Pharmaceutical Biology

ISSN: 1388-0209 (Print) 1744-5116 (Online) Journal homepage: informahealthcare.com/journals/iphb20

Resveratrol as an Inhibitor of Carcinogenesis

John M. Pezzuto

To cite this article: John M. Pezzuto (2008) Resveratrol as an Inhibitor of Carcinogenesis, Pharmaceutical Biology, 46:7-8, 443-573, DOI: 10.1080/13880200802116610

To link to this article: https://doi.org/10.1080/13880200802116610

Pharmaceutical Biology
2008, Vol. 46, Nos. 7–8, pp. 443–573

informa
healthcare

Resveratrol as an Inhibitor of Carcinogenesis[1,2]

John M. Pezzuto

College of Pharmacy, University of Hawaii at Hilo, Hilo, Hawaii, USA

Abstract

Given the high probability of developing cancer over the period of a normal life span, cancer chemoprevention provides an attractive therapeutic strategy for the delay or reversal of this process. A variety of phytochemicals, such as sulfides, isothiocyanates, glucosinolates, flavonoids, carotenoids, phenols, and diarylhepanoids, are known to mediate chemopreventive responses. Resveratrol, a ubiquitous stilbene found in the diet of human beings (e.g., as a component of grapes and wine), was uncovered by bioassay-guided fractionation and found to mediate cancer chemopreventive activity in a murine model with mechanisms involving various stages of the carcinogenic process. This work spurred a myriad of studies that are summarized in this article. As demonstrated with *in vitro* and cell culture models, resveratrol functions through a plethora of mechanisms, which can vary from model to model. Results from differential gene expression studies are daunting. Irrespective of the precise mechanism, however, efficacy has been demonstrated in some animal models, and a critical evaluation of resveratrol data relative to the characteristics of a promising cancer chemopreventive agent leads to favorable consideration. Animal studies have shown cancer inhibitory activity in a number of models, including adenoma, skin, breast, colon, esophagus, glioma, intestinal, liver, and neuroblastoma. Biomarkers are known, and ample quantities of compound can be produced. Dietary administration is feasible. Several small-scale human trials are under way, and human intervention trials may follow. As learned by past experience, data from these trials are necessary prior to drawing any conclusions, but the current cancer chemopreventive profile of resveratrol provides promise for widespread use in the future.

Keywords: Biological activity, cancer chemoprevention, drug discovery, metabolites, plant secondary metabolites, resveratrol, stilbenoids.

Introduction

A summarized by the World Health Organization, cancer leads to about 12% of human deaths (2), claiming more than 10,000,000 lives each year. In the United States, cancer is the second leading cause of death, being responsible for approximately one in every four deaths. Interestingly, it is believed that at least one-third of all cancers could be prevented (3, 4). As such, primary and secondary prevention strategies are reasonable approaches to reduce the occurrence of this disease (5–7) and subsequent deaths. Primary prevention strategies involve removing causative agents and other life style modifications that decrease the risk of cancer, as exemplified by smoking cessation and screening tests to detect precancerous lesions. Unfortunately, not all causative agents are known, and other suspected carcinogens are too widespread to prevent all exposure.

Secondary prevention, cancer chemoprevention, involves the use of nontoxic natural and/or synthetic agents to decrease the risk of malignant tumor development or spread (8, 9). Cancer chemoprevention is a multidisciplinary field of research that has evolved from numerous scientific observations (10). For example, epidemiologic studies have linked diets high in fresh fruits and vegetables to lower cancer rates. This dietary link is perhaps most strongly supported by studies reporting the cancer risk of migrants from areas of low incidence to high incidence. These studies demonstrated that the incidence of cancer among children of migrants is similar to that of the general population (11).

Accepted: April 7, 2008.

[1]This review has been revised, expanded, and updated from a previous chapter (see. Ref. 1) on the same subject.

[2]Due to the unique nature of this review, the format is atypical. The references are presented by number, rather than by author name and year, and the tables are presented at the end of the text, as they are so extensive.

Address correspondence to: John M. Pezzuto, College of Pharmacy, University of Hawaii at Hilo, 34 Rainbow Dr., Hilo, HI 96720, Tel.: (808) 933-2909; Fax: (808) 933-2981; E-mail: pezzuto@hawaii.edu

DOI: 10.1080/13880200802116610

Another important breakthrough has been the prevention of experimentally induced cancer in laboratory animals. It was subsequently postulated that dietary components, particularly specific nutrients and/or phytochemicals found in fruits and vegetables, could be used to prevent cancer in human beings (9, 12). More recently, research in cancer biology has elucidated molecular mechanisms of cancer chemopreventive agents (6, 10, 13). Much of the theoretical basis for cancer chemoprevention is the understanding that cancer develops over time through the process of carcinogenesis (14). This process has been broken down into distinct yet overlapping stages, namely, initiation, promotion, and progression. The evolution of these stages is believed to take 10 to 40 years, during which various genetic mutations must occur (10, 15). The field of cancer chemoprevention is focused on reversing, halting, or delaying these stages of carcinogenesis by means of secondary prevention (8–10).

Cancer chemopreventive agents have been classified according to the stage of carcinogenesis in which they have demonstrated activity and are broadly termed *blocking* and *suppressing* agents (8). Blocking agents act by preventing the initiation stage through a variety of mechanisms such as directly detoxifying carcinogens, stimulating detoxifying enzymes, and inhibiting carcinogen formation. Suppressing agents act at the promotion and progression stages through mechanisms such as inhibition of arachidonic acid metabolism, induction of cell differentiation, and inhibition of ornithine decarboxylase activity (4, 8, 16). In the case of hormone-dependent cancers, suppressing agents may act by preventing the hormone from binding to its receptor, as exemplified by the use of the selective estrogen receptor modulators, tamoxifen and raloxifene, for breast cancer prevention (4, 15).

Overview of Cancer Chemoprevention Trials Involving Phytochemicals

Many early cancer chemoprevention studies were focused on nutrients such as vitamin C, calcium, and retinoids (9, 11). In the past several decades, nonnutrient phytochemicals found in fruits and vegetables have been examined, and a number of promising natural product leads have resulted from this research effort (15, 17, 18). For example, green tea extract and pure compounds such as caffeic acid phenethyl ester, capsaicin, curcumin, 6-gingerol, indole-3-carbinol, lycopene, and perillyl alcohol are undergoing clinical trials for their cancer chemopreventive activities (15, 19, 20). The U.S. National Cancer Institute is supporting the evaluation of potential cancer chemopreventive agents at different levels of preclinical development and clinical trials (18). Examples of natural products currently under preclinical or clinical development for cancer chemoprevention include curcumin and lycopene, which are in a phase I study for the prevention of colon cancer, and a soy protein supplement is in a phase II trial for the prevention of prostate cancer in patients with elevated prostate-specific antigens (21). Moreover, soy isoflavones are also involved in a randomized study in preventing further development of cancer in patients with stage I or stage II prostate cancer (21). Polyphenon E (green tea extract), in combination with low-dose aspirin, is in a phase II randomized study to prevent cancer in women at high risk for developing breast cancer (22, 23). Other natural products currently being investigated include *S*-allyl-L-cysteine, epigallocatechin gallate, genistein, folic acid, and quercetin (19, 24).

Discovery and Characterization of Natural Product Inhibitors of Carcinogenesis

With support provided by the National Cancer Institute, we have conducted a program project entitled "Natural Inhibitors of Carcinogenesis" since 1991. The major aim of this project has been the discovery of new cancer chemopreventive agents from plants, particularly those that are edible. We are now beginning to explore marine microorganisms for chemopreventive activity. The project involves botanical, biological, chemical, biostatistical, and administrative aspects (25–28). Terrestrial plant materials selected for investigation are prioritized based on information obtained from the NAPRALERT database (29). Edible plants or species with reported biological activity related to cancer chemoprevention, plants with no history of toxicity, and those poorly investigated phytochemically are selected for preliminary investigation, and a small amount of plant material is collected (25–27).

The panel of *in vitro* bioassays used for the discovery of potential cancer chemopreventive drugs includes screening tests that are typically enzyme- or cell-based assays (26, 30). These assays are adapted to high-throughput measurement techniques performed relatively rapidly in order to uncover the biological properties of a large number of candidate substances (26, 30). The initial bioassays afford a strategic framework for the evaluation of agents according to defined criteria, to provide evidence of agent efficacy, and to serve to generate valuable dose-response, toxicity, and pharmacokinetic data required prior to phase I clinical safety testing (26, 30, 31).

Thus, preliminary screening is performed with an ethyl acetate–soluble partition extract using a battery of short-term *in vitro* bioassays (26). Bioactive extracts are further evaluated in a mouse mammary organ culture (MMOC) model as a secondary discriminator (32, 33). The battery of short-term *in vitro* assays was developed to monitor tumorigenesis at different stages. For example, antimutagenicity activity, antioxidant activity, and induction of NADPH:quinone reductase activity has been monitored to evaluate inhibition of carcinogenesis at the initiation stage (34–37). Monitoring inhibition of carcinogenesis at the promotion stage has been performed by evaluating the inhibition of phorbol ester–induced ornithine decarboxylase

activity, inhibition of cyclooxygenase-1 and -2 activity, inhibition of phorbol dibutyrate receptor binding, and inhibition of transformation of JB6 mouse epidermal cells (38–41). Induction of HL-60 human promyelocytic leukemia cell differentiation and inhibition of aromatase, antiestrogenic, estrogenic, and estrone sulfatase activities have been used to monitor inhibition of carcinogenesis at the progression stage (42–45). Various additional assays are under development, such as inhibition of quinone reductase 2, RxR, NF-κB, and Keap.

Plant extracts showing potency and/or selectivity in preliminary biological screening procedures are selected for bioassay-guided fractionation to isolate the active principle or principles. Crude methanol extracts are partitioned using solvents of varying polarities and then chromatographed by either gravity-, flash-, or low-pressure column over silica, alumina, ion-exchange resins, polyamide, reversed-phase silica gel, size-exclusion gels, or other solid-phase supporting material (27, 46). Analytical thin-layer and high-pressure liquid chromatography (HPLC) techniques are used to help determine optimal solvent systems for the maximal separation of active components of fractions (47). Other separation techniques, such as droplet countercurrent chromatography (DCCC), high-speed countercurrent chromatography (HSCCC), and semipreparative HPLC are used occasionally for complex mixtures of active constituents (27, 47, 48). A more innovative procedure using LC-MS/MS has been devised (49).

After pure active isolates are evaluated in all of the available *in vitro* assays, selected compounds are evaluated in the *ex vivo* mouse mammary organ culture model (32, 33). Highly promising leads may be selected for testing in full-term animal tumorigenesis models, such as the two-stage mouse skin model using 7,12-dimethylbenz(*a*)anthracene (DMBA) as initiator and 12-*O*-tetradecanoylphorbol 13-acetate (TPA) as promoter, and in the rat and mouse mammary carcinogenesis models with DMBA or *N*-methyl-*N*-nitrosourea (MNU) as the carcinogens (25, 26, 40). Other animal models may be used as well.

Potential Cancer Chemopreventive Agents from Plants

As an example of the success of this program, over a recent period of approximately 5 years, a total of 166 active compounds were isolated and biologically evaluated in our laboratories from 32 plant species (50). The active metabolites were obtained using activity-guided fractionation with a preselected *in vitro* assay to monitor their purification process. These active compounds were found to represent 29 major secondary metabolite compound classes including alkaloids (of the β-carboline alkaloid, indoloquinoline alkaloids, and steroidal types), amides, benzenoids, benzofurans, cardiac glycosides, ceramides, a coumarin, diarylheptanoids, diterpenoids, fatty acids, flavonoids (of the aurone, bisaurone, chalcone, flavan, flavanone, flavone, flavonol, flavonone, and isoflavone types), glycerin esters, a β-ionone derivative, an iridoid, lignans, a monoterpenoid, a naphthopyran, norwithanolides, phenylphenalones, a porphyrin derivative, a rocaglamide derivative, rotenoids, sesquiterpene lactones, sesquiterpenoids, simaroubolides, a stilbenolignan, stilbenoids, triterpenoids, and withanolides. Active compounds based on three different types of novel carbon skeletons were obtained during this work, which included seven norwithanolides possessing a new C_{27} skeleton (as opposed to the 28 carbons of the more widespread withanolides) (47, 51), a novel stilbenolignan containing a stilbene-phenylpropane unit with a dioxane moiety (52), and two triterpenes based on a 29-*nor*-3,4-*seco*-cycloartane skeleton (53). Forty-nine new compounds from 19 species were found among the compound classes mentioned above and were classified into 16 major structural classes. A large number of known bioactive compounds were isolated from 32 species and can be grouped into 23 major structural classes. As summarized in Table 1, nine agents resulting from this project are considered promising leads for further development.

The Phenomenon of Resveratrol

One of the most fascinating molecules we have "rediscovered" is resveratrol (Fig. 1). Resveratrol is a natural phytoalexin that is expressed in plants as a defensive response against fungal infections and other environmental stressors (65). The word *alexin* is from the Greek language, meaning "to ward off" or "to protect." Resveratrol may also have alexin-like activity in human beings, protecting against degenerative diseases. Synthesis of resveratrol in grapes is most likely associated with natural stress factors such as exposure to ultraviolet radiation (66), injury, or during fungal or mold invasion (67). Significant amounts of resveratrol were detected in healthy fruit clusters prior to any detectable mold lesions. This suggested that the compound was biosynthesized soon after the recognition of the pathogen by the plant (68). Montero et al. (69) investigated involvement of the plant hormone ethylene in resveratrol synthesis during fruit maturation. High resveratrol content correlated with low ethylene emission. Exogenous application of resveratrol on the fruit surface delayed the increase of ethylene emission and doubled the normal shelf-life of grapes. This response is due to the antifungal activity of resveratrol, indicating the wide potential of such a compound for the control of the microbiota on fruits and practical application as a natural chemical to prolong the shelf-life of fruits (70).

Resveratrol was first recognized as a biologically active compound by Siemann and Creasy (71). The compound is found in several plants, chiefly in red grapes. The highest concentration (50–100 μg/g of grape wet weight) was determined in the grape skin. In wine, *cis*- and *trans*-isomers are present, in the free or glycosylated forms. c*is*-Resveratrol

was not detected in grape skin and juices. Formation of the *cis*-isomer by isomerization or breakdown of the *trans*-form on exposure of wine to light and oxygen has been assumed (72). In dietary supplements, the isomer is not always specified, but in most cases it is the *trans*-form. In red wine, the concentration of the *trans*-isomer ranges between 0.1 and 15 mg/L. The ratio of *cis*- and *trans*-resveratrol in wines varies by region. Climate, the type of grape, and the length of time the skin is kept with the grape during the winemaking process are some factors that influence the level of resveratrol and the ratio of isomers in wine (73). Primarily, the compound is produced in the grape, grape shoots, and vines. Increasing irradiation of harvested grapes by UVB or UVC light enhances yields of resveratrol (72). Most resveratrol-containing supplements marketed in the United States. contain extracts of the root of *Polygonium cuspidatum* Sieb. and Zucc., also known as the Japanese knotweed. The dried root and stem of this plant is used in traditional Japanese folk medicine (Ko-jo-kon) as a circulatory tonic, against fungal diseases, and for various inflammatory and liver diseases (74). Moreover, resveratrol synthase genes have been isolated and inserted into plants, creating transgenic varieties of alfalfa, tobacco, and other plant species with higher *trans*-resveratrol concentrations. Phytoalexins inserted into plants may provide defense against different pathogens (75). Additionally, transgenic plants (e.g., alfalfa) transformed with resveratrol synthesizing genes might become an economical source of the compound for scientific research or dietary supplements (76).

As part of our search for natural product cancer chemopreventive agents, acquisition number 46 (the current total is 7148), a nonedible legume identified as *Cassia quinquangulata* Rich. (Leguminosae), was extracted and found to demonstrate impressive inhibition with cyclooxygenase-1. Activity was also observed in the mouse mammary organ culture (MMOC) model, and the extract was selected for bioassay-guided fractionation. As a result, resveratrol was readily identified as the active principle. In addition to inhibiting cyclooxygenase activity, suggestive of antipromotional activity, the isolate was found to serve as an antioxidant and antimutagen. Further, it induced phase II drug metabolizing enzymes involved chiefly in the detoxification of carginogen metabolites (anti-initiation activity) and induced human promyelocytic leukemia cell differentiation (antiprogression activity). Finally, antitumor and anti-inflammatory effects were observed with mouse and rat models, respectively, providing support for the physiologic significance of the *in vitro* and cell culture data (40).

When these data were published in 1997, a search of MEDLINE revealed a total of 21 articles in the literature, largely relating to the natural occurrence of resveratrol rather than to biologic potential. There was a huge response by the media and public, perhaps because it was otherwise a slow news day, but clearly the public found comfort in the notion of food and beverages (such as grapes and wine) being of benefit for their health. Obviously, in addition to the general population, this notion attracted the attention of the scientific community. As indicated by a recent query of MEDLINE, from 1997 to the present, a total of 1974 articles investigating resveratrol have been published (Fig. 2). Symposia have been conducted (77), funding streams have been created (California Table Grape Commission, http://www.freshCaliforniagrape.com/), companies have been formed (Royalmount Pharma, http://www.royalmountpharma.com/; Sirtris Pharmaceuticals Inc., http://www.sirtrispharma.com/), various commercial products are available (Table 2), patents have been granted (Table 3), and monographs and reviews have been written (Table 4) (78–84). Of some importance, because this molecule is not complex, facile chemical syntheses have been devised, so abundant supplies of resveratrol are available (174–178).

In this review, a synopsis of the literature describing the cancer-related activity of resveratrol will be presented. The results are presented in tabular form, roughly divided into reports studying resveratrol with *in vitro* models, cell culture systems, *in vivo* systems, and clinical trials. In studies wherein multiple models were employed, the article is listed in the table representing the highest level of biological complexity.

In Vitro Studies Conducted with Resveratrol

Relatively few reports have appeared wherein the primary tests were performed mainly with *in vitro* model systems. Some are presented in Table 5. Key observations have demonstrated antioxidant activity (35, 181) and ability to inhibit protein kinases (186, 188, 189), cyclooxygenases (179, 199, 200), cytochromes P450 (190), and tyrosinase (183). Cr-induced damage to DNA can be prevented, probably through radical scavenging (184). Metabolism has also been established, through glucuronidation and sulfonation, conversion to piceatannol, and metabolism can be modulated by flavonoids such as quercetin (182, 185, 187). Mammalian proteins capable of binding resveratrol have been identified (120, 180). The crystal structure of resveratrol bound to the active site of cyclooxygenase as been deduced (Mesecar et al., submitted for publication), indicating some precise mechanisms are beginning to be defined.

Cell Culture Studies Conducted with Resveratrol

Clearly, as summarized in Table 6, the majority of studies that have been performed to investigate the mode of resveratrol action involve cultured cells. In our original report (40), HL-60 and Hepa 1c1c7 cells were used, and these responses have been confirmed and expanded. As models of human cancers, prostate, colon, lung, breast, ovarian, renal, hepatoma, leukemic, bronchial, neuroblastoma, cervical, lymphoma, medulloblastoma, endometrial,

esophageal, melanoma, pancreatic, gastric, epidermal, thyroid, fibroblast, retinoblastoma, and squamous cells as well as macrophages, monocytes, myofibroblasts, transformed and transfected cells, and organ culture systems have been used. Activities may vary from system to system, but some generalizations apply. Certainly, apoptosis is a common mode of action, and the response is generally dependent on p53 (223, 225, 242, 254, 280, 289, 298, 300, 326, 348). A number of related factors can be modulated by resveratrol, such as activation of caspases, decreases in Bcl-2 and Bcl-x^L, increases in Bax, inhibition of S-type cyclins and cyclin-dependent kinases, activation of c-jun NH_2-terminal kinase, and interference with NF-κB and AP-1 mediated cascades. Of course, nonapoptotic cell death pathways have also been observed, as well as induction of cell differentiation (40, 292). In some cases, p53-independent apoptosis has been reported (241, 309).

A number of studies have demonstrated the potential of resveratrol to inhibit cell invasion (320, 321, 366, 382, 387, 395, 412, 418, 421, 435, 440) and angiogenesis factors (215, 430, 444). Cell transformation can be blocked (264, 348, 351). As with *in vitro* studies, ribonucleotide reductase (281, 350), cyclooxygenases (79, 449), *i*NOS (80, 220, 293), and various kinases (240, 244, 248, 266, 310) are inhibited. The compound can function as an antioxidant (354, 428) or a prooxidant (377, 402, 420, 436, 438). Cathepsin D is regulated (379), hypoxia-induced protein is inhibited (387), and telomerase is downregulated (375). Various enzymes are modulated (cf. 308, 365, 431), as is polyamine metabolism (116, 265). Clearly, a large number of mechanisms have been explored.

In hormone-responsive cell types, a variety of studies have been performed to assess the hormonal (estrogenic or androgenic) potential of resveratrol (213, 226, 231, 234, 237, 262, 269, 278, 285, 317, 331, 346, 352), largely due to the structural similarity with diethylstibestrol (DES). Data range from superagonistic in transient transfection studies with reporter genes to completely inactive. The compound has been described as an estrogen (213, 231, 269, 278, 352) and an antiestrogen (307, 317, 346, 412). No binding (372) or low binding (317, 331) has been observed with estrogen receptors. Activity can be mediated in ER cell lines (cf. 433); androgen receptor (340) and PSA levels (270, 337) can be reduced. This remains a somewhat controvercial topic. Most typically, however, weak hormonal activity has been observed in the absence of the native steroid, and antihormonal activity has been observed with the addition of native hormone.

As might be expected, further studies have been performed to investigate structural derivatives of resveratrol, either naturally occurring stilbenes or synthetic analogues, as well as *cis*- and *trans*-isomers (178, 199, 200, 212, 245, 249, 255, 257, 261, 264, 285, 288, 294, 301, 304, 308, 311, 327, 363, 386, 407, 425, 426). These data are of interest, as is the generation and subsequent biologic potential of resveratrol metabolites and results obtained with cell culture models of transport (124, 233, 265, 276). In the area of cancer chemotherapy, the ability of resveratrol to modulate the toxic side effects of dacarbazine, taxol, vincristine, vinorelbine, cyclosporin A, retinoic acid, 5-fluorouracil, and so forth, have been investigated (236, 238, 250, 272, 303, 325, 367, 380, 388, 392, 419, 424, 450). In addition, several studies have illustrated enhanced radiation-induced cell death in the presence of resveratrol (229, 306, 378, 429, 432). Further, effects in combination with various other agents such as quercetin have been examined (284, 291, 339, 347, 422, 423).

