymal transition phenotype of cancer cells, which are typically drug resistant. MiRNAs may also be used as biomarkers for diagnosis and prognosis. Thus miRNAs are emerging as targets for cancer therapy.[43] The manipulation of miRNAs and other genes in animal models can increase or decrease lifespan. Transcriptional and posttranscriptional regulatory mechanisms, some of which involve miRNAs, as well as modifications to chromatin and histones, can influence longevity. A decline in the function of stem cells might also be responsible for some aspects of mammalian aging or senescence which is also a mechanism of inhibiting tumor cell proliferation.[44]

Wnt pathway

One reason why specific inhibitors that target only one pathway have typically failed in cancer treatment is the complexities of the communication between multiple signaling networks. *In vitro* and *in vivo* studies have demonstrated that natural products such as isoflavones, indole-3-carbinol (I3C), 3,3′-diindolylmethane (DIM), curcumin, (–)-epigallocatechin-3-gallate (EGCG), resveratrol, and lycopene have inhibitory effects on human and animal cancers through targeting multiple cellular signaling pathways, and thus these "natural agents" could be classified as multitargeted agents.

The Wnt signaling pathway consists of a network of proteins most well known for its role in embryogenesis and cancer, though this network is also involved in normal physiological processes in adult animals.[45] The canonical Wnt pathway describes a series of events that occur when Wnt proteins bind to cell surface receptors of the frizzled family, causing the receptors to activate the disheveled family of proteins and, ultimately, a change in the amount of β-catenin that reaches the nucleus. Recently it was reported that resveratrol suppresses colon cancer cell proliferation and elevates apoptosis even in the presence of IGF-1 (via suppression of IGF-1R/Akt/Wnt signaling pathways and activation of p53), suggesting its potential role as a chemotherapeutic agent.[46] The effects of low concentrations of resveratrol on the Wnt pathway was evaluated; and in the absence of effects on cell proliferation, resveratrol significantly inhibited Wnt signaling in colon-derived cells, which do not have a basally activated Wnt pathway.[47] This inhibitory effect may be due in part to regulation of intracellular