The overall mechanism that is facilitated by resveratrol is undoubtedly complex. As demonstrated by differential expression studies in various cell cultures (216, 268, 270, 295, 416), hundreds of genes are affected by treatment with resveratrol. These results are quite profound and are consistent with the raft of responses observed in numerous model systems. The overall physiologic significance remains to be defined (451).

In Vivo Studies Conducted with Resveratrol

On an intuitive level, data obtained with studies performed with *in vivo* models appear to be of greatest relevance to the human situation: "the proof is in the pudding." It was clear from the outset that resveratrol is capable of mediating physiologic responses in animal models. In our original report (40), anti-inflammatory activity was observed in rats, and inhibition of tumorigenesis was observed in the two-stage mouse skin model. Importantly, in the rat inflammation model, resveratrol was administered orally, so a preliminary indication of bioavailability and systemic activity was also provided.

Clearly, however, experimental outcomes are dependent on the particular model and protocol that is applied. Inhibition in the two-stage mouse skin system has been confirmed (452, 453) and greatly expanded with activity being observed in UV-induced skin cancer models (454–457). These data are very promising and suggest utility for the prevention of skin cancer.

As a logical extension of the numerous mechanistic studies performed with cell culture models described above, many animal studies have been reported in the literature (Table 7). In part, these studies have been designed to examine some biomarkers of carcinogenesis (464, 483, 496, 501), a few derivatives of resveratrol (465, 491), and to investigate absorption and metabolism (465, 474, 478, 507). In addition, of course, a variety of antitumor models have been employed. With mice, resveratrol reduced biomarkers of lung carcinogenesis produced in benzo(*a*)pyrene-treated mice (471) but not tumorigenesis (461). We also found that resveratrol was not active in the benzo(*a*)pyrene mouse lung tumorigenesis model (unpublished data), nor was it active in a mixed-carcinogen lung cancer model (487). A positive response was observed, however, with Lewis lung carcinoma–bearing mice (485). This response may have been due to an anti-angiogeneric response mediated by resveratrol (485),

as has been noted in various other antitumor models (493, 497, 500).

In one study, a lack of activity was observed in the *Min* mouse (466), but similar studies reported a reduction of intestinal tumors when resveratrol was tested in this model (484, 503). Aberrant crypts were also reduced in carcinogen-treated rats (486), as were colon tumors in DMH-treated rats (498).

An increase in tumorigenesis was reported when resveratrol was administered to rats treated with *N*-methyl-*N*-nitrosourea (468), but this is contrary to our results wherein an inhibition was observed (483). Activity was also reported in two studies conducted with the DMBA rat mammary carcinogenesis model (476, 489), as well as the HER-2/new spontaneous breast cancer model (502). A positive response was also reported with the NMBA esophageal model (477), as well as with some combination regimens (450, 492). Finally, although activity was not observed with 4T1 breast cancer (482), B16 melanoma (478), and leukemia (481), positive responses were demonstrated with tumor transplant models for hepatoma (378, 450, 469, 472, 473, 488), neuroblastoma (463), sarcoma (467), pancreatic (480), mammary (497), lung (485), glioma (493), laryngeal (499), and gastric (504) cancers.

Conclusions

As summarized above, a great deal of work has been performed over the past several years to characterize the cancer chemopreventive and therapeutic potential of resveratrol. The ultimate objective of this work is to answer one question: Is resveratrol of value to alleviate any type of cancer in human beings? Because human beings are already consuming resveratrol, either as a constituent of the diet or as a dietary supplement, data could already exist to suggest the potential of resveratrol to function in this capacity. Consumption of red wine, for example, implies the ingestion of resveratrol, and correlations can be examined between consumption and cancer incident. However, no clear answers can be derived from such epidemiologic considerations, so the possible efficacy of resveratrol remains an open question. As was learned by the failure of β-carotene to prevent lung cancer (508, 509), human clinical trials are necessary to understand the true efficacy of experimental agents, irrespective of compelling laboratory data that may suggest effectiveness.

Spearheaded by Waun Ki Hong and Michael B. Sporn, a Chemopreventive Working Group recently provided a report describing the prevention of cancer in the current millennium (4). Included in this report was a list of seven desirable/acceptable characterizations of cancer chemopreventive agents. In brief, these will be considered in the context of resveratrol.

1. *Efficacy in preventing cancer*. Resveratrol has been shown to demonstrate efficacy in multiple animal models. Activity in human beings is unknown.
2. *Knowledge about mechanism of inhibition*. As summarized in this article, a great deal of information is available concerning the mechanism of action of resveratrol. Although a straightforward sequence of critical events cannot be defined due to the overtly pleiotropic mode of action, some existing data are certainly valuable.
3. *Information as to likely efficacy in the human*. The most compelling data are derived from animal studies in which resveratrol is administered by the oral route. This has been accomplished. Therefore, although absorption and metabolism (124, 233, 265, 276) requires additional investigation and remains moot to some extent, the potential of efficacy in humans does appear likely. Some indication of toxicity has been suggested (277, 283) and needs to be further defined, but most studies suggest favorable therapeutic indices.
4. *Demonstration of efficacy in experimental animals*. In general, it is not possible to predict efficacy in only one animal model. Efficacy has been demonstrated in breast, skin, esophagus, and colon models, but further tests should be performed in additional models such as bladder, prostate, uterus, and kidney. Resveratrol does not appear active in some mouse lung cancer models.
5. *Lack of toxicity and undesirable side effects*. Certainly, long-term feeding studies have been performed with resveratrol without untoward toxic side-effects (483), but some suggestions of potential toxicity and/or hormonal activity have been put forth. Overall, it seems highly likely that a therapeutic regimen could be devised with an acceptable risk/benefit ratio. Nonetheless, thorough preclinical assessment of resveratrol in acceptable models of toxicity will be required prior to advocating long-term human investigation trials.
6. *Compounds already approved by the FDA for human use or likely to be approved readily*. To obtain FDA approval for clinical trails, it is likely that comprehensive preclinical toxicity trials are necessary. However, these studies are straightforward, and a notable advantage is an ample supply of resveratrol through chemical synthesis. The work needs to be completed prior to drawing conclusions, but existing data suggest acceptable dose regimens could be devised, and it seems likely that FDA approval would follow.
7. *Occurrence of the agent in foods or beverages*. The occurrence of resveratrol in foods or beverages is an obvious advantage in terms of development. It can already be stated with a high degree of confidence that consumption of limited quantities of resveratrol is not harmful to human beings, and great flexibility becomes available in terms of long-term dosing strategies.

Consistent with these suggestions, some limited data are available from studies conducted with human beings,

and four small-scale phase trials are under way (Table 8). First and foremost, as predicted from animal and cell culture studies, resveratrol is readily absorbed after oral administration and rapidly metabolized (507, 510, 512). The primary metabolites are sulfates and glucuronides. These metabolites require further investigation as they are probably responsible for the biological response mediated by resveratrol administration. In addition, resveratrol is present, albeit in low concentrations, so physiologic responses would need to be facilitated by the parent compound with great specificity and avidy. A combination effect is feasible, especially as so many potential targets have been identified.

In sum, a great deal of time, money, and intellectual capital has been invested in the exploration of resveratrol. From a purely academic point of view, considering the structural simplicity of resveratrol, the extent of this effort is incredible. Implicitly, however, the shear magnitude of investigation supports the intrinsic value of this compound. Based on the criteria discussed above, and the overall favorable characteristics of resveratrol, it is reasonable to advocate further development as a cancer chemopreventive agent. Perhaps this review will have some value in facilitating the process.

Acknowledgments

The author is grateful to faculty colleagues associated with this research project, namely, Drs. C-j. Chang, B. Craig, M. Cushman, W. Fenical, H.H.S. Fong, A.D. Mesecar, R.C. Moon, and R.B. van Breemen, and to many postdoctoral associates, graduate students, and research assistants who worked in the laboratory in support of this research. Special thanks are extended to Elizabeth Ryan for help in organizing this manuscript and collating the descriptions given in the tables. The support of collaborators throughout the world who have participated in the selection, collection, and identification of plant materials used in the current work is also gratefully acknowledged. The current work is supported by program project grant P01 CA48112, funded by the National Cancer Institute, NIH, Bethesda, Maryland, USA.

References

1. Pezzuto J (2006): Resveratrol as an inhibitor of carcinogenesis. In: Aggarwal B, Shishodia S, eds., *Resveratrol in Health and Disease*. New York, Taylor & Francis, pp. 233–383.
2. Stewart B, Kleihues P (2003): *World Cancer Report*. Lyon, IACR Press, pp. 9–19.
3. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun M (2003): Cancer statistics. *CA Cancer J Clin 53*: 5–26.
4. Alberts D, Conney A, Ernster V, Garber J, Greenwald P, Gudas L, Hong W, Kelloff G, Kramer R, Lerman C, Mangelsdorf D, Matter A, Minna J, Nelson W, Pezzuto J, Prendergast F, Rusch V, Sporn M, Wattenberg L, Weinstein B (1999): Prevention of cancer in the next millennium. Report of the Chemoprevention Working Group to the American Association for Cancer Research. *Cancer Res 59*:4743–4758.
5. Kelloff GJ (2000): Perspectives on cancer chemoprevention research and drug development. *Adv Cancer Res 78*: 199–334.
6. Sporn M (1996): The war on cancer. *Lancet 347*: 1377–1381.
7. Greenwald P, Kelloff G, Burch-Whitman C, Kramer B (1995): Chemoprevention. *CA Cancer J Clin 45*: 31–49.
8. Wattenberg L (1985): Chemoprevention of cancer. *Cancer Res 45*: 1–8.
9. Sporn M, Dunlop N, Newton D, Smith J (1976): Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *Fed Proc 35*: 1332–1338.
10. Kelloff G, Hawk E, Karp J, Crowell J, Boone C, Steele V, Lubet R, Sigman C (1997): Progress in clinical chemoprevention. *Semin Oncol 24*: 241–252.
11. Willett W, MacMahon B (1984): Diet and cancer: an overview [second of two parts]. *N Engl J Med 310*: 697–703.
12. Harris C (1991): Chemical and physical carcinogenesis: advances and perspectives for the 1990s. *Cancer Res 51* (Suppl):5023–5044.
13. Flora SD (1998): Mechanisms of inhibitors of mutagenesis and carcinogenesis. *Mutation Res 402*: 151–158.
14. Sporn M (1991): Carcinogenesis and cancer: Different perspectives on the same disease. *Cancer Res 51*: 6215–6218.
15. Kelloff G, Crowell J, Steele V, Lubet R, Boone C, Malone W, Hawk E, Lieberman R, Lawrence J, Kopelovich L, Ali I, Viner J, Sigman C (1999): Progress in cancer chemoprevention. *Ann NY Acad Sci 889*: 1–13.
16. Morse M, Stoner G (1993): Cancer chemoprevention: Principles and prospects. *Carcinogenesis 14*: 1737–1746.
17. Surh Y (1999): Molecular mechanisms of chemopreventive effects of selected dietary and medicinal phenolic substances. *Mutat Res 428*: 305–327.
18. Reddy L, Bhoola K (2003): Natural products for cancer prevention: A global perspective. *Pharmacol Ther 99*: 1–13.
19. Fujiki H, Suganuma M, Imai K, Nakachi K (2002): Green tea: Cancer preventive beverage and/or drug. *Cancer Lett 188*: 9–13.
20. Surh Y-J (2003): Cancer chemoprevention with dietary phytochemicals. *Nature Rev Cancer 3*: 768–780.
21. ClinicalTrials.gov, a service of the U.S. National Institutes of Health. Available at http://clinicaltrials.gov/ct2/results?term=resveratrol. Accessed March 2008.
22. Chow HH, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA, Dorr RT, Hara Y, Alberts DS (2003): Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res 9*: 3312–3319.
23. Fujiki H (1999): Two stages of cancer prevention with green tea. *J Cancer Res Clin 125*: 589–597.
24. Ren W, Qiao Z, Wang H, Zhu L, Zhang L (2003): Flavonoids: promising anticancer agents. *Med Res Rev 23*: 519–534.

25. Pezzuto J (1995): Natural product cancer chemopreventive agents. In: Arnason J, Mata R, Romeo J, eds. *Recent Advances in Phytochemistry*, Vol 29. New York, Plenum Press, pp. 19–45.
26. Pezzuto J, Song L, Lee S, Shamon L, Mata-Greenwood E, Jang J, Jeong H-J, Pisha E, Mehta R, Kinghorn A (1998): Bioassay methods useful for activity-guided isolation of natural product cancer chemopreventive agents. In: Hostettmann K, Gupta M, Marston A, eds. *Chemistry, Biological and Pharmacological Properties of Medicinal Plants from the Americas*. Chur, Switzerland, Harwood Academic Publishers, pp. 81–110.
27. Kinghorn A, Su B-N, Lee D, Gu J-Q, Pezzuto J (2003): Cancer chemopreventive agents discovered by activity-guided fractionation: An update. *Curr Org Chem 7*: 213–226.
28. Pezzuto J, Kosmeder J, Park E, Lee S, Cuendet M, Gills J, Bhat K, Grubjesic S, Park H-S, Mata-Greenwood E, Tan Y, Yu R, Lantvit D, Kinghorn A (2005): Characterization of natural product chemopreventive agents. In: Kelloff G, Hawk E, Sigman C, eds. *Cancer Chemoprevention*, *Volume 2: Strategies for Cancer Chemoprevention*. Totowa, NJ, Humana Press Inc., pp. 3–37.
29. Loub W, Farnsworth N, Soejarto D, Quinn M (1985): NAPRALERT: Computer handling of natural product research data. *J Chem Inf Computer Sci* 25:99–103.
30. Kosmeder JW, II, Pezzuto JM (2001): Intermediate biomarkers. *Cancer Treat Res 106*: 31–61.
31. Crowell J, Holmes C (2001): Agent identification and preclinical testing. *Cancer Treat Res 106*: 1–30.
32. Mehta R, Moon R (1991): Characterization of effective chemopreventive agents in mammary gland *in vitro* using an initiation-promotion protocol. *Anticancer Res 11*: 593–596.
33. Mehta RG, Bhat KP, Hawthorne ME, Kopelovich L, Mehta RR, Christov K, Kelloff GJ, Steele VE, Pezzuto JM (2001): Induction of atypical ductal hyperplasia in mouse mammary gland organ culture. *J Natl Cancer Inst 93*: 1103–1106.
34. Shamon L, Pezzuto J (1997): Assessment of antimutagenic activity with *Salmonella typhimurium* strain TM677. *Methods Cell Sci 19*: 57–62.
35. Lee SK, Mbwambo ZH, Chung H, Luyengi L, Gamez EJ, Mehta RG, Kinghorn AD, Pezzuto JM (1998): Evaluation of the antioxidant potential of natural products. *Comb Chem High Throughput Screen 1*: 35–46.
36. Song LL, Kosmeder JW, 2nd, Lee SK, Gerhauser C, Lantvit D, Moon RC, Moriarty RM, Pezzuto JM (1999): Cancer chemopreventive activity mediated by 4′-bromoflavone, a potent inducer of phase II detoxification enzymes. *Cancer Res 59*: 578–585.
37. Kang YH, Pezzuto JM (2004): Induction of quinone reductase as a primary screen for natural product anticarcinogens. *Methods Enzymol 382*: 380–414.
38. Gerhäuser C, Mar W, Lee S, Suh N, Luo Y, Kosmeder J, Moriarty R, Luyengi L, Kinghorn A, Fong H, Mehta R, Constantinou A, Moon R, Pezzuto J (1995): Rotenoids mediate potent chemopreventive activity through transcriptional regulation of ornithine decarboxylase. *Nature Med 1*: 260–266.
39. Mbwambo ZH, Lee SK, Mshiu EN, Pezzuto JM, Kinghorn AD (1996): Constituents from the stem wood of *Euphorbia quinquecostata* with phorbol dibutyrate receptor-binding inhibitory activity. *J Nat Prod 59*: 1051–1055.
40. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM (1997): Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science 275*: 218–220.
41. El Sayed KA, Hamann MT, Waddling CA, Jensen C, Lee SK, Dunstan CA, Pezzuto JM (1998): Structurally novel bioconversion products of the marine natural product sarcophine effectively inhibit JB6 cell transformation. *J Org Chem 63*: 7449–7455.
42. Suh N, Luyengi L, Fong HH, Kinghorn AD, Pezzuto JM (1995): Discovery of natural product chemopreventive agents utilizing HL-60 cell differentiation as a model. *Anticancer Res 15*: 233–239.
43. Pisha E, Pezzuto J (1997): Cell-based assay for the determination of estrogenic and anti-estrogenic activity. *Meth Cell Sci 19*: 37–43.
44. Jeong HJ, Shin YG, Kim IH, Pezzuto JM (1999): Inhibition of aromatase activity by flavonoids. *Arch Pharm Res 22*: 309–312.
45. Chang LC, Gills JJ, Bhat KP, Luyengi L, Farnsworth NR, Pezzuto JM, Kinghorn AD (2000): Activity-guided isolation of constituents of *Cerbera manghas* with antiproliferative and antiestrogenic activities. *Bioorg Med Chem Lett 10*: 2431–2434.
46. Gamez EJ, Luyengi L, Lee SK, Zhu LF, Zhou BN, Fong HH, Pezzuto JM, Kinghorn AD (1998): Antioxidant flavonoid glycosides from *Daphniphyllum calycinum*. *J Nat Prod 61*: 706–70.
47. Su BN, Park EJ, Nikolic D, Santarsiero BD, Mesecar AD, Vigo JS, Graham JG, Cabieses F, van Breemen RB, Fong HH, Farnsworth NR, Pezzuto JM, Kinghorn AD (2003): Activity-guided isolation of novel norwithanolides from *Deprea subtriflora* with potential cancer chemopreventive activity. *J Org Chem 68*: 2350–2361.
48. Gu JQ, Park EJ, Luyengi L, Hawthorne ME, Mehta RG, Farnsworth NR,Pezzuto JM, Kinghorn AD (2001): Constituents of *Eugenia sandwicensis* with potential cancer chemopreventive activity. *Phytochemistry 58*: 121–127.
49. Johnson B, Nikolic D, van Breemen R (2002): Applications of pulsed ultrafiltration-mass spectrometry. *Mass Spectrom Rev 21*: 76–86.
50. Kinghorn AD, Su BN, Jang DS, Chang LC, Lee D, Gu JQ,Carcache-Blanco EJ, Pawlus AD, Lee SK, Park EJ, Cuendet M, Gills JJ, Bhat K, Park HS, Mata-Greenwood E, Song LL, Jang M, Pezzuto JM (2004): Natural inhibitors of carcinogenesis. *Planta Med 70*: 691–705.
51. Su BN, Park EJ, Nikolic D, Schunke Vigo J, Graham JG, Cabieses F, van Breemen RB, Fong HH, Farnsworth NR, Pezzuto JM, Kinghorn AD (2003): Isolation and characterization of miscellaneous secondary metabolites of *Deprea subtriflora*. *J Nat Prod 66*: 1089–1093.

52. Lee D, Cuendet M, Vigo JS, Graham JG, Cabieses F, Fong HH, Pezzuto JM, Kinghorn AD (2001): A novel cyclooxygenase-inhibitory stilbenolignan from the seeds of *Aiphanes aculeata*. *Org Lett 3*: 2169–2171.
53. Lee D, Park EJ, Cuendet M, Axelrod F, Chavez PI, Fong HH, Pezzuto JM, Kinghorn AD (2001): Cyclooxygenase-inhibitory and antioxidant constituents of the aerial parts of *Antirhea acutata*. *Bioorg Med Chem Lett 11*: 1565–1568.
54. Mehta RG, Liu J, Constantinou A, Thomas CF, Hawthorne M, You M, Gerhäuser C, Pezzuto JM, Moon RC, Moriarty RM (1995): Cancer chemopreventive activity of brassinin, a phytoalexin from cabbage. *Carcinogenesis 16*: 399–404.
55. Gerhäuser C, Lee SK, Kosmeder JW, Moriarty RM, Hamel E, Mehta RG, Moon RC, Pezzuto JM (1997): Regulation of ornithine decarboxylase induction by deguelin, a natural product cancer chemopreventive agent. *Cancer Res 57*: 3429–3435.
56. Udeani GO, Gerhauser C, Thomas CF, Moon RC, Kosmeder JW, Kinghorn AD, Moriarty RM, Pezzuto JM (1997): Cancer chemopreventive activity mediated by deguelin, a naturally occurring rotenoid. *Cancer Res 57*: 3424–3428.
57. Lee HY, Suh YA, Kosmeder JW, Pezzuto JM, Hong WK, Kurie JM (2004): Deguelin-induced inhibition of cyclooxygenase-2 expression in human bronchial epithelial cells. *Clin Cancer Res 10*: 1074–1079.
58. Murillo G, Hirschelman WH, Ito A, Moriarty RM, Kinghorn AD, Pezzuto JM, Mehta G (2007): Zapotin, a phytochemical present in a Mexican fruit, prevents colon carcinogenesis. *Nutr Cancer 57*: 28–37.
59. Mata-Greenwood E, Cuendet M, Sher D, Gustin D, Stock W, Pezzuto JM (2002): Brusatol-mediated induction of leukemic cell differentiation and G(1) arrest is associated with down-regulation of c-myc. *Leukemia 16*: 2275–2284.
60. Cuendet M, Christov K, Lantvit DD, Deng Y, Hedayat S, Helson L, McChesney JD, Pezzuto JM (2004): Multiple myeloma regression mediated by bruceantin. *Clin Cancer Res 10*: 1170–1179.
61. Lee D, Bhat KP, Fong HH, Farnsworth NR, Pezzuto JM, Kinghorn AD (2001): Aromatase inhibitors from *Broussonetia papyrifera*. *J Nat Prod 64*: 1286–1293.
62. Zhang Y, Kensler TW, Cho CG, Posner GH, Talalay P (1994): Anticarcinogenic activities of sulforaphane and structurally related synthetic norbornyl isothiocyanates. *Proc Natl Acad Sci USA 91*: 3147–3150.
63. Gerhäuser C, You M, Liu J, Moriarty RM, Hawthorne M, Mehta RG, Moon RC, Pezzuto JM (1997): Cancer chemopreventive potential of sulforamate, a novel analogue of sulforaphane that induces phase 2 drug-metabolizing enzymes. *Cancer Res 57*: 272–278.
64. Kosmeder II JW, Hirschelman WH, Song LS, Park EJ, Tan Y, Yu R, Hawthorne M, Mehta RG, Grubbs CJ, Lubet RA, Moriarty RM, Pezzuto JM. Cancer chemopreventive activity of oxomate, a monofunctional inducer of Phase II detoxification enzymes. 224th American Chemical Society National Meeting. Boston, Massachusetts, August 18–22, 2002.
65. Stewart JR, Artime MC, O'Brian CA (2003): Resveratrol: a candidate nutritional substance for prostate cancer prevention. *J Nutr 133*: 2440S-2443S.
66. Creasy L, Coffee M (1988): Phytoalexin production potential of grape berries. *J Am Soc Hortic Sci 113*: 230–234.
67. Schwekendiek A, Pfeffer G, Kindl H (1992): Pine stilbene synthase cDNA, a tool for probing environmental stress. *FEBS Lett 301*: 41–44.
68. Jeandet P, Douillet-Breuil AC, Bessis R, Debord S, Sbaghi M, Adrian M (2002): Phytoalexins from the *Vitaceae*: biosynthesis, phytoalexin gene expression in transgenic plants, antifungal activity, and metabolism. *J Agric Food Chem 50*: 2731–2741.
69. Montero C, Cristescu S, Jimenez J, Orea J, Hekkert StL, Harren F, Urena AG (2003): *trans*-Resveratrol and grape disease resistance, a dynamic study by high-resolution laser-based techniques. *Plant Physiol 131*: 129–138.
70. Hawksworth D (2003): Micological research news. *Mycol Res 107*: 769–770.
71. Siemann G, Creasy L (1992): Concentration of the phytoalexin resveratrol in wine. *Am J Ecol Viticul 43*: 49–52.
72. Cantos E, Garcia-Viguera C, Pascual-Teresa S, Tomas-Barberan F (2000): Effect of postharvest ultraviolet irradiation on resveratrol and other phenolics of cv. Napoleon table grapes. *J Agric Food Chem 48*: 4604–4612.
73. Careri M, Corradini C, Elviri L, Nicoletti I, Zagnoni I (2003): Direct HPLC analysis of quercetin and trans-resveratrol in red wine, grape, and winemaking byproducts. *J Agric Food Chem 51*: 5226–5231.
74. Nonomura S, Kanagawa H, Makimoto A (1963): Chemical constituents of polygonaceous plants. I. Studies on the components of Ko-jo-kon (*Polygonum cuspidatum* SIEB et ZUCC). *Yukugaku Zasshi 83*: 983–988.
75. Hain R, Reif HJ, Krause E, Langebartels R, Kindl H, Vornam B, Wiese W, Schmelzer E, Schreier PH, Stocker RH, Stenzel K (1993): Disease resistance results from foreign phytoalexin expression in a novel plant. *Nature 361*: 153–156.
76. Paiva N (1999): *Engineering Resveratrol Accumulation into Alfalfa and Other Food Plants*. International Molecular Farming Conference. London, Ontario, Canada, p. 134.
77. Proceedings of a Conference Exploring the Power of Phytochemicals: Research Advances on Grape Compounds (1998): Pezzuto J, Steele V, eds, Lisse, The Netherlands, Swets and Zeitlinger, (A supplement of *Pharm Biol*).
78. Bhat KPL, Kosmeder JW, 2nd, Pezzuto JM (2001): Biological effects of resveratrol. *Antioxid Redox Signal 3*: 1041–1064.
79. Subbaramaiah K, Chung WJ, Michaluart P, Telang N, Tanabe T, Inoue H, Jang M, Pezzuto JM, Dannenberg AJ (1998): Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. *J Biol Chem 273*: 21875–21882.

80. Jang M, Pezzuto JM (1999): Cancer chemopreventive activity of resveratrol. *Drugs Exp Clin Res 25*: 65–77.
81. Bhat KP, Pezzuto JM (2002): Cancer chemopreventive activity of resveratrol. *Ann N Y Acad Sci 957*: 210–229.
82. Pezzuto J, Kondratyuk T, Shalaev E (2006): Cancer chemoprevention by wine polyphenols and resveratrol. In: Baer-Dubowska W, Bartoszek A, Malejka-Giganti D, eds. *Carcinogenic and Anticarcinogenic Food Components*. Boca Raton, FL, CRC Press, pp. 239–282.
83. Bagchi D (2000): *Resveratrol and Human Health*. Columbus, OH: McGraw Hill.
84. Aggarwal B, Shishodia S (2006): *Resveratrol in Health and Disease*. Boca Raton, FL, Taylor & Francis.
85. Szumilo J (2006): Resveratrol—evaluation of anticancer activity. *Pol Merkur Lekarski 20*: 362–364.
86. Baur JA, Sinclair DA (2006): Therapeutic potential of resveratrol: The *in vivo* evidence. *Nat Rev Drug Discov 5*: 493–506.
87. Delmas D, Lancon A, Colin D, Jannin B, Latruffe N (2006): Resveratrol as a chemopreventive agent: A promising molecule for fighting cancer. *Curr Drug Targets 7*: 423–442.
88. Aggarwal BB, Shishodia S (2006): Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem Pharmacol 71*: 1397–1421.
89. Trosko JE (2005): The role of stem cells and gap junctions as targets for cancer chemoprevention and chemotherapy. *Biomed Pharmacother 59 Suppl 2*: S326–331.
90. Yance DR, Jr., Sagar SM (2006): Targeting angiogenesis with integrative cancer therapies. *Integr Cancer Ther 5*: 9–29.
91. Baliga MS, Katiyar SK (2006): Chemoprevention of photocarcinogenesis by selected dietary botanicals. *Photochem Photobiol Sci 5*: 243–253.
92. Anderson LM (2005): Cancer biology and hormesis: Comments on Calabrese. *Crit Rev Toxicol 35*: 583–586.
93. Garg AK, Buchholz TA, Aggarwal BB (2005): Chemosensitization and radiosensitization of tumors by plant polyphenols. *Antioxid Redox Signal 7*: 1630–1647.
94. Ovesna Z, Horvathova-Kozics K (2005): Structure-activity relationship of *trans*-resveratrol and its analogues. *Neoplasma 52*: 450–455.
95. Trosko JE, Chang CC, Upham BL, Tai MH (2005): The role of human adult stem cells and cell-cell communication in cancer chemoprevention and chemotherapy strategies. *Mutat Res 591*: 187–197.
96. Kundu JK, Surh YJ (2004): Molecular basis of chemoprevention by resveratrol: NF-κB and AP-1 as potential targets. *Mutat Res 555*: 65–80.
97. Bode AM, Dong Z (2004): Targeting signal transduction pathways by chemopreventive agents. *Mutat Res 555*: 33–51.
98. Signorelli P, Ghidoni R (2005): Resveratrol as an anticancer nutrient: Molecular basis, open questions and promises. *J Nutr Biochem 16*: 449–466.
99. Shimizu M, Weinstein IB (2005): Modulation of signal transduction by tea catechins and related phytochemicals. *Mutat Res 591*: 147–160.
100. Morris BJ (2005): A forkhead in the road to longevity: The molecular basis of lifespan becomes clearer. *J Hypertens 23*: 1285–1309.
101. Tisdale MJ (2005): The ubiquitin-proteasome pathway as a therapeutic target for muscle wasting. *J Support Oncol 3*: 209–217.
102. Stopper H, Schmitt E, Kobras K (2005): Genotoxicity of phytoestrogens. *Mutat Res 574*: 139–155.
103. Guastalla JP, Bachelot T, Ray-Coquard I (2004): Cyclooxygenase 2 and breast cancer. From biological concepts to clinical trials. *Bull Cancer 91 Suppl 2*: S99–108.
104. de la Lastra CA, Villegas I (2005): Resveratrol as an anti-inflammatory and anti-aging agent: Mechanisms and clinical implications. *Mol Nutr Food Res 49*: 405–430.
105. Ulrich S, Wolter F, Stein JM (2005): Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in carcinogenesis. *Mol Nutr Food Res 49*: 452–461.
106. Ray A (2005): Cancer preventive role of selected dietary factors. *Indian J Cancer 42*: 15–24.
107. Kimura Y (2005): New anticancer agents: *In vitro* and *in vivo* evaluation of the antitumor and antimetastatic actions of various compounds isolated from medicinal plants. *In Vivo 19*: 37–60.
108. Pervaiz S (2004): Chemotherapeutic potential of the chemopreventive phytoalexin resveratrol. *Drug Resist Updat 7*: 333–344.
109. Le Corre L, Chalabi N, Delort L, Bignon YJ, Bernard-Gallon DJ (2005). Resveratrol and breast cancer chemoprevention: Molecular mechanisms. *Mol Nutr Food Res 49*: 462–471.
110. Granados-Soto V (2003): Pleiotropic effects of resveratrol. *Drug News Perspect 16*: 299–307.
111. Atten MJ, Godoy-Romero E, Attar BM, Milson T, Zopel M, Holian O (2005): Resveratrol regulates cellular PKC alpha and delta to inhibit growth and induce apoptosis in gastric cancer cells. *Invest New Drugs 23*: 111–119.
112. Gescher A (2004): Polyphenolic phytochemicals versus non-steroidal anti-inflammatory drugs: Which are better cancer chemopreventive agents? *J Chemother 16 Suppl 4*: 3–6.
113. Manson MM, Farmer PB, Gescher A, Steward WP (2005): Innovative agents in cancer prevention. *Recent Results Cancer Res 166*: 257–275.
114. Oak MH, El Bedoui J, Schini-Kerth VB (2005): Antiangiogenic properties of natural polyphenols from red wine and green tea. *J Nutr Biochem 16*: 1–8.
115. Choi SM, Lee BM (2004): An alternative mode of action of endocrine-disrupting chemicals and chemoprevention. *J Toxicol Environ Health B Crit Rev 7*: 451–463.
116. Wolter F, Ulrich S, Stein J (2004): Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in colorectal cancer: Key role of polyamines? *J Nutr 134*: 3219–3222.
117. Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y (2004): Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. *Anticancer Res 24*: 2783–2840.

118. Dorai T, Aggarwal BB (2004): Role of chemopreventive agents in cancer therapy. *Cancer Lett 215*: 129–140.
119. Aggarwal BB, Takada Y, Oommen OV (2004): From chemoprevention to chemotherapy: Common targets and common goals. *Expert Opin Invest Drugs 13*: 1327–1338.
120. Jannin B, Menzel M, Berlot JP, Delmas D, Lancon A, Latruffe N (2004): Transport of resveratrol, a cancer chemopreventive agent, to cellular targets: plasmatic protein binding and cell uptake. *Biochem Pharmacol 68*: 1113–1118.
121. Simopoulos AP (2004): The traditional diet of Greece and cancer. *Eur J Cancer Prev 13*: 219–230.
122. Park JW, Clark OH (2004): Redifferentiation therapy for thyroid cancer. *Surg Clin North Am 84*: 921–943.
123. Ho SM (2004): Estrogens and anti-estrogens: Key mediators of prostate carcinogenesis and new therapeutic candidates. *J Cell Biochem 91*: 491–503.
124. Li Y, Shin YG, Yu C, Kosmeder JW, Hirschelman WH, Pezzuto JM, van Breemen RB (2003): Increasing the throughput and productivity of Caco-2 cell permeability assays using liquid chromatography-mass spectrometry: Application to resveratrol absorption and metabolism. *Comb Chem High Throughput Screen 6*: 757–767.
125. Gescher AJ, Steward WP (2003): Relationship between mechanisms, bioavailibility, and preclinical chemopreventive efficacy of resveratrol: A conundrum. *Cancer Epidemiol Biomarkers Prev 12*: 953–957.
126. Bianchini F, Vainio H (2003): Wine and resveratrol: Mechanisms of cancer prevention? *Eur J Cancer Prev 12*: 417–425.
127. Bhavnani BR (2003): Estrogens and menopause: Pharmacology of conjugated equine estrogens and their potential role in the prevention of neurodegenerative diseases such as Alzheimer's. *J Steroid Biochem Mol Biol 85*: 473–482.
128. Frank GC (2003): From sandwiches to center stage. Peanuts pack a powerful nutritional punch. *Adv Nurse Pract 11*: 85–87, 95.
129. Lopez-Velez M, Martinez-Martinez F, Del Valle-Ribes C (2003): The study of phenolic compounds as natural antioxidants in wine. *Crit Rev Food Sci Nutr 43*: 233–244.
130. Kimura Y (2003): Pharmacological studies on resveratrol. *Methods Find Exp Clin Pharmacol 25*: 297–310.
131. Aziz MH, Kumar R, Ahmad N (2003): Cancer chemoprevention by resveratrol: *In vitro* and *in vivo* studies and the underlying mechanisms (review). *Int J Oncol 23*: 17–28.
132. Corpet DE, Pierre F (2003): Point: From animal models to prevention of colon cancer. Systematic review of chemoprevention in min mice and choice of the model system. *Cancer Epidemiol Biomarkers Prev 12*: 391–400.
133. Cal C, Garban H, Jazirehi A, Yeh C, Mizutani Y, Bonavida B (2003): Resveratrol and cancer: Chemoprevention, apoptosis, and chemo-immunosensitizing activities. *Curr Med Chem Anticancer Agents 3*: 77–93.
134. Safe SH, Pallaroni L, Yoon K, Gaido K, Ross S, McDonnell D (2002): Problems for risk assessment of endocrine-active estrogenic compounds. *Environ Health Perspect 110 Suppl 6*: 925–929.
135. Guengerich FP, Chun YJ, Kim D, Gillam EM, Shimada T (2003): Cytochrome P450 1B1: A target for inhibition in anticarcinogenesis strategies. *Mutat Res 523–524*: 173–182.
136. Dong Z (2003): Molecular mechanism of the chemopreventive effect of resveratrol. *Mutat Res 523–524*: 145–150.
137. Roemer K, Mahyar-Roemer M (2002): The basis for the chemopreventive action of resveratrol. *Drugs Today (Barc) 38*: 571–580.
138. Thampatty BP, Rosenkranz HS (2002): Structural concepts in cancer prevention. *Eur J Cancer Prev* 11 Suppl 2:S76–85.
139. Kris-Etherton PM, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert KF, Griel AE, Etherton TD (2002): Bioactive compounds in foods: Their role in the prevention of cardiovascular disease and cancer. *Am J Med 113 Suppl 9B*: 71S-88S.
140. Park EJ, Pezzuto JM (2002): Botanicals in cancer chemoprevention. *Cancer Metastasis Rev 21*: 231–255.
141. Ratan HL, Steward WP, Gescher AJ, Mellon JK (2002): Resveratrol—a prostate cancer chemopreventive agent? *Urol Oncol 7*: 223–227.
142. Mehta RG, Pezzuto JM (2002): Discovery of cancer preventive agents from natural products: From plants to prevention. *Curr Oncol Rep 4*: 478–486.
143. Culig Z, Klocker H, Bartsch G, Hobisch A (2002): Androgen receptors in prostate cancer. *Endocr Relat Cancer 9*: 155–170.
144. Tsan MF, White JE, Maheshwari JG, Chikkappa G (2002): Anti-leukemia effect of resveratrol. *Leuk Lymphoma 43*: 983–987.
145. Milner JA, McDonald SS, Anderson DE, Greenwald P (2001): Molecular targets for nutrients involved with cancer prevention. *Nutr Cancer 41*: 1–16.
146. Savouret JF, Quesne M (2002): Resveratrol and cancer: A review. *Biomed Pharmacother 56*: 84–87.
147. Ignatowicz E, Baer-Dubowska W (2001): Resveratrol, a natural chemopreventive agent against degenerative diseases. *Pol J Pharmacol 53*: 557–569.
148. Bode AM, Dong Z (2000): Signal transduction pathways: Targets for chemoprevention of skin cancer. *Lancet Oncol 1*: 181–188.
149. Afaq F, Adhami VM, Ahmad N, Mukhtar H (2002): Botanical antioxidants for chemoprevention of photocarcinogenesis. *Front Biosci 7*: d784–792.
150. Stierum R, Burgemeister R, van Helvoort A, Peijnenburg A, Schutze K, Seidelin M, Vang O, van Ommen B (2001): Functional food ingredients against colorectal cancer. An example project integrating functional genomics, nutrition and health. *Nutr Metab Cardiovasc Dis 11*: 94–98.
151. Safe SH, Pallaroni L, Yoon K, Gaido K, Ross S, Saville B, McDonnell D (2001): Toxicology of environmental estrogens. *Reprod Fertil Dev 13*: 307–315.
152. Wargovich MJ (2001): Colon cancer chemoprevention with ginseng and other botanicals. *J Korean Med Sci 16 Suppl*: S81–86.
153. Simopoulos AP (2001): The Mediterranean diets: What is so special about the diet of Greece? The scientific evidence. *J Nutr 131*: 3065S-3073S.

154. Surh YJ, Chun KS, Cha HH, Han SS, Keum YS, Park KK, Lee SS (2001): Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: Down-regulation of COX-2 and iNOS through suppression of NF-κB activation. *Mutat Res 480–481*: 243–268.
155. Kong AN, Yu R, Hebbar V, Chen C, Owuor E, Hu R, Ee R, Mandlekar S (2001): Signal transduction events elicited by cancer prevention compounds. *Mutat Res 480–481*: 231–241.
156. Ciolino HP, Yeh GC (2001): The effects of resveratrol on CYP1A1 expression and aryl hydrocarbon receptor function *in vitro*. *Adv Exp Med Biol 492*: 183–193.
157. Soleas GJ, Diamandis EP, Goldberg DM (2001): The world of resveratrol. *Adv Exp Med Biol 492*: 159–182.
158. Gusman J, Malonne H, Atassi G (2001): A reappraisal of the potential chemopreventive and chemotherapeutic properties of resveratrol. *Carcinogenesis 22*: 1111–1117.
159. Pervaiz S (2001): Resveratrol—from the bottle to the bedside? *Leuk Lymphoma 40*: 491–498.
160. Yang CS, Landau JM, Huang MT, Newmark HL (2001): Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annu Rev Nutr 21*: 381–406.
161. Olas B, Wachowicz B (2001): Biological activity of resveratrol. *Postepy Hig Med Dosw 55*: 71–79.
162. Ahmad N, Katiyar SK, Mukhtar H (2001): Antioxidants in chemoprevention of skin cancer. *Curr Probl Dermatol 29*: 128–139.
163. Dong Z (2000): Effects of food factors on signal transduction pathways. *Biofactors 12*: 17–28.
164. Cuendet M, Pezzuto JM (2000): The role of cyclooxygenase and lipoxygenase in cancer chemoprevention. *Drug Metabol Drug Interact 17*: 109–157.
165. Hadi SM, Asad SF, Singh S, Ahmad A (2000): Putative mechanism for anticancer and apoptosis-inducing properties of plant-derived polyphenolic compounds. *IUBMB Life 50*: 167–171.
166. Huber J (2000): Phytoestrogens and SERMS, alternatives to classical hormone therapy? *Ther Umsch 57*: 651–654.
167. Weisburger JH (1999): Mechanisms of action of antioxidants as exemplified in vegetables, tomatoes and tea. *Food Chem Toxicol 37*: 943–948.
168. Lin JK, Tsai SH (1999): Chemoprevention of cancer and cardiovascular disease by resveratrol. *Proc Natl Sci Counc Repub China B 23*: 99–106.
169. Calabrese G (1999): Nonalcoholic compounds of wine: The phytoestrogen resveratrol and moderate red wine consumption during menopause. *Drugs Exp Clin Res 25*: 111–114.
170. Tredici G, Miloso M, Nicolini G, Galbiati S, Cavaletti G, Bertelli A (1999): Resveratrol, map kinases and neuronal cells: Might wine be a neuroprotectant? *Drugs Exp Clin Res 25*: 99–103.
171. Soleas GJ, Diamandis EP, Goldberg DM (1997): Wine as a biological fluid: History, production, and role in disease prevention. *J Clin Lab Anal 11*: 287–313.
172. Russo GL (2007): Ins and outs of dietary phytochemicals in cancer chemoprevention. *Biochem Pharmacol 74*: 533–544.
173. Malemud CJ (2007): Inhibitors of stress-activated protein/mitogen-activated protein kinase pathways. *Curr Opin Pharmacol 7*: 339–343.
174. Pettit GR, Grealish MP, Jung MK, Hamel E, Pettit RK, Chapuis JC, Schmidt JM (2002): Antineoplastic agents. 465. Structural modification of resveratrol: Sodium resverastatin phosphate. *J Med Chem 45*: 2534–2542.
175. Kim S, Ko H, Park JE, Jung S, Lee SK, Chun YJ (2002): Design, synthesis, and discovery of novel *trans*-stilbene analogues as potent and selective human cytochrome P450 1B1 inhibitors. *J Med Chem 45*: 160–164.
176. Thakkar K, Geahlen RL, Cushman M (1993): Synthesis and protein-tyrosine kinase inhibitory activity of polyhydroxylated stilbene analogues of piceatannol. *J Med Chem 36*: 2950–2955.
177. Cushman M, Nagarathnam D, Gopal D, He HM, Lin CM, Hamel E (1992): 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 35*: 2293–2306.
178. Roberti M, Pizzirani D, Simoni D, Rondanin R, Baruchello R, Bonora C, Buscemi F, Grimaudo S, Tolomeo M (2003): Synthesis and biological evaluation of resveratrol and analogues as apoptosis-inducing agents. *J Med Chem 46*: 3546–3554.
179. Szewczuk LM, Penning TM (2004): Mechanism-based inactivation of COX-1 by red wine *m*-hydroquinones: A structure-activity relationship study. *J Nat Prod 67*: 1777–1782.
180. Wang Z, Hsieh TC, Zhang Z, Ma Y, Wu JM (2004): Identification and purification of resveratrol targeting proteins using immobilized resveratrol affinity chromatography. *Biochem Biophys Res Commun 323*: 743–749.
181. Leonard SS, Xia C, Jiang BH, Stinefelt B, Klandorf H, Harris GK, Shi X (2003): Resveratrol scavenges reactive oxygen species and effects radical-induced cellular responses. *Biochem Biophys Res Commun 309*: 1017–1026.
182. Potter GA, Patterson LH, Wanogho E, Perry PJ, Butler PC, Ijaz T, Ruparelia KC, Lamb JH, Farmer PB, Stanley LA, Burke MD (2002): The cancer preventative agent resveratrol is converted to the anticancer agent piceatannol by the cytochrome P450 enzyme CYP1B1. *Br J Cancer 86*: 774–778.
183. Kim YM, Yun J, Lee CK, Lee H, Min KR, Kim Y (2002): Oxyresveratrol and hydroxystilbene compounds. Inhibitory effect on tyrosinase and mechanism of action. *J Biol Chem 277*: 16340–16344.
184. Burkhardt S, Reiter RJ, Tan DX, Hardeland R, Cabrera J, Karbownik M (2001): DNA oxidatively damaged by chromium(III) and H_2O_2 is protected by the antioxidants melatonin, N_1-acetyl-N_2-formyl-5-methoxykynuramine, resveratrol and uric acid. *Int J Biochem Cell Biol 33*: 775–783.
185. de Santi C, Pietrabissa A, Mosca F, Pacifici GM (2000): Glucuronidation of resveratrol, a natural product present in grape and wine, in the human liver. *Xenobiotica 30*: 1047–1054.