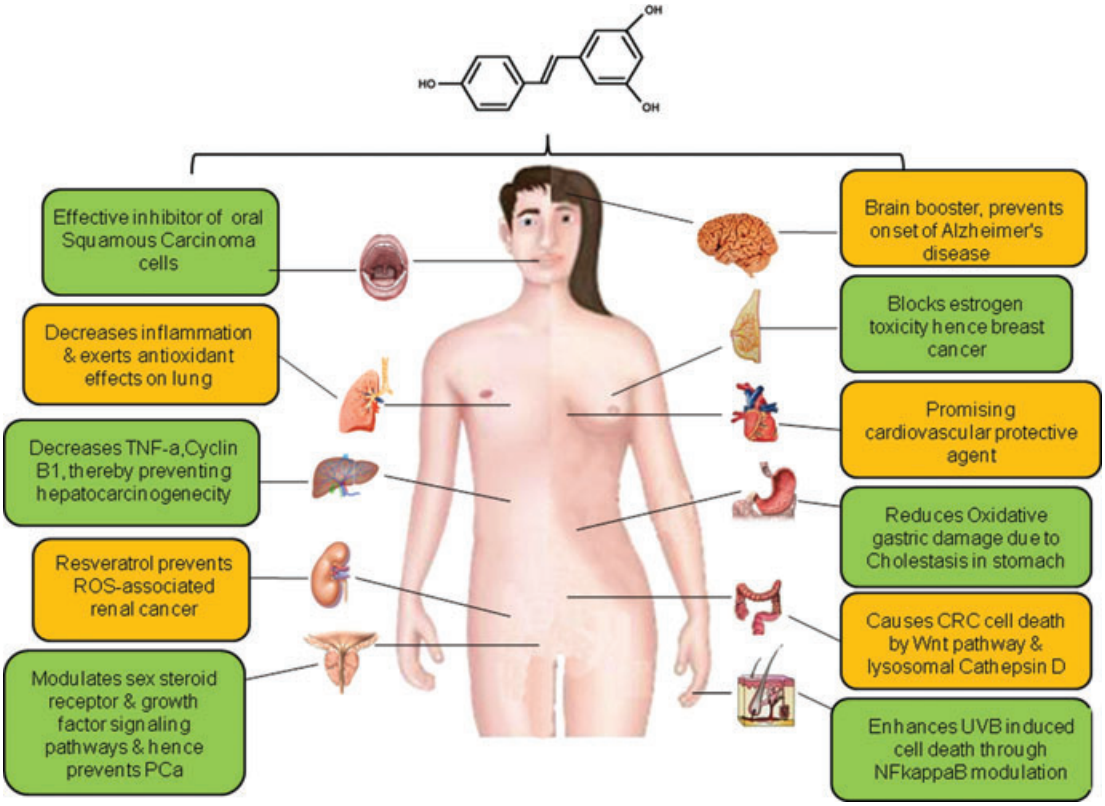

Figure 1. Beneficial health effects of resveratrol.

β-catenin localization.[47] Resveratrol inhibited proliferation and induced apoptosis in colon cancer cells by reducing both of survivin expression and the Wnt/β-catenin signaling pathway.[48]

Conclusion

Resveratrol, a natural nonflavonoid polyphenol found in grapes and red wine, is recognized as a bioactive agent with potential benefits for health. A large number of pharmacological properties, including cardioprotective, antioxidant, and anticancer effects, are thought to be associated with its beneficial effects (Figure 1). Few studies have been performed with resveratrol in humans, and the results of these studies appear fragmentary and sometimes contradictory due to variations in conditions of administration, protocols, and methods of assessment; for example, it appears that the presence of the matrix in which resveratrol is administered (e.g., in alcohol, or other polyphenolic compounds in wine) or feeding conditions (fed versus fasting) results in discrepancies between studies. Although differences in resveratrol administration, doses, and assay methods make data from different studies difficult to compare, these data nevertheless provide important information and raise some interesting questions. First, resveratrol seems to be well tolerated; however, no information is available on long-term administration. For use in chronic diseases such as diabetes, colorectal cancer, or Alzheimer's disease, or for the prevention of cardiovascular disease and antiaging antioxidative care, resveratrol administration would occur over several months/years at doses that have yet to be determined. Although resveratrol is considered a food supplement and a relatively safe natural medication, further investigations are required to determine its long-term effects. Second, resveratrol is rapidly absorbed and metabolized, mainly as sulfo- and gluco-conjugates that are excreted in urine. This high metabolic rate probably allows the transport, the distribution, and the excretion of resveratrol. In rodents, the gut epithelium has been shown to be highly implicated in the metabolic process, resulting in polar

resveratrol compounds that require specific transporters to cross cell membranes. Several ATP-binding cassette transporters may be involved in the tissue distribution and subsequent elimination of resveratrol from the body. However, concentrations of free *trans*-resveratrol are very low in plasma, and hence several authors have raised doubts about its efficiency. Because many lacunae in our understanding of resveratrol action and biochemistry remain to be filled, humans clinical trials have understandably lagged behind other animal and *in vitro* studies.