186. Stewart JR, Christman KL, O'Brian CA (2000): Effects of resveratrol on the autophosphorylation of phorbol ester-responsive protein kinases: Inhibition of protein kinase D but not protein kinase C isozyme autophosphorylation. *Biochem Pharmacol 60*: 1355–1359.
187. de Santi C, Pietrabissa A, Spisni R, Mosca F, Pacifici GM (2000): Sulphation of resveratrol, a natural product present in grapes and wine, in the human liver and duodenum. *Xenobiotica 30*: 609–617.
188. Garcia-Garcia J, Micol V, de Godos A, Gomez-Fernandez JC (1999): The cancer chemopreventive agent resveratrol is incorporated into model membranes and inhibits protein kinase C alpha activity. *Arch Biochem Biophys 372*: 382–388.
189. Stewart JR, Ward NE, Ioannides CG, O'Brian CA (1999): Resveratrol preferentially inhibits protein kinase C-catalyzed phosphorylation of a cofactor-independent, arginine-rich protein substrate by a novel mechanism. *Biochemistry 38*: 13244–13251.
190. Chun YJ, Kim MY, Guengerich FP (1999): Resveratrol is a selective human cytochrome P450 1A1 inhibitor. *Biochem Biophys Res Commun 262*: 20–24.
191. Feng L, Jin J, Zhang LF, Yan T, Tao WY (2006): Analysis of the resveratrol-binding protein using phage-displayed random peptide library. *Acta Biochim Biophys Sin* (Shanghai) *38*: 342–348.
192. Jo JY, Gonzalez de Mejia E, Lila MA (2006): Catalytic inhibition of human DNA topoisomerase II by interactions of grape cell culture polyphenols. *J Agric Food Chem 54*: 2083–2087.
193. Fukuhara K, Nagakawa M, Nakanishi I, Ohkubo K, Imai K, Urano S, Fukuzumi S, Ozawa T, Ikota N, Mochizuki M, Miyata N, Okuda H (2006): Structural basis for DNA-cleaving activity of resveratrol in the presence of Cu(II). *Bioorg Med Chem 14*: 1437–1443.
194. Srivastava R, Ratheesh A, Gude RK, Rao KV, Panda D, Subrahmanyam G (2005): Resveratrol inhibits type II phosphatidylinositol 4-kinase: A key component in pathways of phosphoinositide turn over. *Biochem Pharmacol 70*: 1048–1055.
195. Ahmad A, Syed FA, Singh S, Hadi SM (2005): Prooxidant activity of resveratrol in the presence of copper ions: Mutagenicity in plasmid DNA. *Toxicol Lett 159*: 1–12.
196. Onuki J, Almeida EA, Medeiros MH, Di Mascio P (2005): Inhibition of 5-aminolevulinic acid-induced DNA damage by melatonin, N1-acetyl-N2-formyl-5-methoxykynuramine, quercetin or resveratrol. *J Pineal Res 38*: 107–115.
197. Lu Z, Zhang Y, Liu H, Yuan J, Zheng Z, Zou G (2007): Transport of a cancer chemopreventive polyphenol, resveratrol: Interaction with serum albumin and hemoglobin. *J Fluoresc 17*: 580–587.
198. Frojdo S, Cozzone D, Vidal H, Pirola L (2007): Resveratrol is a class IA phosphoinositide 3-kinase inhibitor. *Biochem J 406*: 511–518.
199. Waffo-Teguo P, Hawthorne ME, Cuendet M, Merillon JM, Kinghorn AD, Pezzuto JM, Mehta RG (2001): Potential cancer-chemopreventive activities of wine stilbenoids and flavans extracted from grape (*Vitis vinifera*) cell cultures. *Nutr Cancer 40*: 173–179.
200. Mutoh M, Takahashi M, Fukuda K, Matsushima-Hibiya Y, Mutoh H, Sugimura T, Wakabayashi K (2000): Suppression of cyclooxygenase-2 promoter-dependent transcriptional activity in colon cancer cells by chemopreventive agents with a resorcin-type structure. *Carcinogenesis 21*: 959–963.
201. Castello L, Tessitore L (2005): Resveratrol inhibits cell cycle progression in U937 cells. *Oncol Rep 13*: 133–137.
202. Narayanan NK, Narayanan BA, Nixon DW (2004): Resveratrol-induced cell growth inhibition and apoptosis is associated with modulation of phosphoglycerate mutase B in human prostate cancer cells: Two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis and mass spectrometry evaluation. *Cancer Detect Prev 28*: 443–452.
203. Shih A, Zhang S, Cao HJ, Boswell S, Wu YH, Tang HY, Lennartz MR, Davis FB, Davis PJ, Lin HY (2004): Inhibitory effect of epidermal growth factor on resveratrol-induced apoptosis in prostate cancer cells is mediated by protein kinase C-alpha. *Mol Cancer Ther 3*: 1355–1364.
204. Scifo C, Cardile V, Russo A, Consoli R, Vancheri C, Capasso F, Vanella A, Renis M (2004): Resveratrol and propolis as necrosis or apoptosis inducers in human prostate carcinoma cells. *Oncol Res 14*: 415–426.
205. Delmas D, Rebe C, Micheau O, Athias A, Gambert P, Grazide S, Laurent G, Latruffe N, Solary E (2004): Redistribution of CD95, DR4 and DR5 in rafts accounts for the synergistic toxicity of resveratrol and death receptor ligands in colon carcinoma cells. *Oncogene 23*: 8979–8986.
206. Ma X, Tian X, Huang X, Yan F, Qiao D (2007): Resveratrol-induced mitochondrial dysfunction and apoptosis are associated with Ca(2+) and mCICR-mediated MPT activation in HepG2 cells. *Mol Cell Biochem 302*: 99–109.
207. Wang S, Wang X, Yan J, Xie X, Fan F, Zhou X, Han L, Chen J (2007): Resveratrol inhibits proliferation of cultured rat cardiac fibroblasts: Correlated with NO-cGMP signaling pathway. *Eur J Pharmacol 567*: 26–35.
208. Su JL, Yang CY, Zhao M, Kuo ML, Yen ML (2007): Forkhead proteins are critical for bone morphogenetic protein-2 regulation and anti-tumor activity of resveratrol. *J Biol Chem 282*: 19385–19398.
209. Nonn L, Duong D, Peehl DM (2007): Chemopreventive anti-inflammatory activities of curcumin and other phytochemicals mediated by MAP kinase phosphatase-5 in prostate cells. *Carcinogenesis 28*: 1188–1196.
210. Kim YA, Kim GY, Park KY, Choi YH (2007): Resveratrol inhibits nitric oxide and prostaglandin E2 production by lipopolysaccharide-activated C6 microglia. *J Med Food 10*: 218–224.
211. Benitez DA, Pozo-Guisado E, Clementi M, Castellon E, Fernandez-Salguero PM (2007): Non-genomic action of resveratrol on androgen and oestrogen receptors in prostate cancer: Modulation of the phosphoinositide 3-kinase pathway. *Br J Cancer 96*: 1595–1604.

212. Lee EJ, Min HY, Joo Park H, Chung HJ, Kim S, Nam Han Y, Lee SK (2004): G2/M cell cycle arrest and induction of apoptosis by a stilbenoid, 3,4,5-trimethoxy-4′-bromo-*cis*-stilbene, in human lung cancer cells. *Life Sci 75*: 2829–2839.
213. Bianco NR, Chaplin LJ, Montano MM (2005): Differential induction of quinone reductase by phytoestrogens and protection against oestrogen-induced DNA damage. *Biochem J 385*: 279–287.
214. Yuan H, Pan Y, Young CY (2004): Overexpression of c-Jun induced by quercetin and resverol inhibits the expression and function of the androgen receptor in human prostate cancer cells. *Cancer Lett 213*: 155–163.
215. Cao Z, Fang J, Xia C, Shi X, Jiang BH (2004): *trans*-3,4,5′-Trihydroxystibene inhibits hypoxia-inducible factor 1alpha and vascular endothelial growth factor expression in human ovarian cancer cells. *Clin Cancer Res 10*: 5253–5263.
216. Shi T, Liou LS, Sadhukhan P, Duan ZH, Novick AC, Hissong JG, Almasan A, DiDonato JA (2004): Effects of resveratrol on gene expression in renal cell carcinoma. *Cancer Biol Ther 3*: 882–888.
217. Fulda S, Debatin KM (2004): Sensitization for anticancer drug-induced apoptosis by the chemopreventive agent resveratrol. *Oncogene 23*: 6702–6711.
218. Hyun JY, Chun YS, Kim TY, Kim HL, Kim MS, Park JW (2004): Hypoxia-inducible factor 1alpha-mediated resistance to phenolic anticancer. *Chemotherapy 50*: 119–126.
219. Schneider Y, Fischer B, Coelho D, Roussi S, Gosse F, Bischoff P, Raul F (2004): (*Z*)-3,5,4′-Tri-*O*-methyl-resveratrol, induces apoptosis in human lymphoblastoid cells independently of their p53 status. *Cancer Lett 211*: 155–161.
220. Quiney C, Dauzonne D, Kern C, Fourneron JD, Izard JC, Mohammad RM, Kolb JP, Billard C (2004): Flavones and polyphenols inhibit the NO pathway during apoptosis of leukemia B-cells. *Leuk Res 28*: 851–861.
221. Zhang S, Cao HJ, Davis FB, Tang HY, Davis PJ, Lin HY (2004): Estrogen inhibits resveratrol-induced post-translational modification of p53 and apoptosis in breast cancer cells. *Br J Cancer 91*: 178–185.
222. Liu J, Wang Q, Wu DC, Wang XW, Sun Y, Chen XY, Zhang KL, Li H (2004): Differential regulation of CYP1A1 and CYP1B1 expression in resveratrol-treated human medulloblastoma cells. *Neurosci Lett 363*: 257–261.
223. Laux MT, Aregullin M, Berry JP, Flanders JA, Rodriguez E (2004): Identification of a p53-dependent pathway in the induction of apoptosis of human breast cancer cells by the natural product, resveratrol. *J Altern Complement Med 10*: 235–239.
224. Berge G, Ovrebo S, Botnen IV, Hewer A, Phillips DH, Haugen A, Mollerup S (2004): Resveratrol inhibits benzo[*a*]pyrene-DNA adduct formation in human bronchial epithelial cells. *Br J Cancer 91*: 333–338.
225. Liontas A, Yeger H (2004): Curcumin and resveratrol induce apoptosis and nuclear translocation and activation of p53 in human neuroblastoma. *Anticancer Res 24*: 987–998.
226. Le Corre L, Fustier P, Chalabi N, Bignon YJ, Bernard-Gallon D (2004): Effects of resveratrol on the expression of a panel of genes interacting with the BRCA1 oncosuppressor in human breast cell lines. *Clin Chim Acta 344*: 115–121.
227. Jeong WS, Kim IW, Hu R, Kong AN (2004): Modulatory properties of various natural chemopreventive agents on the activation of NF-κB signaling pathway. *Pharm Res 21*: 661–670.
228. Jeong WS, Kim IW, Hu R, Kong AN (2004): Modulation of AP-1 by natural chemopreventive compounds in human colon HT-29 cancer cell line. *Pharm Res 21*: 649–660.
229. Baatout S, Derradji H, Jacquet P, Ooms D, Michaux A, Mergeay M (2004): Enhanced radiation-induced apoptosis of cancer cell lines after treatment with resveratrol. *Int J Mol Med 13*: 895–902.
230. Feng YH, Zhu YN, Liu J, Ren YX, Xu JY, Yang YF, Li XY, Zou JP (2004): Differential regulation of resveratrol on lipopolysacchride-stimulated human macrophages with or without IFN-gamma pre-priming. *Int Immunopharmacol 4*: 713–720.
231. Gehm BD, Levenson AS, Liu H, Lee EJ, Amundsen BM, Cushman M, Jordan VC, Jameson JL (2004): Estrogenic effects of resveratrol in breast cancer cells expressing mutant and wild-type estrogen receptors: Role of AF-1 and AF-2. *J Steroid Biochem Mol Biol 88*: 223–234.
232. Cooray HC, Janvilisri T, van Veen HW, Hladky SB, Barrand MA (2004): Interaction of the breast cancer resistance protein with plant polyphenols. *Biochem Biophys Res Commun 317*: 269–275.
233. Lancon A, Delma D, Osman H, Thenot JP, Jannin B, Latruffe N (2004): Human hepatic cell uptake of resveratrol: Involvement of both passive diffusion and carrier-mediated process. *Biochem Biophys Res Commun 316*: 1132–1137.
234. Gao S, Liu GZ, Wang Z (2004): Modulation of androgen receptor-dependent transcription by resveratrol and genistein in prostate cancer cells. *Prostate 59*: 214–225.
235. Cheung CY, Chen J, Chang TK (2004): Evaluation of a real-time polymerase chain reaction method for the quantification of CYP1B1 gene expression in MCF-7 human breast carcinoma cells. *J Pharmacol Toxicol Methods 49*: 97–104.
236. Ahmad KA, Clement MV, Hanif IM, Pervaiz S (2004): Resveratrol inhibits drug-induced apoptosis in human leukemia cells by creating an intracellular milieu nonpermissive for death execution. *Cancer Res 64*: 1452–1459.
237. Pozo-Guisado E, Lorenzo-Benayas MJ, Fernandez-Salguero PM (2004): Resveratrol modulates the phosphoinositide 3-kinase pathway through an estrogen receptor alpha-dependent mechanism: Relevance in cell proliferation. *Int J Cancer 109*: 167–173.
238. Jazirehi AR, Bonavida B (2004): Resveratrol modifies the expression of apoptotic regulatory proteins and sensitizes non-Hodgkin's lymphoma and multiple myeloma cell lines to paclitaxel-induced apoptosis. *Mol Cancer Ther 3*: 71–84.
239. Opipari AW Jr, Tan L, Boitano AE, Sorenson DR, Aurora A, Liu JR (2004): Resveratrol-induced autophagocytosis in ovarian cancer cells. *Cancer Res 64*: 696–703.
240. Stewart JR, O'Brian CA (2004): Resveratrol antagonizes EGFR-dependent Erk1/2 activation in human

androgen-independent prostate cancer cells with associated isozyme-selective PKC alpha inhibition. *Invest New Drugs 22*: 107–117.

241. Fulda S, Debatin KM (2004): Sensitization for tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis by the chemopreventive agent resveratrol. *Cancer Res 64*: 337–346.
242. Kim YA, Choi BT, Lee YT, Park DI, Rhee SH, Park KY, Choi YH (2004): Resveratrol inhibits cell proliferation and induces apoptosis of human breast carcinoma MCF-7 cells. *Oncol Rep 11*: 441–446.
243. Carraway RE, Hassan S, Cochrane DE (2004): Polyphenolic antioxidants mimic the effects of 1,4-dihydropyridines on neurotensin receptor function in PC3 cells. *J Pharmacol Exp Ther 309*: 92–101.
244. Woo JH, Lim JH, Kim YH, Suh SI, Min DS, Chang JS, Lee YH, Park JW, Kwon TK (2004): Resveratrol inhibits phorbol myristate acetate-induced matrix metalloproteinase-9 expression by inhibiting JNK and PKC delta signal transduction. *Oncogene 23*: 1845–1853.
245. Sala G, Minutolo F, Macchia M, Sacchi N, Ghidoni R (2003): Resveratrol structure and ceramide-associated growth inhibition in prostate cancer cells. *Drugs Exp Clin Res 29*: 263–269.
246. Bruno R, Ghisolfi L, Priulla M, Nicolin A, Bertelli A (2003): Wine and tumors: Study of resveratrol. *Drugs Exp Clin Res 29*: 257–261.
247. Cardile V, Scifo C, Russo A, Falsaperla M, Morgia G, Motta M, Renis M, Imbriani E, Silvestre G (2003): Involvement of HSP70 in resveratrol-induced apoptosis of human prostate cancer. *Anticancer Res 23*: 4921–4926.
248. Kim YA, Rhee SH, Park KY, Choi YH (2003): Antiproliferative effect of resveratrol in human prostate carcinoma cells. *J Med Food 6*: 273–280.
249. Kang JH, Park YH, Choi SW, Yang EK, Lee WJ (2003) Resveratrol derivatives potently induce apoptosis in human promyelocytic leukemia cells. *Exp Mol Med 35*: 467–474.
250. Kubota T, Uemura Y, Kobayashi M, Taguchi H (2003): Combined effects of resveratrol and paclitaxel on lung cancer cells. *Anticancer Res 23*: 4039–4046.
251. Wang Q, Li H, Wang XW, Wu DC, Chen XY, Liu J (2003): Resveratrol promotes differentiation and induces Fas-independent apoptosis of human medulloblastoma cells. *Neurosci Lett 351*: 83–86.
252. Scarlatti F, Sala G, Somenzi G, Signorelli P, Sacchi N, Ghidoni R (2003): Resveratrol induces growth inhibition and apoptosis in metastatic breast cancer cells via *de novo* ceramide signaling. *FASEB J 17*: 2339–2341.
253. Kaneuchi M, Sasaki M, Tanaka Y, Yamamoto R, Sakuragi N, Dahiya R (2003): Resveratrol suppresses growth of Ishikawa cells through down-regulation of EGF. *Int J Oncol 23*: 1167–1172.
254. Kim YA, Lee WH, Choi TH, Rhee SH, Park KY, Choi YH (2003): Involvement of $p21^{WAF1/CIP1}$, pRB, Bax and NF-κB in induction of growth arrest and apoptosis by resveratrol in human lung carcinoma A549 cells. *Int J Oncol 23*: 1143–1149.
255. Schneider Y, Chabert P, Stutzmann J, Coelho D, Fougerousse A, Gosse F, Launay JF, Brouillard R, Raul F (2003): Resveratrol analog (*Z*)-3,5,4′-trimethoxystilbene is a potent anti-mitotic drug inhibiting tubulin polymerization. *Int J Cancer 107*: 189–196.
256. Delmas D, Rebe C, Lacour S, Filomenko R, Athias A, Gambert P, Cherkaoui-Malki M, Jannin B, Dubrez-Daloz L, Latruffe N, Solary E (2003): Resveratrol-induced apoptosis is associated with Fas redistribution in the rafts and the formation of a death-inducing signaling complex in colon cancer cells. *J Biol Chem 278*: 41482–41490.
257. Ito T, Akao Y, Yi H, Ohguchi K, Matsumoto K, Tanaka T, Iinuma M, Nozawa Y (2003): Antitumor effect of resveratrol oligomers against human cancer cell lines and the molecular mechanism of apoptosis induced by vaticanol C. *Carcinogenesis 24*: 1489–1497.
258. Fustier P, Le Corre L, Chalabi N, Vissac-Sabatier C, Communal Y, Bignon YJ, Bernard-Gallon DJ (2003): Resveratrol increases BRCA1 and BRCA2 mRNA expression in breast tumour cell lines. *Br J Cancer 89*: 168–172.
259. El-Mowafy AM, Alkhalaf M (2003): Resveratrol activates adenylyl-cyclase in human breast cancer cells: A novel, estrogen receptor-independent cytostatic mechanism. *Carcinogenesis 24*: 869–873.
260. Bernhard D, Schwaiger W, Crazzolara R, Tinhofer I, Kofler R, Csordas A (2003): Enhanced MTT-reducing activity under growth inhibition by resveratrol in CEM-C7H2 lymphocytic leukemia cells. *Cancer Lett 195*: 193–199.
261. Kim S, Min SY, Lee SK, Cho WJ (2003): Comparative molecular field analysis study of stilbene derivatives active against A549 lung carcinoma. *Chem Pharm Bull* (Tokyo) *51*: 516–521.
262. Wietzke JA, Welsh J (2003): Phytoestrogen regulation of a Vitamin D3 receptor promoter and 1,25-dihydroxyvitamin D3 actions in human breast cancer cells. *J Steroid Biochem Mol Biol 84*: 149–157.
263. Estrov Z, Shishodia S, Faderl S, Harris D, Van Q, Kantarjian HM, Talpaz M, Aggarwal BB (2003): Resveratrol blocks interleukin-1beta-induced activation of the nuclear transcription factor NF-κB, inhibits proliferation, causes S-phase arrest, and induces apoptosis of acute myeloid leukemia cells. *Blood 102*: 987–995.
264. She QB, Ma WY, Wang M, Kaji A, Ho CT, Dong Z (2003): Inhibition of cell transformation by resveratrol and its derivatives: Differential effects and mechanisms involved. *Oncogene 22*: 2143–2150.
265. Wolter F, Turchanowa L, Stein J (2003): Resveratrol-induced modification of polyamine metabolism is accompanied by induction of c-Fos. *Carcinogenesis 24*: 469–474.
266. Liang YC, Tsai SH, Chen L, Lin-Shiau SY, Lin JK (2003): Resveratrol-induced G2 arrest through the inhibition of CDK7 and p34CDC2 kinases in colon carcinoma HT29 cells. *Biochem Pharmacol 65*: 1053–1060.
267. Zhou HB, Yan Y, Sun YN, Zhu JR (2003): Resveratrol induces apoptosis in human esophageal carcinoma cells. *World J Gastroenterol 9*: 408–411.