Several studies on elucidating the effects of resveratrol demonstrate that it may have potential beneficial activities against cancer, cardiovascular disease, diabetes, and autoimmune diseases; and it may even interfere with the normal physiological processes of aging. But to fully realize the potential of resveratrol, clinical trials are needed. Its analogues, with improved pharmacokinetic and pharmacodynamics, will also help the field move forward. Safety during long-term administration, combined with its cost and future therapeutic potential, makes resveratrol an ideal agent for both prevention and therapy of chronic illnesses, either alone or in combination with other drugs. Reverse pharmacology, in the case of resveratrol, is likely to prove correct Hippocrates correct, who remarked 25 centuries ago, "Let food be thy medicine and medicine be thy food." Natural products such as resveratrol have gained considerable attention as cancer chemopreventive or cardioprotective agents and as antitumor agents. Among its wide range of biological activities, resveratrol has been reported to interfere with many intracellular signaling pathways that regulate cell survival or apoptosis. Hence, resveratrol may hold promise in the near future as a chemotherapeutic drug in the treatment of cancer and other diseases.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Patel, V.B., S. Misra, B.B. Patel & A.P. Majumdar. 2010. Colorectal cancer: chemopreventive role of curcumin and resveratrol. *Nutr. Cancer*. **62:** 958–967.
2. Gullett, N.P., A.R. Ruhul Amin, S. Bayraktar, *et al*. 2010. Cancer prevention with natural compounds. *Semin. Oncol.* **37:** 258–281.
3. Kraft, T.E., D. Parisotto, C. Schempp & T. Efferth. 2009. Fighting cancer with red wine? Molecular mechanisms of resveratrol. *Crit. Rev. Food Sci. Nutr*. **49:** 782–799.
4. Sadruddin, S. & R.J. Arora. 2009. Resveratrol: biologic and therapeutic implications. *Cardiometab. Syndr*. **4:** 102–106.
5. Granados-Principal, S., J.L. Quiles, C.L. Ramirez-Tortosa, *et al*. 2010. New advances in molecular mechanisms and the prevention of adriamycin toxicity by antioxidant nutrients. *Food Chem. Toxicol*. **48:** 1425–1438.
6. Liu, E.H., L.W. Qi, Q. Wu, *et al*. 2009. Anticancer agents derived from natural products. *Mini. Rev. Med. Chem.* **9:** 1547–1555.
7. Liu, B.L., X. Zhang, W. Zhang & H.N. Zhen. 2007. New enlightenment of French Paradox: resveratrol's potential for cancer chemoprevention and anti-cancer therapy. *Cancer Biol. Ther.* **6:** 1833–1836.
8. Jang, M., L. Cai, G.O. Udeani, *et al*. 1997. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* **275:** 218–220.
9. Baur, J.A. & D.A. Sinclair. 2006. Therapeutic potential of resveratrol: the in vivo evidence. *Nat. Rev. Drug Discov.* **5:** 493–506.
10. Athar, M., J.H. Back, X. Tang, *et al*. 2007. Resveratrol: a review of preclinical studies for human cancer prevention. *Toxicol. Appl. Pharmacol.* **224:** 274–283.
11. Boocock, D.J., G.E. Faust, K.R. Patel, *et al*. 2007. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. *Cancer Epidemiol. Biomarkers Prev.* **16:** 1246–1252.
12. Niles, R.M., C.P. Cook, G.G. Meadows, *et al*. 2006. Resveratrol is rapidly metabolized in athymic (nu/nu) mice and does not inhibit human melanoma xenograft tumor growth. *J. Nutr.* **136:** 2542–2456.
13. Wenzel, E., T. Soldo, H. Erbersdobler & V. Somoza. 2005. Bioactivity and metabolism of trans-resveratrol orally administered to Wistar rats. *Mol. Nutr. Food Res.* **49:** 482–494.
14. Gao, X., Y.X. Xu, G. Divine, *et al*. 2002. Disparate in vitro and in vivo antileukemic effects of resveratrol, a natural polyphenolic compound found in grapes. *J. Nutr.* **132:** 2076–2081.
15. Kimura, Y. & H. Okuda. 2001. Resveratrol isolated from Polygonum cuspidatum root prevents tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma-bearing mice. *J. Nutr.* **131:** 1844–1849.
16. Li, Z.G., T. Hong, Y. Shimada, *et al*. 2002. Suppression of N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in F344 rats by resveratrol. *Carcinogenesis* **23:** 1531–1536.
17. Falschlehner, C., T.M. Ganten, R. Koschny, *et al*. 2009. TRAIL and other TRAIL receptor agonists as novel cancer therapeutics. *Adv. Exp. Med. Biol.* **647:** 195–206.
18. Pervaiz, S. 2001. Resveratrol: from the bottle to the bedside? *Leuk. Lymphoma* **40:** 491–498.
19. Gatouillat, G., E. Balasse, D. Joseph-Pietras, *et al*. 2010. Resveratrol induces cell-cycle disruption and apoptosis in chemoresistant B16 melanoma. *J. Cell Biochem.* [Epub ahead of print].
20. Brizuela, L., A. Dayon, N. Doumerc, *et al*. 2010. The sphingosine kinase-1 survival pathway is a molecular target for the tumor-suppressive tea and wine polyphenols in prostate cancer. *FASEB J*. [Epub ahead of print].