268. Yang SH, Kim JS, Oh TJ, Kim MS, Lee SW, Woo SK, Cho HS, Choi YH, Kim YH, Rha SY, Chung HC, An SW (2003): Genome-scale analysis of resveratrol-induced gene expression profile in human ovarian cancer cells using a cDNA microarray. *Int J Oncol* 22:741–750.
269. Levenson AS, Gehm BD, Pearce ST, Horiguchi J, Simons LA, Ward JE, 3rd, Jameson JL, Jordan VC (2003): Resveratrol acts as an estrogen receptor (ER) agonist in breast cancer cells stably transfected with ER alpha. *Int J Cancer 104*: 587–596.
270. Narayanan BA, Narayanan NK, Re GG, Nixon DW (2003): Differential expression of genes induced by resveratrol in LNCaP cells: P53-Mediated molecular targets. *Int J Cancer 104*: 204–212.
271. Niles RM, McFarland M, Weimer MB, Redkar A, Fu YM, Meadows GG (2003): Resveratrol is a potent inducer of apoptosis in human melanoma cells. *Cancer Lett 190*: 157–163.
272. Nicolini G, Rigolio R, Scuteri A, Miloso M, Saccomanno D, Cavaletti G, Tredici G (2003): Effect of *trans*-resveratrol on signal transduction pathways involved in paclitaxel-induced apoptosis in human neuroblastoma SH-SY5Y cells. *Neurochem Int 42*: 419–429.
273. Hayashibara T, Yamada Y, Nakayama S, Harasawa H, Tsuruda K, Sugahara K, Miyanishi T, Kamihira S, Tomonaga M, Maita T (2002): Resveratrol induces downregulation in survivin expression and apoptosis in HTLV-1-infected cell lines: A prospective agent for adult T cell leukemia chemotherapy. *Nutr Cancer 44*: 193–201.
274. Roy M, Chakraborty S, Siddiqi M, Bhattacharya RK (2002): Induction of apoptosis in tumor cells by natural phenolic compounds. *Asian Pac J Cancer Prev 3*: 61–67.
275. Billard C, Izard JC, Roman V, Kern C, Mathiot C, Mentz F, Kolb JP (2002): Comparative antiproliferative and apoptotic effects of resveratrol, epsilon-viniferin and vine-shots derived polyphenols (vineatrols) on chronic B lymphocytic leukemia cells and normal human lymphocytes. *Leuk Lymphoma 43*: 1991–2002.
276. Latruffe N, Delmas D, Jannin B, Cherkaoui Malki M, Passilly-Degrace P, Berlot JP (2002): Molecular analysis on the chemopreventive properties of resveratrol, a plant polyphenol microcomponent. *Int J Mol Med 10*: 755–760.
277. Schmitt E, Lehmann L, Metzler M, Stopper H (2002): Hormonal and genotoxic activity of resveratrol. *Toxicol Lett 136*: 133–142.
278. Brownson DM, Azios NG, Fuqua BK, Dharmawardhane SF, Mabry TJ (2002): Flavonoid effects relevant to cancer. *J Nutr 132*: 3482S–3489S.
279. Ding XZ, Adrian TE (2002): Resveratrol inhibits proliferation and induces apoptosis in human pancreatic cancer cells. *Pancreas 25*: e71–76.
280. Kuo PL, Chiang LC, Lin CC (2002): Resveratrol-induced apoptosis is mediated by p53-dependent pathway in Hep G2 cells. *Life Sci 72*: 23–34.
281. Pozo-Guisado E, Alvarez-Barrientos A, Mulero-Navarro S, Santiago-Josefat B, Fernandez-Salguero PM (2002): The antiproliferative activity of resveratrol results in apoptosis in MCF-7 but not in MDA-MB-231 human breast cancer cells: cell-specific alteration of the cell cycle. *Biochem Pharmacol 64*: 1375–1386.
282. Mahyar-Roemer M, Kohler H, Roemer K (2002): Role of Bax in resveratrol-induced apoptosis of colorectal carcinoma cells. *BMC Cancer 2*: 27–35.
283. Hsieh T, Halicka D, Lu X, Kunicki J, Guo J, Darzynkiewicz Z, Wu J (2002): Effects of resveratrol on the G_0-G_1 transition and cell cycle progression of mitogenically stimulated human lymphocytes. *Biochem Biophys Res Commun 297*: 1311–1317.
284. Melzig MF, Escher F (2002): Induction of neutral endopeptidase and angiotensin-converting enzyme activity of SK-N-SH cells *in vitro* by quercetin and resveratrol. *Pharmazie 57*: 556–558.
285. Morris GZ, Williams RL, Elliott MS, Beebe SJ (2002): Resveratrol induces apoptosis in LNCaP cells and requires hydroxyl groups to decrease viability in LNCaP and DU 145 cells. *Prostate 52*: 319–329.
286. Dubuisson JG, Dyess DL, Gaubatz JW (2002): Resveratrol modulates human mammary epithelial cell *O*-acetyltransferase, sulfotransferase, and kinase activation of the heterocyclic amine carcinogen *N*-hydroxy-PhIP. *Cancer Lett 182*: 27–32.
287. Ferry-Dumazet H, Garnier O, Mamani-Matsuda M, Vercauteren J, Belloc F, Billiard C, Dupouy M, Thiolat D, Kolb JP, Marit G, Reiffers J, Mossalayi MD (2002): Resveratrol inhibits the growth and induces the apoptosis of both normal and leukemic hematopoietic cells. *Carcinogenesis 23*: 1327–1333.
288. Kim HJ, Chang EJ, Bae SJ, Shim SM, Park HD, Rhee CH, Park JH, Choi SW (2002): Cytotoxic and antimutagenic stilbenes from seeds of *Paeonia lactiflora*. *Arch Pharm Res 25*: 293–299.
289. Lin HY, Shih A, Davis FB, Tang HY, Martino LJ, Bennett JA, Davis PJ (2002): Resveratrol induced serine phosphorylation of p53 causes apoptosis in a mutant p53 prostate cancer cell line. *J Urol 168*: 748–755.
290. Delmas D, Passilly-Degrace P, Jannin B, Cherkaoui Malki M, Latruffe N (2002): Resveratrol, a chemopreventive agent, disrupts the cell cycle control of human SW480 colorectal tumor cells. *Int J Mol Med 10*: 193–199.
291. Wolter F, Stein J (2002): Resveratrol enhances the differentiation induced by butyrate in Caco-2 colon cancer cells. *J Nutr 132*: 2082–2086.
292. Asou H, Koshizuka K, Kyo T, Takata N, Kamada N, Koeffier HP (2002): Resveratrol, a natural product derived from grapes, is a new inducer of differentiation in human myeloid leukemias. *Int J Hematol 75*: 528–533.
293. Roman V, Billard C, Kern C, Ferry-Dumazet H, Izard JC, Mohammad R, Mossalayi DM, Kolb JP (2002): Analysis of resveratrol-induced apoptosis in human B-cell chronic leukaemia. *Br J Haematol 117*: 842–851.
294. Rimando AM, Cuendet M, Desmarchelier C, Mehta RG, Pezzuto JM, Duke SO (2002): Cancer chemopreventive and antioxidant activities of pterostilbene, a naturally occurring

analogue of resveratrol. *J Agric Food Chem 50*: 3453–3457.
295. Narayanan BA, Narayanan NK, Stoner GD, Bullock BP (2002): Interactive gene expression pattern in prostate cancer cells exposed to phenolic antioxidants. *Life Sci 70*: 1821–1839.
296. Kuwajerwala N, Cifuentes E, Gautam S, Menon M, Barrack ER, Reddy GP (2002): Resveratrol induces prostate cancer cell entry into S phase and inhibits DNA synthesis. *Cancer Res 62*: 2488–2492.
297. Holian O, Wahid S, Atten MJ, Attar BM (2002): Inhibition of gastric cancer cell proliferation by resveratrol: Role of nitric oxide. *Am J Physiol Gastrointest Liver Physiol 282*: G809–816.
298. She QB, Huang C, Zhang Y, Dong Z (2002): Involvement of c-jun NH_2-terminal kinases in resveratrol-induced activation of p53 and apoptosis. *Mol Carcinog 33*: 244–250.
299. Joe AK, Liu H, Suzui M, Vural ME, Xiao D, Weinstein IB (2002): Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. *Clin Cancer Res 8*: 893–903.
300. Shih A, Davis FB, Lin HY, Davis PJ (2002): Resveratrol induces apoptosis in thyroid cancer cell lines via a MAPK- and p53-dependent mechanism. *J Clin Endocrinol Metab 87*: 1223–1232.
301. Lee SH, Ryu SY, Kim HB, Kim MY, Chun YJ (2002): Induction of apoptosis by 3,4′-dimethoxy-5-hydroxystilbene in human promyeloid leukemic HL-60 cells. *Planta Med 68*: 123–127.
302. Pendurthi UR, Meng F, Mackman N, Rao LV (2002): Mechanism of resveratrol-mediated suppression of tissue factor gene expression. *Thromb Haemost 87*: 155–162.
303. Sun ZJ, Pan CE, Liu HS, Wang GJ (2002): Anti-hepatoma activity of resveratrol *in vitro*. *World J Gastroenterol 8*: 79–81.
304. Ito T, Akao Y, Tanaka T, Iinuma M, Nozawa Y (2002): Vaticanol C, a novel resveratrol tetramer, inhibits cell growth through induction of apoptosis in colon cancer cell lines. *Biol Pharm Bull 25*: 147–148.
305. Wolter F, Clausnitzer A, Akoglu B, Stein J (2002): Piceatannol, a natural analog of resveratrol, inhibits progression through the S phase of the cell cycle in colorectal cancer cell lines. *J Nutr 132*: 298–302.
306. Zoberi I, Bradbury CM, Curry HA, Bisht KS, Goswami PC, Roti Roti JL, Gius D (2002): Radiosensitizing and antiproliferative effects of resveratrol in two human cervical tumor cell lines. *Cancer Lett 175*: 165–173.
307. Serrero G, Lu R (2001): Effect of resveratrol on the expression of autocrine growth modulators in human breast cancer cells. *Antioxid Redox Signal 3*: 969–979.
308. Heo YH, Kim S, Park JE, Jeong LS, Lee SK (2001): Induction of quinone reductase activity by stilbene analogs in mouse Hepa 1c1c7 cells. *Arch Pharm Res 24*: 597–600.
309. Mahyar-Roemer M, Katsen A, Mestres P, Roemer K (2001): Resveratrol induces colon tumor cell apoptosis independently of p53 and precede by epithelial differentiation, mitochondrial proliferation and membrane potential collapse. *Int J Cancer 94*: 615–622.
310. Atten MJ, Attar BM, Milson T, Holian O (2001): Resveratrol-induced inactivation of human gastric adenocarcinoma cells through a protein kinase C-mediated mechanism. *Biochem Pharmacol 62*: 1423–1432.
311. Nam KA, Kim S, Heo YH, Lee SK (2001): Resveratrol analog, 3,5,2′,4′-tetramethoxy-*trans*-stilbene, potentiates the inhibition of cell growth and induces apoptosis in human cancer cells. *Arch Pharm Res 24*: 441–445.
312. Wieder T, Prokop A, Bagci B, Essmann F, Bernicke D, Schulze-Osthoff K, Dorken B, Schmalz HG, Daniel PT, Henze G (2001): Piceatannol, a hydroxylated analog of the chemopreventive agent resveratrol, is a potent inducer of apoptosis in the lymphoma cell line BJAB and in primary, leukemic lymphoblasts. *Leukemia 15*: 1735–1742.
313. Adhami VM, Afaq F, Ahmad N (2001): Involvement of the retinoblastoma (pRb)-E2F/DP pathway during antiproliferative effects of resveratrol in human epidermoid carcinoma (A431) cells. *Biochem Biophys Res Commun 288*: 579–585.
314. Lee JE, Safe S (2001): Involvement of a post-transcriptional mechanism in the inhibition of CYP1A1 expression by resveratrol in breast cancer cells. *Biochem Pharmacol 62*: 1113–1124.
315. Park JW, Choi YJ, Suh SI, Baek WK, Suh MH, Jin IN, Min DS, Woo JH, Chang JS, Passaniti A, Lee YH, Kwon TK (2001): Bcl-2 overexpression attenuates resveratrol-induced apoptosis in U937 cells by inhibition of caspase-3 activity. *Carcinogenesis 22*: 1633–1639.
316. Sgambato A, Ardito R, Faraglia B, Boninsegna A, Wolf FI, Cittadini A (2001): Resveratrol, a natural phenolic compound, inhibits cell proliferation and prevents oxidative DNA damage. *Mutat Res 496*: 171–180.
317. Bhat KP, Pezzuto JM (2001): Resveratrol exhibits cytostatic and antiestrogenic properties with human endometrial adenocarcinoma (Ishikawa) cells. *Cancer Res 61*: 6137–6144.
318. Wolter F, Akoglu B, Clausnitzer A, Stein J (2001): Downregulation of the cyclin D1/Cdk4 complex occurs during resveratrol-induced cell cycle arrest in colon cancer cell lines. *J Nutr 131*: 2197–2203.
319. Dorrie J, Gerauer H, Wachter Y, Zunino SJ (2001): Resveratrol induces extensive apoptosis by depolarizing mitochondrial membranes and activating caspase-9 in acute lymphoblastic leukemia cells. *Cancer Res 61*: 4731–4739.
320. De Ledinghen V, Monvoisin A, Neaud V, Krisa S, Payrastre B, Bedin C, Desmouliere A, Bioulac-Sage P, Rosenbaum J (2001): *trans*-Resveratrol, a grapevine-derived polyphenol, blocks hepatocyte growth factor-induced invasion of hepatocellular carcinoma cells. *Int J Oncol 19*: 83–88.
321. Kozuki Y, Miura Y, Yagasaki K (2001): Resveratrol suppresses hepatoma cell invasion independently of its antiproliferative action. *Cancer Lett 167*: 151–156.
322. Ahmad N, Adhami VM, Afaq F, Feyes DK, Mukhtar H (2001): Resveratrol causes WAF-1/p21-mediated G(1)-phase arrest of cell cycle and induction of apoptosis in human epidermoid carcinoma A431 cells. *Clin Cancer Res 7*: 1466–1473.

323. Nakagawa H, Kiyozuka Y, Uemura Y, Senzaki H, Shikata N, Hioki K, Tsubura A (2001): Resveratrol inhibits human breast cancer cell growth and may mitigate the effect of linoleic acid, a potent breast cancer cell stimulator. *J Cancer Res Clin Oncol 127*: 258–264.
324. Mollerup S, Ovrebo S, Haugen A (2001): Lung carcinogenesis: Resveratrol modulates the expression of genes involved in the metabolism of PAH in human bronchial epithelial cells. *Int J Cancer 92*: 18–25.
325. Nicolini G, Rigolio R, Miloso M, Bertelli AA, Tredici G (2001): Anti-apoptotic effect of *trans*-resveratrol on paclitaxel-induced apoptosis in the human neuroblastoma SH-SY5Y cell line. *Neurosci Lett 302*: 41–44.
326. She QB, Bode AM, Ma WY, Chen NY, Dong Z (2001): Resveratrol-induced activation of p53 and apoptosis is mediated by extracellular-signal-regulated protein kinases and p38 kinase. *Cancer Res 61*: 1604–1610.
327. Lu J, Ho CH, Ghai G, Chen KY (2001): Resveratrol analog, 3,4,5,4′-tetrahydroxystilbene, differentially induces pro-apoptotic p53/Bax gene expression and inhibits the growth of transformed cells but not their normal counterparts. *Carcinogenesis 22*: 321–328.
328. Park JW, Choi YJ, Jang MA, Lee YS, Jun DY, Suh SI, Baek WK, Suh MH, Jin IN, Kwon TK (2001): Chemopreventive agent resveratrol, a natural product derived from grapes, reversibly inhibits progression through S and G2 phases of the cell cycle in U937 cells. *Cancer Lett 163*: 43–49.
329. Kampa M, Hatzoglou A, Notas G, Damianaki A, Bakogeorgou E, Gemetzi C, Kouroumalis E, Martin PM, Castanas E (2000): Wine antioxidant polyphenols inhibit the proliferation of human prostate cancer cell lines. *Nutr Cancer 37*: 223–233.
330. Bernhard D, Tinhofer I, Tonko M, Hubl H, Ausserlechner MJ, Greil R, Kofler R, Csordas A (2000): Resveratrol causes arrest in the S-phase prior to Fas-independent apoptosis in CEM-C7H2 acute leukemia cells. *Cell Death Differ 7*: 834–842.
331. Bowers JL, Tyulmenkov VV, Jernigan SC, Klinge CM (2000): Resveratrol acts as a mixed agonist/antagonist for estrogen receptors alpha and beta. *Endocrinology 141*: 3657–3667.
332. Nielsen M, Ruch RJ, Vang O (2000): Resveratrol reverses tumor-promoter-induced inhibition of gap-junctional intercellular communication. *Biochem Biophys Res Commun 275*: 804–809.
333. Schneider Y, Vincent F, Duranton B, Badolo L, Gosse F, Bergmann C, Seiler N, Raul F (2000): Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells. *Cancer Lett 158*: 85–91.
334. Holmes-McNary M, Baldwin AS, Jr (2000): Chemopreventive properties of *trans*-resveratrol are associated with inhibition of activation of the IκB kinase. *Cancer Res 60*: 3477–3483.
335. Delmas D, Jannin B, Cherkaoui Malki M, Latruffe N (2000): Inhibitory effect of resveratrol on the proliferation of human and rat hepatic derived cell lines. *Oncol Rep 7*: 847–852.
336. Tsan MF, White JE, Maheshwari JG, Bremner TA, Sacco J (2000): Resveratrol induces Fas signalling-independent apoptosis in THP-1 human monocytic leukaemia cells. *Br J Haematol 109*: 405–412.
337. Hsieh TC, Wu JM (2000): Grape-derived chemopreventive agent resveratrol decreases prostate-specific antigen (PSA) expression in LNCaP cells by an androgen receptor (AR)-independent mechanism. *Anticancer Res 20*: 225–228.
338. Godichaud S, Krisa S, Couronne B, Dubuisson L, Merillon JM, Desmouliere A, Rosenbaum J (2000): Deactivation of cultured human liver myofibroblasts by *trans*-resveratrol, a grapevine-derived polyphenol. *Hepatology 31*: 922–931.
339. Elattar TM, Virji AS (1999): The effect of red wine and its components on growth and proliferation of human oral squamous carcinoma cells. *Anticancer Res 19*: 5407–5414.
340. Mitchell SH, Zhu W, Young CY (1999): Resveratrol inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. *Cancer Res 59*: 5892–5895.
341. Ulsperger E, Hamilton G, Raderer M, Baumgartner G, Hejna M, Hoffmann O, Mallinger R (1999): Resveratrol pretreatment desensitizes AHTO-7 human osteoblasts to growth stimulation in response to carcinoma cell supernatants. *Int J Oncol 15*: 955–959.
342. Surh YJ, Hurh YJ, Kang JY, Lee E, Kong G, Lee SJ (1999): Resveratrol, an antioxidant present in red wine, induces apoptosis in human promyelocytic leukemia (HL-60) cells. *Cancer Lett 140*: 1–10.
343. Hsieh TC, Burfeind P, Laud K, Backer JM, Traganos F, Darzynkiewicz Z, Wu JM (1999): Cell cycle effects and control of gene expression by resveratrol in human breast carcinoma cell lines with different metastatic potentials. *Int J Oncol 15*: 245–252.
344. Hsieh TC, Wu JM (1999): Differential effects on growth, cell cycle arrest, and induction of apoptosis by resveratrol in human prostate cancer cell lines. *Exp Cell Res 249*: 109–115.
345. Miloso M, Bertelli AA, Nicolini G, Tredici G (1999): Resveratrol-induced activation of the mitogen-activated protein kinases, ERK1 and ERK2, in human neuroblastoma SH-SY5Y cells. *Neurosci Lett 264*: 141–144.
346. Lu R, Serrero G (1999): Resveratrol, a natural product derived from grape, exhibits antiestrogenic activity and inhibits the growth of human breast cancer cells. *J Cell Physiol 179*: 297–304.
347. Elattar TM, Virji AS (1999): Modulating effect of resveratrol and quercetin on oral cancer cell growth and proliferation. *Anticancer Drugs 10*: 187–193.
348. Huang C, Ma WY, Goranson A, Dong Z (1999): Resveratrol suppresses cell transformation and induces apoptosis through a p53-dependent pathway. *Carcinogenesis 20*: 237–242.
349. Clement MV, Hirpara JL, Chawdhury SH, Pervaiz S (1998): Chemopreventive agent resveratrol, a natural product derived from grapes, triggers CD95 signaling-dependent apoptosis in human tumor cells. *Blood 92*: 996–1002.