21. Li, H., W.K. Wu, Z. Zheng, *et al*. 2010. 3,3′,4,5,5′-pentahydroxy-trans-stilbene, a resveratrol derivative, induces apoptosis in colorectal carcinoma cells via oxidative stress. *Eur. J. Pharmacol.* **637:** 55–61.
22. Madan, E., S. Prasad, P. Roy, *et al*. 2008. Regulation of apoptosis by resveratrol through JAK/STAT and mitochondria mediated pathway in human epidermoid carcinoma A431 cells. *Biochem. Biophys. Res. Commun.* **377:** 1232–1237.
23. Staudt, L.M. 2010. Oncogenic activation of NF-kappaB. *Cold Spring Harb. Perspect. Biol.* **2:** a000109.
24. Kucharczak, J., M.J. Simmons, Y. Fan & C. Gélinas. 2003. To be, or not to be: NF-kappaB is the answer–role of Rel/NF-kappaB in the regulation of apoptosis. *Oncogene*. **22:** 8961–8982.
25. Sughra, K., A. Birbach, R. de Martin & J.A. Schmid. 2010. Interaction of the TNFR-receptor associated factor TRAF1 with I-kappa B kinase-2 and TRAF2 indicates a regulatory function for NF-kappa B signaling. *PLoS One* **5:** e12683.
26. Csaki, C., A. Mobasheri & M. Shakibaei. 2009. Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1beta-induced NF-kappaB-mediated inflammation and apoptosis. *Arthritis Res. Ther.* **11:** R165.
27. Roy, P., E. Madan, N. Kalra, *et al*. 2009. Resveratrol enhances ultraviolet B-induced cell death through nuclear factor-kappaB pathway in human epidermoid carcinoma A431 cells. Biochem. *Biophys. Res. Commun.* **384:** 215–220.
28. Benitez, D.A., M.A. Hermoso, E. Pozo-Guisado, *et al*. 2009. Regulation of cell survival by resveratrol involves inhibition of NF kappa B-regulated gene expression in prostate cancer cells. *Prostate.* **69:** 1045–1054.
29. Yang, Y.T., C.J. Weng, C.T. Ho & G.C. Yen. 2009. Resveratrol analog-3,5,4′-trimethoxy-trans-stilbene inhibits invasion of human lung adenocarcinoma cells by suppressing the MAPK pathway and decreasing matrix metalloproteinase-2 expression. *Mol. Nutr. Food Res.* **53:** 407–416.
30. Shakibaei, M., C. Csaki, S. Nebrich & A. Mobasheri. 2008. Resveratrol suppresses interleukin-1beta-induced inflammatory signaling and apoptosis in human articular chondrocytes: potential for use as a novel nutraceutical for the treatment of osteoarthritis. *Biochem. Pharmacol.* **76:** 1426–1439.
31. Harikumar, K.B. & B.B. Aggarwal. 2008. Resveratrol: a multitargeted agent for age-associated chronic diseases. *Cell Cycle* **7:** 1020–1035.
32. Sun, X., Y. Zhang, J. Wang, *et al*. 2010. Beta-arrestin 2 modulates resveratrol-induced apoptosis and regulation of Akt/GSK3beta pathways in human endometrial cancer cells. *Biochim. Biophys. Acta.* [Epub ahead of print].
33. Park, E.S., Y. Lim, J.T. Hong, *et al*. 2010. Pterostilbene, a natural dimethylated analog of resveratrol, inhibits rat aortic vascular smooth muscle cell proliferation by blocking Akt-dependent pathway. *Vascul. Pharmacol.* **53:** 61–67.