350. Fontecave M, Lepoivre M, Elleingand E, Gerez C, Guittet O (1998): Resveratrol, a remarkable inhibitor of ribonucleotide reductase. *FEBS Lett 421*: 277–279.
351. Jang M, Pezzuto J (1998): Resveratrol blocks eicosanoid production and chemically induced cellular transformation: Implications for cancer chemoprevention. *Pharm Biol 36*: 28–34.
352. Gehm BD, McAndrews JM, Chien PY, Jameson JL (1997): Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. *Proc Natl Acad Sci USA 94*: 14138–14143.
353. Ulrich S, Loitsch SM, Rau O, von Knethen A, Brune B, Schubert-Zsilavecz M, Stein JM (2006): Peroxisome proliferator-activated receptor gamma as a molecular target of resveratrol-induced modulation of polyamine metabolism. *Cancer Res 66*: 7348–7354.
354. Michels G, Watjen W, Weber N, Niering P, Chovolou Y, Kampkotter A, Proksch P, Kahl R (2006): Resveratrol induces apoptotic cell death in rat H4IIE hepatoma cells but necrosis in C6 glioma cells. *Toxicology 225*: 173–182.
355. Alkhalaf M, Jaffal S (2006): Potent antiproliferative effects of resveratrol on human osteosarcoma SJSA1 cells: Novel cellular mechanisms involving the ERKs/p53 cascade. *Free Radic Biol Med 41*: 318–325.
356. Lin HY, Lansing L, Merillon JM, Davis FB, Tang HY, Shih A, Vitrac X, Krisa S, Keating T, Cao HJ, Bergh J, Quackenbush S, Davis PJ (2006): Integrin alphaVbeta3 contains a receptor site for resveratrol. *FASEB J* 20:1742–1744.
357. Seve M, Chimienti F, Devergnas S, Aouffen M, Douki T, Chantegrel J, Cadet J, Favier A (2005): Resveratrol enhances UVA-induced DNA damage in HaCaT human keratinocytes. *Med Chem 1*: 629–633.
358. Kim AL, Zhu Y, Zhu H, Han L, Kopelovich L, Bickers DR, Athar M (2006): Resveratrol inhibits proliferation of human epidermoid carcinoma A431 cells by modulating MEK1 and AP-1 signalling pathways. *Exp Dermatol 15*: 538–546.
359. Aziz MH, Nihal M, Fu VX, Jarrard DF, Ahmad N (2006): Resveratrol-caused apoptosis of human prostate carcinoma LNCaP cells is mediated via modulation of phosphatidylinositol 3′-kinase/Akt pathway and Bcl-2 family proteins. *Mol Cancer Ther 5*: 1335–1341.
360. Roberti M, Pizzirani D, Recanatini M, Simoni D, Grimaudo S, Di Cristina A, Abbadessa V, Gebbia N, Tolomeo M (2006): Identification of a terphenyl derivative that blocks the cell cycle in the G0-G1 phase and induces differentiation in leukemia cells. *J Med Chem 49*: 3012–3018.
361. Kim YA, Lim SY, Rhee SH, Park KY, Kim CH, Choi BT, Lee SJ, Park YM, Choi YH (2006): Resveratrol inhibits inducible nitric oxide synthase and cyclooxygenase-2 expression in beta-amyloid-treated C6 glioma cells. *Int J Mol Med 17*: 1069–1075.
362. Ma XD, Yan F, Ma AD, Wang HJ (2006): Resveratrol induces HepG2 cell apoptosis by depolarizing mitochondrial membrane. *Nan Fang Yi Ke Da Xue Xue Bao 26*: 406–408, 413.
363. Yoo KM, Kim S, Moon BK, Kim SS, Kim KT, Kim SY, Choi SY (2006): Potent inhibitory effects of resveratrol derivatives on progression of prostate cancer cells. *Arch Pharm* (Weinheim) *339*: 238–241.
364. Mohan J, Gandhi AA, Bhavya BC, Rashmi R, Karunagaran D, Indu R, Santhoshkumar TR (2006): Caspase-2 triggers Bax-Bak-dependent and -independent cell death in colon cancer cells treated with resveratrol. *J Biol Chem 281*: 17599–17611.
365. Wang Y, Lee KW, Chan FL, Chen S, Leung LK (2006): The red wine polyphenol resveratrol displays bilevel inhibition on aromatase in breast cancer cells. *Toxicol Sci 92*: 71–77.
366. Balestrieri C, Felice F, Piacente S, Pizza C, Montoro P, Oleszek W, Visciano V, Balestrieri ML (2006): Relative effects of phenolic constituents from *Yucca schidigera* Roezl. bark on Kaposi's sarcoma cell proliferation, migration, and PAF synthesis. *Biochem Pharmacol 71*: 1479–1487.
367. Scifo C, Milasi A, Guarnera A, Sinatra F, Renis M (2006): Resveratrol and propolis extract: An insight into the morphological and molecular changes induced in DU145 cells. *Oncol Res 15*: 409–421.
368. Pohland T, Wagner S, Mahyar-Roemer M, Roemer K (2006): Bax and Bak are the critical complementary effectors of colorectal cancer cell apoptosis by chemopreventive resveratrol. *Anticancer Drugs 17*: 471–478.
369. Kotha A, Sekharam M, Cilenti L, Siddiquee K, Khaled A, Zervos AS, Carter B, Turkson J, Jove R (2006): Resveratrol inhibits Src and Stat3 signaling and induces the apoptosis of malignant cells containing activated Stat3 protein. *Mol Cancer Ther 5*: 621–629.
370. Wen X, Walle T (2007): Cytochrome P450 1B1, a novel chemopreventive target for benzo[*a*]pyrene-initiated human esophageal cancer. *Cancer Lett 246*: 109–114.
371. Lee SC, Chan J, Clement MV, Pervaiz S (2006): Functional proteomics of resveratrol-induced colon cancer cell apoptosis: Caspase-6-mediated cleavage of lamin A is a major signaling loop. *Proteomics 6*: 2386–2394.
372. Larrosa M, Gonzalez-Sarrias A, Garcia-Conesa MT, Tomas-Barberan FA, Espin JC (2006): Urolithins, ellagic acid-derived metabolites produced by human colonic microflora, exhibit estrogenic and antiestrogenic activities. *J Agric Food Chem 54*: 1611–1620.
373. Choi JK, Murillo G, Su BN, Pezzuto JM, Kinghorn AD, Mehta RG (2006): Ixocarpalactone A isolated from the Mexican tomatillo shows potent antiproliferative and apoptotic activity in colon cancer cells. *FEBS J 273*: 5714–5723.
374. Tsuji PA, Walle T (2006): Inhibition of benzo[*a*]pyrene-activating enzymes and DNA binding in human bronchial epithelial BEAS-2B cells by methoxylated flavonoids. *Carcinogenesis 27*: 1579–1585.
375. Lanzilli G, Fuggetta MP, Tricarico M, Cottarelli A, Serafino A, Falchetti R, Ravagnan G, Turriziani M, Adamo R, Franzese O, Bonmassar E (2006): Resveratrol down-regulates the growth and telomerase activity of breast cancer cells *in vitro*. *Int J Oncol 28*: 641–648.
376. Shimizu T, Nakazato T, Xian MJ, Sagawa M, Ikeda Y, Kizaki M (2006): Resveratrol induces apoptosis of human malignant B cells by activation of caspase-3 and p38 MAP kinase pathways. *Biochem Pharmacol 71*: 742–750.

377. Azmi AS, Bhat SH, Hanif S, Hadi SM (2006): Plant polyphenols mobilize endogenous copper in human peripheral lymphocytes leading to oxidative DNA breakage: A putative mechanism for anticancer properties. *FEBS Lett 580*: 533–538.
378. Liao HF, Kuo CD, Yang YC, Lin CP, Tai HC, Chen YY, Chen YJ (2005): Resveratrol enhances radiosensitivity of human non-small cell lung cancer NCI-H838 cells accompanied by inhibition of nuclear factor-κB activation. *J Radiat Res* (Tokyo) *46*: 387–393.
379. Vyas S, Asmerom Y, De Leon DD (2006): Insulin-like growth factor II mediates resveratrol stimulatory effect on cathepsin D in breast cancer cells. *Growth Factors 24*: 79–87.
380. Yang S, Irani K, Heffron SE, Jurnak F, Meyskens FL, Jr (2005): Alterations in the expression of the apurinic/ apyrimidinic endonuclease-1/redox factor-1 (APE/Ref-1) in human melanoma and identification of the therapeutic potential of resveratrol as an APE/Ref-1 inhibitor. *Mol Cancer Ther 4*: 1923–1935.
381. Young LF, Martin KR (2006): Time-dependent resveratrol-mediated mRNA and protein expression associated with cell cycle in WR-21 cells containing mutated human c-Ha-Ras. *Mol Nutr Food Res 50*: 70–77.
382. Garcia Mediero JM, Ferruelo Alonso A, Paez Borda A, Lujan Galan M, Angulo Cuesta J, Chiva Robles V, Berenguer Sanchez A (2005): Effect of polyphenols from the Mediterranean diet on proliferation and mediators of *in vitro* invasiveness of the MB-49 murine bladder cancer cell line. *Actas Urol Esp 29*: 743–749.
383. Arimochi H, Morita K (2005): High salt culture conditions suppress proliferation of rat C6 glioma cell by arresting cell-cycle progression at S-phase. *J Mol Neurosci 27*: 293–301.
384. Supornsilchai V, Svechnikov K, Seidlova-Wuttke D, Wuttke W, Soder O (2005): Phytoestrogen resveratrol suppresses steroidogenesis by rat adrenocortical cells by inhibiting cytochrome P450 c21-hydroxylase. *Horm Res 64*: 280–286.
385. Boissy P, Andersen TL, Abdallah BM, Kassem M, Plesner T, Delaisse JM (2005): Resveratrol inhibits myeloma cell growth, prevents osteoclast formation, and promotes osteoblast differentiation. *Cancer Res 65*: 9943–9952.
386. Minutolo F, Sala G, Bagnacani A, Bertini S, Carboni I, Placanica G, Prota G, Rapposelli S, Sacchi N, Macchia M, Ghidoni R (2005): Synthesis of a resveratrol analogue with high ceramide-mediated proapoptotic activity on human breast cancer cells. *J Med Chem 48*: 6783–6786.
387. Zhang Q, Tang X, Lu QY, Zhang ZF, Brown J, Le AD (2005): Resveratrol inhibits hypoxia-induced accumulation of hypoxia-inducible factor-1alpha and VEGF expression in human tongue squamous cell carcinoma and hepatoma cells. *Mol Cancer Ther 4*: 1465–1474.
388. Zunino SJ, Storms DH (2006): Resveratrol-induced apoptosis is enhanced in acute lymphoblastic leukemia cells by modulation of the mitochondrial permeability transition pore. *Cancer Lett 240*: 123–134.
389. Nifli AP, Kampa M, Alexaki VI, Notas G, Castanas E (2005): Polyphenol interaction with the T47D human breast cancer cell line. *J Dairy Res 72 Spec No*: 44–50.
390. Harris DM, Besselink E, Henning SM, Go VL, Heber D (2005): Phytoestrogens induce differential estrogen receptor alpha- or beta-mediated responses in transfected breast cancer cells. *Exp Biol Med* (Maywood) *230*: 558–568.
391. Katula KS, McCain JA, Radewicz AT (2005): Relative ability of dietary compounds to modulate nuclear factor-κB activity as assessed in a cell-based reporter system. *J Med Food 8*: 269–274.
392. Cao Y, Wang F, Liu HY, Fu ZD, Han R (2005): Resveratrol induces apoptosis and differentiation in acute promyelocytic leukemia (NB4) cells. *J Asian Nat Prod Res 7*: 633–641.
393. Miller ME, Holloway AC, Foster WG (2005): Benzo[*a*]pyrene increases invasion in MDA-MB-231 breast cancer cells via increased COX-II expression and prostaglandin E2 (PGE2) output. *Clin Exp Metastasis 22*: 149–156.
394. Yang C, Wu J, Zhang R, Zhang P, Eckard J, Yusuf R, Huang X, Rossman TG, Frenkel K (2005): Caffeic acid phenethyl ester (CAPE) prevents transformation of human cells by arsenite (As) and suppresses growth of As-transformed cells. *Toxicology 213*: 81–96.
395. Gagliano N, Moscheni C, Torri C, Magnani I, Bertelli AA, Gioia M (2005): Effect of resveratrol on matrix metalloproteinase-2 (MMP-2) and Secreted Protein Acidic and Rich in Cysteine (SPARC) on human cultured glioblastoma cells. *Biomed Pharmacother 59*: 359–364.
396. Young LF, Hantz HL, Martin KR (2005): Resveratrol modulates gene expression associated with apoptosis, proliferation and cell cycle in cells with mutated human c-Ha-Ras, but does not alter c-Ha-Ras mRNA or protein expression. *J Nutr Biochem 16*: 663–674.
397. Vyas S, Asmerom Y, De Leon DD (2005): Resveratrol regulates insulin-like growth factor-II in breast cancer cells. *Endocrinology 146*: 4224–4233.
398. Chow AW, Murillo G, Yu C, van Breemen RB, Boddie AW, Pezzuto JM, Das Gupta TK, Mehta RG (2005): Resveratrol inhibits rhabdomyosarcoma cell proliferation. *Eur J Cancer Prev 14*: 351–356.
399. Hsieh TC, Wang Z, Hamby CV, Wu JM (2005): Inhibition of melanoma cell proliferation by resveratrol is correlated with upregulation of quinone reductase 2 and p53. *Biochem Biophys Res Commun 334*: 223–230.
400. Kowalski J, Samojedny A, Paul M, Pietsz G, Wilczok T (2005): Effect of apigenin, kaempferol and resveratrol on the expression of interleukin-1beta and tumor necrosis factor-alpha genes in J774.2 macrophages. *Pharmacol Rep 57*: 390–394.
401. Tyagi A, Singh RP, Agarwal C, Siriwardana S, Sclafani RA, Agarwal R (2005): Resveratrol causes Cdc2-tyr15 phosphorylation via ATM/ATR-Chk1/2-Cdc25C pathway as a central mechanism for S phase arrest in human ovarian carcinoma Ovcar-3 cells. *Carcinogenesis 26*: 1978–1987.
402. Azmi AS, Bhat SH, Hadi SM (2005): Resveratrol-Cu^{II} induced DNA breakage in human peripheral lymphocytes:

Implications for anticancer properties. *FEBS Lett 579*: 3131–3135.
403. Wen X, Walle T (2005): Preferential induction of CYP1B1 by benzo[*a*]pyrene in human oral epithelial cells: Impact on DNA adduct formation and prevention by polyphenols. *Carcinogenesis 26*: 1774–1781.
404. Bottone FG, Jr., Moon Y, Kim JS, Alston-Mills B, Ishibashi M, Eling TE (2005): The anti-invasive activity of cyclooxygenase inhibitors is regulated by the transcription factor ATF3 (activating transcription factor 3). *Mol Cancer Ther 4*: 693–703.
405. Wu ML, Li H, Wu DC, Wang XW, Chen XY, Kong QY, Ma JX, Gao Y, Liu J (2005): CYP1A1 and CYP1B1 expressions in medulloblastoma cells are AhR-independent and have no direct link with resveratrol-induced differentiation and apoptosis. *Neurosci Lett* 384:33–37.
406. Jacobs MN, Nolan GT, Hood SR (2005): Lignans, bacteriocides and organochlorine compounds activate the human pregnane X receptor (PXR). *Toxicol Appl Pharmacol 209*: 123–133.
407. Tolomeo M, Grimaudo S, Di Cristina A, Roberti M, Pizzirani D, Meli M, Dusonchet L, Gebbia N, Abbadessa V, Crosta L, Barucchello R, Grisolia G, Invidiata F, Simoni D (2005): Pterostilbene and 3′-hydroxypterostilbene are effective apoptosis-inducing agents in MDR and BCR-ABL-expressing leukemia cells. *Int J Biochem Cell Biol 37*: 1709–1726.
408. Matsumura A, Ghosh A, Pope GS, Darbre PD (2005): Comparative study of oestrogenic properties of eight phytoestrogens in MCF7 human breast cancer cells. *J Steroid Biochem Mol Biol 94*: 431–443.
409. Galfi P, Jakus J, Molnar T, Neogrady S, Csordas A (2005): Divergent effects of resveratrol, a polyphenolic phytostilbene, on free radical levels and type of cell death induced by the histone deacetylase inhibitors butyrate and trichostatin A. *J Steroid Biochem Mol Biol 94*: 39–47.
410. Waite KA, Sinden MR, Eng C (2005): Phytoestrogen exposure elevates PTEN levels. *Hum Mol Genet 14*: 1457–1463.
411. Jiang H, Zhang L, Kuo J, Kuo K, Gautam SC, Groc L, Rodriguez AI, Koubi D, Hunter TJ, Corcoran GB, Seidman MD, Levine RA (2005): Resveratrol-induced apoptotic death in human U251 glioma cells. *Mol Cancer Ther 4*: 554–561.
412. Azios NG, Dharmawardhane SF (2005): Resveratrol and estradiol exert disparate effects on cell migration, cell surface actin structures, and focal adhesion assembly in MDA-MB-231 human breast cancer cells. *Neoplasia 7*: 128–140.
413. Chatterjee A, Bagchi D, Yasmin T, Stohs SJ (2005): Antimicrobial effects of antioxidants with and without clarithromycin on *Helicobacter pylori*. *Mol Cell Biochem 270*: 125–130.
414. Monthakantirat O, De-Eknamkul W, Umehara K, Yoshinaga Y, Miyase T, Warashina T, Noguchi H (2005): Phenolic constituents of the rhizomes of the Thai medicinal plant *Belamcanda chinensis* with proliferative activity for two breast cancer cell lines. *J Nat Prod 68*: 361–364.
415. Andreescu S, Sadik OA, McGee DW (2005): Effect of natural and synthetic estrogens on A549 lung cancer cells: Correlation of chemical structures with cytotoxic effects. *Chem Res Toxicol 18*: 466–474.
416. Jones SB, DePrimo SE, Whitfield ML, Brooks JD (2005): Resveratrol-induced gene expression profiles in human prostate cancer cells. *Cancer Epidemiol Biomarkers Prev 14*: 596–604.
417. Fulda S, Debatin KM (2005): Resveratrol-mediated sensitisation to TRAIL-induced apoptosis depends on death receptor and mitochondrial signalling. *Eur J Cancer 41*: 786–798.
418. Rodrigue CM, Porteu F, Navarro N, Bruyneel E, Bracke M, Romeo PH, Gespach C, Garel MC (2005): The cancer chemopreventive agent resveratrol induces tensin, a cell-matrix adhesion protein with signaling and antitumor activities. *Oncogene 24*: 3274–3284.
419. Horvath Z, Saiko P, Illmer C, Madlener S, Hoechtl T, Bauer W, Erker T, Jaeger W, Fritzer-Szekeres M, Szekeres T (2005): Synergistic action of resveratrol, an ingredient of wine, with Ara-C and tiazofurin in HL-60 human promyelocytic leukemia cells. *Exp Hematol 33*: 329–335.
420. Pozo-Guisado E, Merino JM, Mulero-Navarro S, Lorenzo-Benayas MJ, Centeno F, Alvarez-Barrientos A, Fernandez-Salguero PM (2005): Resveratrol-induced apoptosis in MCF-7 human breast cancer cells involves a caspase-independent mechanism with downregulation of Bcl-2 and NF-κB. *Int J Cancer 115*: 74–84.
421. Miura D, Miura Y, Yagasaki K (2004): Resveratrol inhibits hepatoma cell invasion by suppressing gene expression of hepatocyte growth factor via its reactive oxygen species-scavenging property. *Clin Exp Metastasis 21*: 445–451.
422. Mertens-Talcott SU, Percival SS (2005): Ellagic acid and quercetin interact synergistically with resveratrol in the induction of apoptosis and cause transient cell cycle arrest in human leukemia cells. *Cancer Lett 218*: 141–151.
423. Lee SH, Kim JS, Yamaguchi K, Eling TE, Baek SJ (2005): Indole-3-carbinol and 3,3′-diindolylmethane induce expression of NAG-1 in a p53-independent manner. *Biochem Biophys Res Commun 328*: 63–69.
424. Rigolio R, Miloso M, Nicolini G, Villa D, Scuteri A, Simone M, Tredici G (2005): Resveratrol interference with the cell cycle protects human neuroblastoma SH-SY5Y cell from paclitaxel-induced apoptosis. *Neurochem Int 46*: 205–211.
425. Gosslau A, Chen M, Ho CT, Chen KY (2005): A methoxy derivative of resveratrol analogue selectively induced activation of the mitochondrial apoptotic pathway in transformed fibroblasts. *Br J Cancer 92*: 513–521.
426. Cardile V, Lombardo L, Spatafora C, Tringali C (2005): Chemo-enzymatic synthesis and cell-growth inhibition activity of resveratrol analogues. *Bioorg Chem 33*: 22–33.
427. Wietzke JA, Ward EC, Schneider J, Welsh J (2005): Regulation of the human vitamin D3 receptor promoter in breast cancer cells is mediated through Sp1 sites. *Mol Cell Endocrinol 230*: 59–68.
428. Awad AB, Burr AT, Fink CS (2005): Effect of resveratrol and beta-sitosterol in combination on reactive oxygen species