34. Bai, Y., Q.Q. Mao, J. Qin, *et al*. 2010. Resveratrol induces apoptosis and cell cycle arrest of human T24 bladder cancer cells in vitro and inhibits tumor growth in vivo. *Cancer Sci.* **101:** 488–493.
35. Parekh, P., L. Motiwale, N. Naik & K.V. Rao. 2010. Downregulation of cyclin D1 is associated with decreased levels of p38 MAP kinases, Akt/PKB and Pak1 during chemopreventive effects of resveratrol in liver cancer cells. *Exp. Toxicol. Pathol.* [Epub ahead of print].
36. Queen, B.L. & T.O. Tollefsbol. 2010. Polyphenols and aging. *Curr. Aging Sci.* **3:** 34–42.
37. Chung, S., H. Yao, S. Caito, *et al*. Regulation of SIRT1 in cellular functions: role of polyphenols. *Arch. Biochem. Biophys.* **501:** 79–90.
38. de Kreutzenberg, S.V., G. Ceolotto, I. Papparella, *et al*. 2010. Downregulation of the longevity-associated protein sirtuin 1 in insulin resistance and metabolic syndrome: potential biochemical mechanisms. *Diabetes* **59:** 1006–1015.
39. Hofseth, L.J., U.P. Singh, N.P. Singh, *et al*. 2010. Taming the beast within: resveratrol suppresses colitis and prevents colon cancer. *Aging (Albany NY)*. **2:** 183–184.
40. Cui, X., Y. Jin, A.B. Hofseth, *et al.* 2010. Resveratrol suppresses colitis and colon cancer associated with colitis. *Cancer Prev. Res. (Phila).*;**3** : 549–59. Epub 2010 Mar 23.
41. Arunachalam, G., H. Yao, I.K. Sundar, *et al*. 2010. SIRT1 regulates oxidant- and cigarette smoke-induced eNOS acetylation in endothelial cells: role of resveratrol. *Biochem. Biophys. Res. Commun.* **393:** 66–72.
42. Wang, J., Q. Wang, H. Liu, *et al*. 2010. MicroRNA expression and its implication for the diagnosis and therapeutic strategies of gastric cancer. *Cancer Lett.* **297:** 137–143.
43. Li, Y., D. Kong, Z. Wang & F.H. Sarkar. 2010. Regulation of microRNAs by natural agents: an emerging field in chemoprevention and chemotherapy research. *Pharm. Res.* **27:** 1027–1041.
44. Marques, F.Z., M.A. Markus & B.J. Morris. 2010. The molecular basis of longevity, and clinical implications. *Maturitas* **65:** 87–91.
45. Sarkar, F.H., Y. Li, Z. Wang & D. Kong. 2009. Cellular signaling perturbation by natural products. *Cell Signal.* **21:** 1541–1547.
46. Vanamala, J., L. Reddivari, S. Radhakrishnan & C. Tarver. 2010. Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways. *BMC Cancer*. **10:** 238.
47. Hope, C., K. Planutis, M. Planutiene, *et al*. 2008. Low concentrations of resveratrol inhibit Wnt signal throughput in colon-derived cells: implications for colon cancer prevention. *Mol. Nutr. Food Res.* **52:** 52–61.
48. Sakoguchi-Okada, N., F. Takahashi-Yanaga, K. Fukada, *et al*. 2007. Celecoxib inhibits the expression of survivin via the suppression of promoter activity in human colon cancer cells. *Biochem. Pharmacol.* **73:** 1318–1329.