and prostaglandin release by PC-3 cells. *Prostaglandins Leukot Essent Fatty Acids 72*: 219–226.
429. Baatout S, Derradji H, Jacquet P, Mergeay M (2005): Increased radiation sensitivity of an eosinophilic cell line following treatment with epigallocatechin-gallate, resveratrol and curcuma. *Int J Mol Med 15*: 337–352.
430. Cao Y, Fu ZD, Wang F, Liu HY, Han R (2005): Anti-angiogenic activity of resveratrol, a natural compound from medicinal plants. *J Asian Nat Prod Res 7*: 205–213.
431. Tsuji PA, Walle T (2007): Benzo[*a*]pyrene-induced cytochrome P450 1A and DNA binding in cultured trout hepatocytes - inhibition by plant polyphenols. *Chem Biol Interact 169*: 25–31.
432. Scarlatti F, Sala G, Ricci C, Maioli C, Milani F, Minella M, Botturi M, Ghidoni R (2007): Resveratrol sensitization of DU145 prostate cancer cells to ionizing radiation is associated to ceramide increase. *Cancer Lett 253*: 124–130.
433. Alkhalaf M (2007): Resveratrol-induced growth inhibition in MDA-MB-231 breast cancer cells is associated with mitogen-activated protein kinase signaling and protein translation. *Eur J Cancer Prev 16*: 334–341.
434. Hibasami H, Takagi K, Ishii T, Tsujikawa M, Imai N, Honda I (2007): Induction of apoptosis by rhapontin having stilbene moiety, a component of rhubarb (*Rheum officinale* Baillon) in human stomach cancer KATO III cells. *Oncol Rep 18*: 347–351.
435. Tang FY, Chiang EP, Sun YC (2008): Resveratrol inhibits heregulin-beta1-mediated matrix metalloproteinase-9 expression and cell invasion in human breast cancer cells. *J Nutr Biochem 19*: 287–294.
436. Shankar S, Siddiqui I, Srivastava RK (2007): 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 304*: 273–285.
437. Ulrich S, Huwiler A, Loitsch S, Schmidt H, Stein JM (2007): *De novo* ceramide biosynthesis is associated with resveratrol-induced inhibition of ornithine decarboxylase activity. *Biochem Pharmacol 74*: 281–289.
438. Heiss EH, Schilder YD, Dirsch VM (2007): Chronic treatment with resveratrol induces redox stress- and ataxia telangiectasia-mutated (ATM)-dependent senescence in p53-positive cancer cells. *J Biol Chem 282*: 26759–26766.
439. Hansen T, Seidel A, Borlak J (2007): The environmental carcinogen 3-nitrobenzanthrone and its main metabolite 3-aminobenzanthrone enhance formation of reactive oxygen intermediates in human A549 lung epithelial cells. *Toxicol Appl Pharmacol 221*: 222–234.
440. Gunther S, Ruhe C, Derikito MG, Bose G, Sauer H, Wartenberg M (2007): Polyphenols prevent cell shedding from mouse mammary cancer spheroids and inhibit cancer cell invasion in confrontation cultures derived from embryonic stem cells. *Cancer Lett 250*: 25–35.
441. Dolfini E, Roncoroni L, Dogliotti E, Sala G, Erba E, Sacchi N, Ghidoni R (2007): Resveratrol impairs the formation of MDA-MB-231 multicellular tumor spheroids concomitant with ceramide accumulation. *Cancer Lett 249*: 143–147.
442. Sakoguchi-Okada N, Takahashi-Yanaga F, Fukada K, Shiraishi F, Taba Y, Miwa Y, Morimoto S, Iida M, Sasaguri T (2007): Celecoxib inhibits the expression of survivin via the suppression of promoter activity in human colon cancer cells. *Biochem Pharmacol 73*: 1318–1329.
443. Trincheri NF, Nicotra G, Follo C, Castino R, Isidoro C (2007): Resveratrol induces cell death in colorectal cancer cells by a novel pathway involving lysosomal cathepsin D. *Carcinogenesis 28*: 922–931.
444. Tang X, Zhang Q, Nishitani J, Brown J, Shi S, Le AD (2007): Overexpression of human papillomavirus type 16 oncoproteins enhances hypoxia-inducible factor 1 alpha protein accumulation and vascular endothelial growth factor expression in human cervical carcinoma cells. *Clin Cancer Res 13*: 2568–2576.
445. Golkar L, Ding XZ, Ujiki MB, Salabat MR, Kelly DL, Scholtens D, Fought AJ, Bentrem DJ, Talamonti MS, Bell RH, Adrian TE (2007): Resveratrol inhibits pancreatic cancer cell proliferation through transcriptional induction of macrophage inhibitory cytokine-1. *J Surg Res 138*: 163–169.
446. Clarke DM, Robilotto AT, Rhee E, VanBuskirk RG, Baust JG, Gage AA, Baust JM (2007): Cryoablation of renal cancer: variables involved in freezing-induced cell death. *Technol Cancer Res Treat 6*: 69–79.
447. Ebert B, Seidel A, Lampen A (2007): Phytochemicals induce breast cancer resistance protein in Caco-2 cells and enhance the transport of benzo[*a*]pyrene-3-sulfate. *Toxicol Sci 96*: 227–236.
448. Bhardwaj A, Sethi G, Vadhan-Raj S, Bueso-Ramos C, Takada Y, Gaur U, Nair AS, Shishodia S, Aggarwal BB (2007): Resveratrol inhibits proliferation, induces apoptosis, and overcomes chemoresistance through down-regulation of STAT3 and nuclear factor-κB-regulated antiapoptotic and cell survival gene products in human multiple myeloma cells. *Blood 109*: 2293–2302.
449. Subbaramaiah K, Michaluart P, Chung WJ, Tanabe T, Telang N, Dannenberg AJ (1999): Resveratrol inhibits cyclooxygenase-2 transcription in human mammary epithelial cells. *Ann N Y Acad Sci 889*: 214–223.
450. Wu SL, Sun ZJ, Yu L, Meng KW, Qin XL, Pan CE (2004): Effect of resveratrol and in combination with 5-FU on murine liver cancer. *World J Gastroenterol 10*: 3048–3052.
451. Pezzuto JM (2004): Resveratrol: A whiff that induces a biologically specific tsunami. *Cancer Biol Ther 3*: 889–890.
452. Kapadia GJ, Azuine MA, Tokuda H, Takasaki M, Mukainaka T, Konoshima T, Nishino H (2002): Chemopreventive effect of resveratrol, sesamol, sesame oil and sunflower oil in the Epstein-Barr virus early antigen activation assay and the mouse skin two-stage carcinogenesis. *Pharmacol Res 45*: 499–505.
453. Soleas GJ, Grass L, Josephy PD, Goldberg DM, Diamandis EP (2006): A comparison of the anticarcinogenic properties of four red wine polyphenols. *Clin Biochem 39*: 492–497.
454. Reagan-Shaw S, Afaq F, Aziz MH, Ahmad N (2004): Modulations of critical cell cycle regulatory events during

chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin. *Oncogene 23*: 5151–5160.

455. Adhami VM, Afaq F, Ahmad N (2003): Suppression of ultraviolet B exposure-mediated activation of NF-κB in normal human keratinocytes by resveratrol. *Neoplasia 5*: 74–82.
456. Afaq F, Adhami VM, Ahmad N (2003): Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice. *Toxicol Appl Pharmacol 186*: 28–37.
457. Aziz MH, Reagan-Shaw S, Wu J, Longley BJ, Ahmad N (2005): Chemoprevention of skin cancer by grape constituent resveratrol: Relevance to human disease? *FASEB J 19*: 1193–1195.
458. Kim H, Hall P, Smith M, Kirk M, Prasain JK, Barnes S, Grubbs C (2004): Chemoprevention by grape seed extract and genistein in carcinogen-induced mammary cancer in rats is diet dependent. *J Nutr 134*: 3445S-3452S.
459. Wyke SM, Russell ST, Tisdale MJ (2004): Induction of proteasome expression in skeletal muscle is attenuated by inhibitors of NF-κB activation. *Br J Cancer 91*: 1742–1750.
460. Crowell JA, Korytko PJ, Morrissey RL, Booth TD, Levine BS (2004): Resveratrol-associated renal toxicity. *Toxicol Sci 82*: 614–619.
461. Berge G, Ovrebo S, Eilertsen E, Haugen A, Mollerup S (2004): Analysis of resveratrol as a lung cancer chemopreventive agent in A/J mice exposed to benzo[*a*]pyrene. *Br J Cancer 91*: 1380–1383.
462. Fu ZD, Cao Y, Wang KF, Xu SF, Han R (2004): Chemopreventive effect of resveratrol to cancer. *Ai Zheng 23*: 869–873.
463. Chen Y, Tseng SH, Lai HS, Chen WJ (2004): Resveratrol-induced cellular apoptosis and cell cycle arrest in neuroblastoma cells and antitumor effects on neuroblastoma in mice. *Surgery 136*: 57–66.
464. Khanduja KL, Bhardwaj A, Kaushik G (2004): Resveratrol inhibits *N*-nitrosodiethylamine-induced ornithine decarboxylase and cyclooxygenase in mice. *J Nutr Sci Vitaminol (Tokyo) 50*: 61–65.
465. Sale S, Verschoyle RD, Boocock D, Jones DJ, Wilsher N, Ruparelia KC, Potter GA, Farmer PB, Steward WP, Gescher AJ (2004): Pharmacokinetics in mice and growth-inhibitory properties of the putative cancer chemopreventive agent resveratrol and the synthetic analogue trans 3,4,5,4′-tetramethoxystilbene. *Br J Cancer 90*: 736–744.
466. Ziegler CC, Rainwater L, Whelan J, McEntee MF (2004): Dietary resveratrol does not affect intestinal tumorigenesis in Apc(Min/+) mice. *J Nutr 134*: 5–10.
467. Mishima S, Matsumoto K, Futamura Y, Araki Y, Ito T, Tanaka T, Iinuma M, Nozawa Y, Akao Y (2003): Antitumor effect of stilbenoids from *Vateria indica* against allografted sarcoma S-180 in animal model. *J Exp Ther Oncol 3*: 283–288.
468. Sato M, Pei RJ, Yuri T, Danbara N, Nakane Y, Tsubura A (2003): Prepubertal resveratrol exposure accelerates *N*-methyl-*N*-nitrosourea-induced mammary carcinoma in female Sprague-Dawley rats. *Cancer Lett 202*: 137–145.
469. Yu L, Sun ZJ, Wu SL, Pan CE (2003): Effect of resveratrol on cell cycle proteins in murine transplantable liver cancer. *World J Gastroenterol 9*: 2341–2343.
470. Breinholt VM, Molck AM, Svendsen GW, Daneshvar B, Vinggaard AM, Poulsen M, Dragsted LO (2003): Effects of dietary antioxidants and 2-amino-3-methylimidazo[4,5-f]-quinoline (IQ) on preneoplastic lesions and on oxidative damage, hormonal status, and detoxification capacity in the rat. *Food Chem Toxicol 41*: 1315–1323.
471. Revel A, Raanani H, Younglai E, Xu J, Rogers I, Han R, Savouret JF, Casper RF (2003): Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects lung from DNA damage and apoptosis caused by benzo[*a*]pyrene. *J Appl Toxicol 23*: 255–261.
472. Liu HS, Pan CE, Yang W, Liu XM (2003): Antitumor and immunomodulatory activity of resveratrol on experimentally implanted tumor of H22 in Balb/c mice. *World J Gastroenterol 9*: 1474–1476.
473. Miura D, Miura Y, Yagasaki K (2003): Hypolipidemic action of dietary resveratrol, a phytoalexin in grapes and red wine, in hepatoma-bearing rats. *Life Sci 73*: 1393–1400.
474. Vitrac X, Desmouliere A, Brouillaud B, Krisa S, Deffieux G, Barthe N, Rosenbaum J, Merillon JM (2003): Distribution of [^{14}C]-*trans*-resveratrol, a cancer chemopreventive polyphenol, in mouse tissues after oral administration. *Life Sci 72*: 2219–2233.
475. Li H, Cheng Y, Wang H, Sun H, Liu Y, Liu K, Peng S (2003): Inhibition of nitrobenzene-induced DNA and hemoglobin adductions by dietary constituents. *Appl Radiat Isot 58*: 291–298.
476. Banerjee S, Bueso-Ramos C, Aggarwal BB (2002): Suppression of 7,12-dimethylbenz(*a*)anthracene-induced mammary carcinogenesis in rats by resveratrol: Role of nuclear factor-κB, cyclooxygenase 2, and matrix metalloprotease 9. *Cancer Res 62*: 4945–4954.
477. Li ZG, Hong T, Shimada Y, Komoto I, Kawabe A, Ding Y, Kaganoi J, Hashimoto Y, Imamura M (2002): Suppression of *N*-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in F344 rats by resveratrol. *Carcinogenesis 23*: 1531–1536.
478. Asensi M, Medina I, Ortega A, Carretero J, Bano MC, Obrador E, Estrela JM (2002): Inhibition of cancer growth by resveratrol is related to its low bioavailability. *Free Radic Biol Med 33*: 387–398.
479. Rimando AM, Nagmani R, Feller DR, Yokoyama W (2005): Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters. *J Agric Food Chem 53*: 3403–3407.
480. Mouria M, Gukovskaya AS, Jung Y, Buechler P, Hines OJ, Reber HA, Pandol SJ (2002): Food-derived polyphenols inhibit pancreatic cancer growth through mitochondrial cytochrome C release and apoptosis. *Int J Cancer 98*: 761–769.
481. Gao X, Xu YX, Divine G, Janakiraman N, Chapman RA, Gautam SC (2002): Disparate *in vitro* and

in vivo antileukemic effects of resveratrol, a natural polyphenolic compound found in grapes. *J Nutr 132*: 2076–2081.
482. Bove K, Lincoln DW, Tsan MF (2002): Effect of resveratrol on growth of 4T1 breast cancer cells *in vitro* and *in vivo*. *Biochem Biophys Res Commun* 291:1001–1005.
483. Bhat KP, Lantvit D, Christov K, Mehta RG, Moon RC, Pezzuto JM (2001): Estrogenic and antiestrogenic properties of resveratrol in mammary tumor models. *Cancer Res 61*: 7456–7463.
484. Schneider Y, Duranton B, Gosse F, Schleiffer R, Seiler N, Raul F (2001): Resveratrol inhibits intestinal tumorigenesis and modulates host-defense-related gene expression in an animal model of human familial adenomatous polyposis. *Nutr Cancer 39*: 102–107.
485. Kimura Y, Okuda H (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.
486. Tessitore L, Davit A, Sarotto I, Caderni G (2000): Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting bax and $p21^{CIP}$ expression. *Carcinogenesis 21*: 1619–1622.
487. Hecht SS, Kenney PM, Wang M, Trushin N, Agarwal S, Rao AV, Upadhyaya P (1999): Evaluation of butylated hydroxyanisole, myo-inositol, curcumin, esculetin, resveratrol and lycopene as inhibitors of benzo[*a*]pyrene plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice. *Cancer Lett 137*: 123–130.
488. Carbo N, Costelli P, Baccino FM, Lopez-Soriano FJ, Argiles JM (1999): Resveratrol, a natural product present in wine, decreases tumour growth in a rat tumour model. *Biochem Biophys Res Commun 254*: 739–743.
489. Whitsett T, Carpenter M, Lamartiniere CA (2006): Resveratrol, but not EGCG, in the diet suppresses DMBA-induced mammary cancer in rats. *J Carcinog 5*: 15–25.
490. Valenzano DR, Cellerino A (2006): Resveratrol and the pharmacology of aging: A new vertebrate model to validate an old molecule. *Cell Cycle 5*: 1027–1032.
491. Lee EO, Lee HJ, Hwang HS, Ahn KS, Chae C, Kang KS, Lu J, Kim SH (2006): Potent inhibition of Lewis lung cancer growth by heyneanol A from the roots of *Vitis amurensis* through apoptotic and anti-angiogenic activities. *Carcinogenesis 27*: 2059–2069.
492. Rezk YA, Balulad SS, Keller RS, Bennett JA (2006): Use of resveratrol to improve the effectiveness of cisplatin and doxorubicin: Study in human gynecologic cancer cell lines and in rodent heart. *Am J Obstet Gynecol 194*: e23–26.
493. Chen JC, Chen Y, Lin JH, Wu JM, Tseng SH (2006): Resveratrol suppresses angiogenesis in gliomas: Evaluation by color Doppler ultrasound. *Anticancer Res 26*: 1237–1245.
494. Busquets S, Ametller E, Fuster G, Olivan M, Raab V, Argiles JM, Lopez-Soriano FJ (2007): Resveratrol, a natural diphenol, reduces metastatic growth in an experimental cancer model. *Cancer Lett 245*: 144–148.
495. Barta I, Smerak P, Polivkova Z, Sestakova H, Langova M, Turek B, Bartova J (2006): Current trends and perspectives in nutrition and cancer prevention. *Neoplasma 53*: 19–25.
496. Walle T, Walle UK, Sedmera D, Klausner M (2006): Benzo[*a*]pyrene-induced oral carcinogenesis and chemoprevention: Studies in bioengineered human tissue. *Drug Metab Dispos 34*: 346–350.
497. Garvin S, Ollinger K, Dabrosin C (2006): Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts *in vivo*. *Cancer Lett 231*: 113–122.
498. Sengottuvelan M, Viswanathan P, Nalini N (2006): Chemopreventive effect of *trans*-resveratrol–a phytoalexin against colonic aberrant crypt foci and cell proliferation in 1,2-dimethylhydrazine induced colon carcinogenesis. *Carcinogenesis 27*: 1038–1046.
499. Li T, Sheng L, Fan GX, Yuan YK, Li T (2005): Preliminary study on anti-tumor function of resveratrol and its immunological mechanism. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 21*: 575–579.
500. Mousa SS, Mousa SS, Mousa SA (2005): Effect of resveratrol on angiogenesis and platelet/fibrin-accelerated tumor growth in the chick chorioallantoic membrane model. *Nutr Cancer 52*: 59–65.
501. Hebbar V, Shen G, Hu R, Kim BR, Chen C, Korytko PJ, Crowell JA, Levine BS, Kong AN (2005): Toxicogenomics of resveratrol in rat liver. *Life Sci 76*: 2299–2314.
502. Provinciali M, Re F, Donnini A, Orlando F, Bartozzi B, Di Stasio G, Smorlesi A (2005): Effect of resveratrol on the development of spontaneous mammary tumors in HER-2/neu transgenic mice. *Int J Cancer 115*: 36–45.
503. Sale S, Tunstall RG, Ruparelia KC, Potter GA, Steward WP, Gescher AJ (2005): Comparison of the effects of the chemopreventive agent resveratrol and its synthetic analog *trans* 3,4,5,4′-tetramethoxystilbene (DMU-212) on adenoma development in the Apc(Min+) mouse and cyclooxygenase-2 in human-derived colon cancer cells. *Int J Cancer 115*: 194–201.
504. Zhou HB, Chen JJ, Wang WX, Cai JT, Du Q (2005): Anticancer activity of resveratrol on implanted human primary gastric carcinoma cells in nude mice. *World J Gastroenterol 11*: 280–284.
505. Porubin D, Hecht SS, Li ZZ, Gonta M, Stepanov I (2007): Endogenous formation of *N′*-nitrosonornicotine in F344 rats in the presence of some antioxidants and grape seed extract. *J Agric Food Chem 55*: 7199–7204.
506. Busquets S, Fuster G, Ametller E, Olivan M, Figueras M, Costelli P, Carbo N, Argiles JM, Lopez-Soriano FJ (2007): Resveratrol does not ameliorate muscle wasting in different types of cancer cachexia models. *Clin Nutr 26*: 239–244.
507. Walle T, Hsieh F, DeLegge MH, Oatis JE, Jr., Walle UK (2004): High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos 32*: 1377–1382.
508. Blumberg J, Block G (1994): The alpha-tocopherol, beta-carotene cancer prevention study in Finland. *Nutr Rev 52*: 242–250.

509. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL Jr, Valanis B, Williams JH Jr, Barnhart S, Cherniack MG, Brodkin CA, Hammar S (1996): Risk factors for lung cancer and for intervention effects in CARET, the beta-carotene and retinol efficacy trial. *J Natl Cancer Inst 88*: 1550–1559.
510. Zamora-Ros R, Urpi-Sarda M, Lamuela-Raventos RM, Estruch R, Vazquez-Agell M, Serrano-Martinez M, Jaeger W, Andres-Lacueva C (2006): Diagnostic performance of urinary resveratrol metabolites as a biomarker of moderate wine consumption. *Clin Chem 52*: 1373–1380.
511. Lekakis J, Rallidis LS, Andreadou I, Vamvakou G, Kazantzoglou G, Magiatis P, Skaltsounis AL, Kremastinos DT (2005): Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. *Eur J Cardiovasc Prev Rehabil 12*: 596–600.
512. Boocock DJ, Faust GE, Patel KR, Schinas AM, Brown VA, Ducharme MP, Booth TD, Crowell JA, Perloff M, Gescher AJ, Steward WP, Brenner DE (2007): Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. *Cancer Epidemiol Biomarkers Prev 16*: 1246–1352.

Table 1. Selective chemopreventive agents identified from natural products.[a]

Plant/source	Compound	Initial targets	Carcinogenesis
Brassica spp.	Brassinin	Quinone reductase	Skin, mammary
Mundulea sericea	Deguelin	Ornithine decarboxylase	Skin, mammary, colon, melanoma
Casimiroa edulis	Zapotin	Differentiation (HL-60) Apoptosis	Colon
Brucea javanica	Brusatol	Differentiation (HL-60)	HL-60
Cassia quinquangulata	Resveratrol	Cyclooxygenase inhibition	Skin, Mammary, colon, prostate
Physalis philadelphica	Withanolide	Quinone reductase	To be determined
Broussonetia papyrifera	Abyssinone II (RAPID)	Aromatase	To be determined
Synthetic	4′-Bromoflavone (RAPID)	Quinone reductase	Mammary
Synthetic	Oxomate	Quinone reductase	Mammary

[a] See references 36, 38, 54–64.

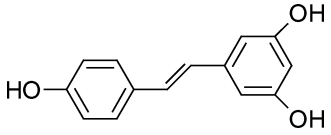

Figure 1. Structure of resveratrol (*trans*-3,4′,5-trihydroxy stilbene).

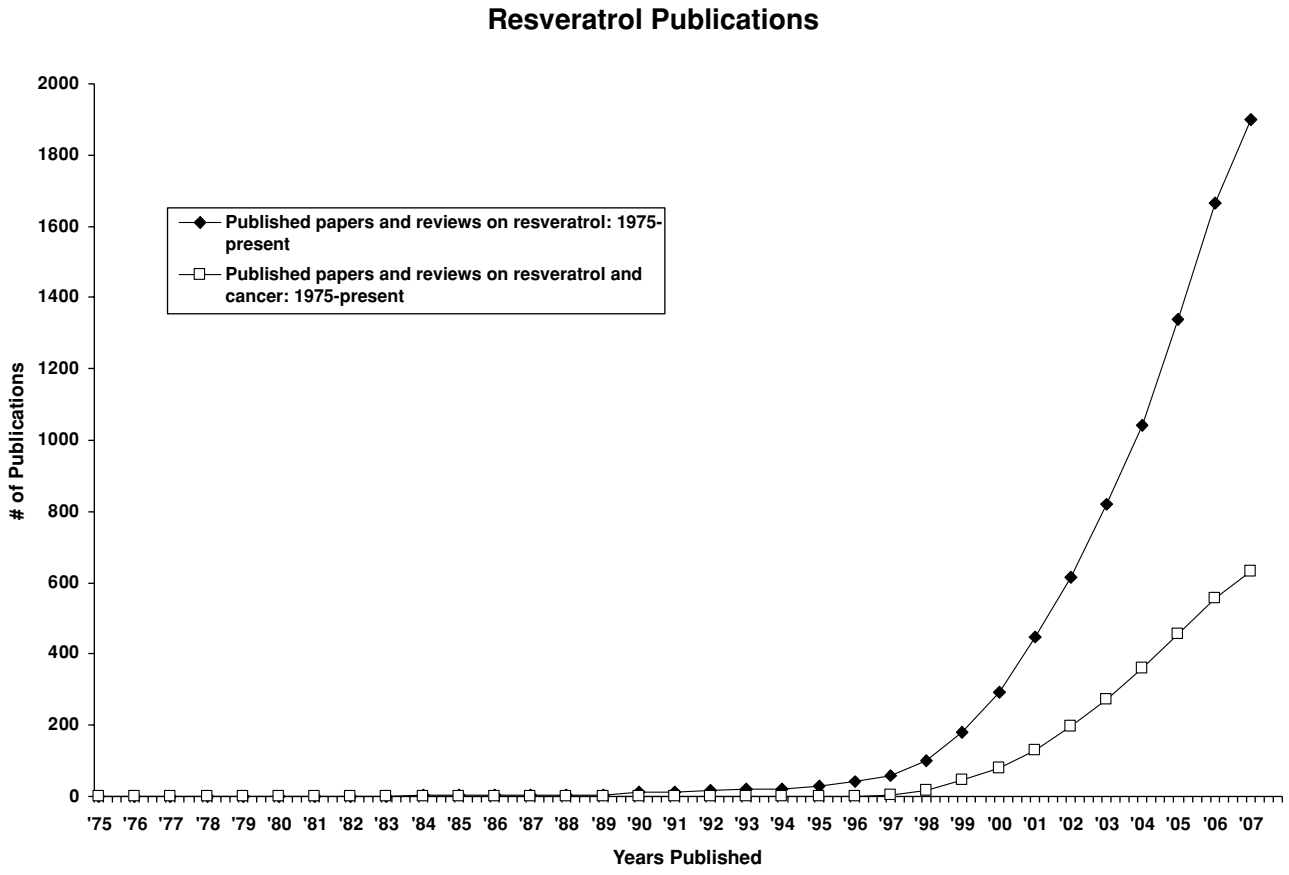

Figure 2. Line chart mapping the number of publications dealing with resveratrol from 1975 to July 2007.

Table 2. Selection of commercial sources of resveratrol.

Product name	Company	Ingredients	Dosage
Resveratrol	BioSynergy Health Alternatives P.O. Box 16833 Boise, ID 83715-6833 http://www.biosynergy.com/	• 160 mg — Japanese knotweed extract 50% –(*Poligonum cuspidatum*) (root) –[standardized to 80 mg resveratrol] • 100 mg — grape seed extract (*Vitis vinefera*) [95% min. proanthocyanidins] • 100 mg — quercetin (as quercetin dihydrate 98%) • Other: magnesium stearate, silicon dioxide, and gelatin. Contains no: sugar, salt, starch, yeast, wheat, gluten, corn, milk, peanuts, egg, or preservatives	120 capsules per container Serving size: – 1 capsule
R-Factors Resveratrol Anti-Aging Complex	Nature's Youth, LLC 12290 Treeline Avenue Fort Myers, FL 33913 http://www.naturesyouth.com/	• 178 mg — R-Factors Sirtuin Complex [α-lipoic acid, banaba leaf extract (*Lagerstroemia speciosa*) (1% corosolic acid), resveratrol, DMAE bitartrate] • Other: dicalcium phosphate, microcrystalline cellulose, croscarmellose sodium, stearic acid, magnesium stearate, silica, and pharmaceutical glaze	60 tablets per container Serving size: – 1 tablet
Mega Resveratrol 99% (MR99T)	Megaresveratrol.com 60 Newtown Rd. (Suite 32) Danbury CT 06810 http://www.megaresveratrol.com/	• 500 mg — resveratrol (yielding 495 mg *trans*-resveratrol) Resveratrol 99.37% HPLC Emodin: Trace (<0.09%)	Recommended daily dosage: 4 capsules (2000 mg) or 1 capsule per each 50 lb body weight
Mega Resveratrol 98% (MR98T)		• 500 mg — resveratrol (yielding 490 mg *trans*-resveratrol) Resveratrol 98.23% HPLC Emodin: Trace (<0.15%)	Recommended daily dosage: 4 capsules (2000 mg) or 1 capsule per each 50 lb body weight
Mega Resveratrol 50% (MR50T)		• 1000 mg — resveratrol (yielding 500 mg *trans*-resveratrol) Resveratrol 50.19% HPLC Emodin: <3.51%	Recommended daily dosage: 8 capsules (4000 mg) or 2 capsules per each 50 lb body weight.
Longevinex	Resveratrol Partners, LLC 457 West Allen #117 San Dimas, CA 91773 http://www.longevinex.com/	• 5 mg — vitamin E as mixed tocopherols 90% • 215 mg — proprietary Longevinex blend of French red wine extract and giant knotweed (*Polygonum cuspidatum*) leaf extract providing 100 mg of *trans*-resveratrol per capsule • 25 mg quercetin dehydrate • 75 mg rice bran extract (IP6) • 380 mg rice bran oil • 55 mg sunflower lecithin	30 capsules per container Serving size: 1 capsule
RevGenetics	RevGenetics http://www.revgenetics.com/	• 1000 mg — giant knotweed (*Polygonum cuspidatum*) and extract (root) (supplying 500 mg *trans*-resveratrol)	30 capsules per container Serving size: one capsule per 50 lb of personal weight per day
Resveratrol Caps	Life Extension Foundation P.O. Box 407189 Ft. Lauderdale, FL 33340-7198 http://www.lef.org/	• 100 mg — resveratrol [100 mg *trans*-resveratrol and its glucosides from whole red grape (*Vitis vinifera*) and *Polygonum cuspidatum* (root) extract] • 120 mg — quercetin (as quercetin dihydrate)	60 capsules per container Serving size: 1 capsule
Vintage Resveratrol	Nature Biology 105 Nobility Ct Roswell, GA 30075-2247 http://www.naturalbiology.com/	• 750 mg — *Vitis vinifera* resveratrol (from French red wine extract) yielding no less than 5% *trans*-resveratrol and its glucosides and 40% polyphenols, proanthocyanidins, anthocyanins, and flavonoids • 90 mg — quercetin • No preservatives, additives, or fillers	100 capsules per container Serving size: 1 capsule

(Continued on next page)

Table 2. Selection of commercial sources of resveratrol. (*Continued*)

Product name	Company	Ingredients	Dosage
PureVino-25	Pure Prescriptions, Inc. 2382 Faraday Avenue Suite 250-4 Carlsbad, CA 92008 http://www.pureprescriptions.com/	• 100 mg — PureVinol-25 proprietary extract (*trans*-resveratrol 25%, red wine polyphenols 20% non-GMO) • Other — rice flour to fill capsule requirement	30 capsules per container Serving size: 1 capsule
Resveratrol Synergy	Jarrow FORMULAS Jarrow Formulas 1824 S. Robertson Blvd Los Angeles, CA 90035	• 100 mg — vitamin C (as ascorbic acid) • 16 mg — resveratrols (200 mg *Polygonum cuspidatum* 8% total resveratrols) [Tiger cane] • 50 mg — grape seed extract (*Vitis vinifera*) (95% polyphenols) • 100 mg — grape skin extract (*Ancellota lambrusco*) (30% polyphenols) • 200 mg — green tea 5:1 extract (*Camellia sinensis*) (45% polyphenolics)	120 tablets per container Serving size: 1 tablet
Revatrol	Revatrol 925 S Federal Highway, Suite 500 Boca Raton, FL 33432 http://www.revatrol.com/	• 100 mg — red wine extract • 100 mg — actual resveratrol • 100 mg — quercetin • 100 mg — acetyl-l-carnitine • 100 mg — α-lipoic acid	30 capsules per container Serving size: 1 capsule
Resveratrol, 10 mg	Physician Formulas 212 Technology Drive, Suite B Irvine, CA 92618 http://www.raysahelian.com/resveratrol.html	• 10 mg — resveratrol (from 40 mg of a 25% extract of *Polygonum cuspidatum* root and rhizome) • Rice flour and gelatin	60 capsules per container Serving size: 1 capsule

Table 3. Select U.S. patents for the use of resveratrol as related to cancer.

Patent and approval date	Title	Inventors
7,026,518 April 11, 2006	Resveratrol analougues.	Gokaraju, Ganga Raju; Gokaraju, Rama Raju; Gottumukkala, Venkata Subbaraju; Somepalli, Venkateswarlu
6,974,895 December 13, 2005	Transgenic legume plants modified to produce resveratrol glucoside and uses thereof.	Paiva, Nancy L.; Hipskind, John D.
6,878,751 April 12, 2005	Administration of resveratrol to treat inflammatory respiratory disorders.	Donnelly, Louise Elizabeth; Barnes, Peter John
6,790,869 September 14, 2004	Resveratrol analogues for prevention of disease.	Ghai, Geetha; Chen, Kuang Yu; Rosen, Robert T.; Wang, Mingfu; Telang, Nitin; Lipkin, Martin; Chi-Tang, H.
6,767,563 July 27, 2004	Immune functions.	Farley, Michael D.
6,544,564 April 8, 2003	Cytotoxic pharmaceutical composition.	Farley, Michael D.
6,414,037 July 2, 2002	Pharmaceutical formulations of resveratrol and methods of use thereof.	Pezzuto, John M.; Moon, Richard C.; Jang, Mei-Shiang; Ouali, Aomar; Lin, Shengzhao; Barillas, Karla Slowing
6,008,260 December 28, 1999	Cancer chemopreventative compositions and method.	Pezzuto, John M.; Moon, Richard C.; Jang, Mei-Shiang

Table 4. Review articles.

Title	Reference
Resveratrol—evaluation of anticancer activity.	85
Therapeutic potential of resveratrol: the *in vivo* evidence.	86
Resveratrol as a chemopreventive agent: a promising molecule for fighting cancer.	87
Molecular targets of dietary agents for prevention and therapy of cancer.	88
The role of stem cells and gap junctions as targets for cancer chemoprevention and chemotherapy.	89
Targeting angiogenesis with integrative cancer therapies.	90
Chemoprevention of photocarcinogenesis by selected dietary botanicals.	91
Cancer biology and hormesis: comments on Calabrese (2005).	92
Chemosensitization and radiosensitization of tumors by plant polyphenols.	93
Structure-activity relationship of *trans*-resveratrol and its analogues.	94
The role of human adult stem cells and cell-cell communication in cancer chemoprevention and chemotherapy strategies.	95
Molecular basis of chemoprevention by resveratrol: NF-κB and AP-1 as potential targets	96
Targeting signal transduction pathways by chemopreventive agents	97
Resveratrol as an anticancer nutrient: molecular basis, open questions and promises.	98
Modulation of signal transduction by tea catechins and related phytochemicals.	99
A forkhead in the road to longevity: the molecular basis of lifespan becomes clearer.	100
The ubiquitin-proteasome pathway as a therapeutic target for muscle wasting.	101
Genotoxicity of phytoestrogens.	102
Cyclooxygenase 2 and breast cancer. From biological concepts to clinical trials.	103
Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications.	104
Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in carcinogenesis.	105
Cancer preventive role of selected dietary factors.	106
New anticancer agents: *in vitro* and *in vivo* evaluation of the antitumor and antimetastatic actions of various compounds isolated from medicinal plants.	107
Chemotherapeutic potential of the chemopreventive phytoalexin resveratrol.	108
Resveratrol and breast cancer chemoprevention: molecular mechanisms.	109
Pleiotropic effects of resveratrol	110
Resveratrol regulates cellular PKC α and δ to inhibit growth and induce apoptosis in gastric cancer cells.	111
Polyphenolic phytochemicals versus non-steroidal anti-inflammatory drugs: which are better cancer chemopreventive agents?	112
Innovative agents in cancer prevention.	113
Antiangiogenic properties of natural polyphenols from red wine and green tea.	114
An alternative mode of action of endocrine-disrupting chemicals and chemoprevention.	115
Molecular mechanisms of the chemopreventive effects of resveratrol and its analogs in colorectal cancer: key role of polyamines?	116
Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies.	117
Role of chemopreventive agents in cancer therapy.	118
From chemoprevention to chemotherapy: common targets and common goals.	119
Natural inhibitors of carcinogenesis.	50
Transport of resveratrol, a cancer chemopreventive agent, to cellular targets: plasmatic protein binding and cell uptake.	120
The traditional diet of Greece and cancer.	121
Redifferentiation therapy for thyroid cancer.	122
Estrogens and anti-estrogens: key mediators of prostate carcinogenesis and new therapeutic candidates.	123
Increasing the throughput and productivity of Caco-2 cell permeability assays using liquid chromatography-mass spectrometry: application to resveratrol absorption and metabolism.	124
Relationship between mechanisms, bioavailibility, and preclinical chemopreventive efficacy of resveratrol: a conundrum.	125
Wine and resveratrol: mechanisms of cancer prevention?	126
Estrogens and menopause: pharmacology of conjugated equine estrogens and their potential role in the prevention of neurodegenerative diseases such as Alzheimer's.	127
From sandwiches to center stage. Peanuts pack a powerful nutritional punch.	128
Resveratrol: a candidate nutritional substance for prostate cancer prevention.	65
The study of phenolic compounds as natural antioxidants in wine.	129
Pharmacological studies on resveratrol.	130
Cancer chemoprevention by resveratrol: *in vitro* and *in vivo* studies and the underlying mechanisms (review).	131
Point: From animal models to prevention of colon cancer. Systematic review of chemoprevention in min mice and choice of the model system.	132
Resveratrol and cancer: chemoprevention, apoptosis, and chemo-immunosensitizing activities.	133
Problems for risk assessment of endocrine-active estrogenic compounds.	134
Cytochrome P450 1B1: A target for inhibition in anticarcinogenesis strategies.	135
Molecular mechanism of the chemopreventive effect of resveratrol.	136

(Continued on next page)

Table 4. Review articles. (*Continued*)

Title	Reference
The basis for the chemopreventive action of resveratrol.	137
Structural concepts in cancer prevention.	138
Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer.	139
Botanicals in cancer chemoprevention.	140
Resveratrol—a prostate cancer chemopreventive agent?	141
Discovery of cancer preventive agents from natural products: from plants to prevention.	142
Androgen receptors in prostate cancer.	143
Anti-leukemia effect of resveratrol.	144
Molecular targets for nutrients involved with cancer prevention.	145
Cancer chemopreventive activity of resveratrol.	81
Resveratrol and cancer: a review.	146
Resveratrol, a natural chemopreventive agent against degenerative diseases.	147
Signal transduction pathways: targets for chemoprevention of skin cancer.	148
Botanical antioxidants for chemoprevention of photocarcinogenesis.	149
Functional food ingredients against colorectal cancer. An example project integrating functional genomics, nutrition and health.	150
Biological effects of resveratrol.	78
Toxicology of environmental estrogens.	151
Colon cancer chemoprevention with ginseng and other botanicals.	152
The Mediterranean diets: What is so special about the diet of Greece? The scientific evidence.	153
Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-κB activation.	154
Signal transduction events elicited by cancer prevention compounds.	155
The effects of resveratrol on CYP1A1 expression and aryl hydrocarbon receptor function *in vitro*.	156
The world of resveratrol.	157
A reappraisal of the potential chemopreventive and chemotherapeutic properties of resveratrol.	158
Resveratrol—from the bottle to the bedside?	159
Inhibition of carcinogenesis by dietary polyphenolic compounds.	160
Biological activity of resveratrol.	161
Antioxidants in chemoprevention of skin cancer.	162
Effects of food factors on signal transduction pathways.	163
The role of cyclooxygenase and lipoxygenase in cancer chemoprevention.	164
Putative mechanism for anticancer and apoptosis-inducing properties of plant-derived polyphenolic compounds.	165
Phytoestrogens and SERMS, alternatives to classical hormone therapy?	166
Mechanisms of action of antioxidants as exemplified in vegetables, tomatoes and tea.	167
Molecular mechanisms of chemopreventive effects of selected dietary and medicinal phenolic substances.	17
Chemoprevention of cancer and cardiovascular disease by resveratrol.	168
Nonalcoholic compounds of wine: the phytoestrogen resveratrol and moderate red wine consumption during menopause.	169
Resveratrol, map kinases and neuronal cells: might wine be a neuroprotectant?	170
Wine as a biological fluid: history, production, and role in disease prevention.	171
Ins and outs of dietary phytochemicals in cancer chemoprevention.	172
Inhibitors of stress-activated protein/mitogen-activated protein kinase pathways.	173

Table 5. Evaluation of resveratrol with *in vitro* model systems.

Model	What was measured	Effect	Ref.
Inhibition of COX-1.	Some constituents found in red wine were tested for inhibition of COX-1.	These agents were found to be as effective as resveratrol with respect to their ability of specifically inactivating COX-1.	179
Resveratrol targeting proteins (RTP).	Resveratrol was immobilized on epoxy-activated agarose forming a resveratrol affinity column (RAC), which was used to detect and isolate RTPs.	These results provide evidence for the existence of distinctive RTPs in mammalian cells and that RAC is a facile approach to identify and purify RTPs.	180
The effect of resveratrol on several different systems involving the hydroxyl, superoxide, metal/enzymatic-induced, and cellular generated radicals.	The rate constant for reaction of resveratrol with the hydroxyl radical was determined, and resveratrol was found to be an effective scavenger of hydroxyl, superoxide, and metal-induced radicals as well as showing antioxidant abilities in cells producing ROS. Resveratrol exhibits a protective effect against lipid peroxidation in cell membranes and DNA damage caused by ROS. Resveratrol was also found to have a significant inhibitory effect on the NF-κB signaling pathway after cellular exposure to metal-induced radicals.	It was concluded that resveratrol in food plays an important antioxidant role.	181
Metabolism of resveratrol by the cytochrome P450 enzyme CYP1B1 to produce piceatannol, a stilbene that has antileukemic activity and is also a tyrosine kinase inhibitor.	The metabolite was identified by high-performance liquid chromatography analysis using fluorescence detection, and the identity of the metabolite was further confirmed by derivatization followed by gas chromatography–mass spectrometry studies using authentic piceatannol for comparison.	This observation provides a novel explanation for the cancer preventative properties of resveratrol. It demonstrates that a natural dietary cancer preventative agent can be converted to a compound with known anticancer activity by an enzyme that is found in human tumors. This result gives insight into the functional role of CYP1B1 and provides evidence for the concept that CYP1B1 in tumors may be functioning as a growth suppressor enzyme.	182
Inhibitory effect on tyrosinase and mechanism of action for oxyresveratrol and hydroxystilbene compounds.	To clarify the mechanism of the depigmenting property of hydroxystilbene compounds, inhibitory actions of oxyresveratrol and its analogues on tyrosinases from mushroom and murine melanoma B-16 have been elucidated in this study. Oxyresveratrol showed potent inhibitory effect with an IC_{50} value of 1.2 μM on mushroom tyrosinase activity, which was 32-fold stronger inhibition than kojic acid, a depigmenting agent used as the cosmetic material with skin-whitening effect and the medical agent for hyperpigmentation disorders. Hydroxystilbene compounds of resveratrol, 3,5-dihydroxy-4′-methoxystilbene, and rhapontigenin also showed more than 50% inhibition at 100 μM on mushroom tyrosinase activity, but other methylated or glycosylated hydroxystilbenes of 3,4′-dimethoxy-5-hydroxystilbene, trimethylresveratrol, piceid, and rhaponticin did not inhibit significantly. None of the hydroxystilbene compounds except oxyresveratrol exhibited more than 50% inhibition at 100 μM on l-tyrosine oxidation by murine tyrosinase activity; oxyresveratrol showed an IC_{50} value of 52.7 μM on the enzyme activity. The kinetics and mechanism for inhibition of mushroom tyrosinase exhibited the reversibility of oxyresveratrol as a noncompetitive inhibitor with l-tyrosine as the substrate. The interaction between oxyresveratrol and tyrosinase exhibited a high affinity reflected in a K*i* value of 3.2–4.2 $\times$ 10^7 M.	Oxyresveratrol did not affect the promoter activity of the tyrosinase gene in murine melanoma B16 at 10 and 100 μM. Therefore, the depigmenting effect of oxyresveratrol works through reversible inhibition of tyrosinase activity rather than suppression of the expression and synthesis of the enzyme. The number and position of hydroxy substituents seem to play an important role in the inhibitory effects of hydroxystilbene compounds on tyrosinase activity.	183

(Continued on next page)

Table 5. Evaluation of resveratrol with *in vitro* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Reduction of DNA damage induced by Cr(III) using free radical scavengers [melatonin, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), resveratrol, and uric acid].	The concentrations that reduced 8-hydroxydeoxyguanosine (8-OH-dG, an index for DNA damage) formation by 50% (IC_{50}) were 0.10 μM for both resveratrol and melatonin, and 0.27 μM for AFMK. The efficacy of uric acid, in terms of its inhibition of DNA damage in the same *in vitro* system, was about 60–150 times less effective than the other scavengers; the IC_{50} for uric acid was 15.24 μM.	These findings suggest that three of the four antioxidants tested in these studies may have utility in protecting against the environmental pollutant Cr, and that the protective effects of these free radical scavengers against Cr(III)-induced carcinogenesis may relate to their direct hydroxyl radical scavenging ability. The formation of 8-OH-dG was likely due to a Cr(III)-mediated Fenton-type reaction that generates hydroxyl radicals, which in turn damage DNA. Once formed, 8-OH-dG can mutate eventually leading to cancer; thus, the implication is that these antioxidants may reduce the incidence of Cr-related cancers.	184
Resveratrol glucuronidation in human liver microsomes and to determine whether flavonoids inhibit resveratrol glucuronidation.	The rate of resveratrol glucuronidation was measured in 10 liver samples. The mean $\pm$ SD and median of resveratrol glucuronidation rates were 0.69 $\pm$ 0.34 and 0.80 nmol/min/mg, respectively. Resveratrol glucuronosyl transferase followed Michaelis-Menten kinetics and the Km and Vmax (mean $\pm$ SD; n = 5) were 0.15 $\pm$ 0.09 mM and 1.3 $\pm$ 0.3 nmol/min/mg, respectively. The intrinsic clearance was 11 $\pm$ 4 $\times$ 10^3 mL/min/mg. The flavonoid quercetin inhibited resveratrol glucuronidation and its IC_{50}(mean $\pm$ SD; n = 3) was 10 $\pm$ 1 μM. Myricetin, catechin, kaempferol, fisetin, and apigenin (all at 20 μM) inhibited resveratrol glucuronidation, and the percent of control ranged between 46% (catechin) to 72% (apigenin).	These results show that resveratrol is glucuronated in the human liver. Glucuronidation may reduce the bioavailability of this compound. However, flavonoids inhibit resveratrol glucuronidation, and such an inhibition might improve the bioavailability of resveratrol.	185
Investigation of the ability of resveratrol to inhibit protein kinase D (PKD).	The study compares the effects of resveratrol against the autophosphorylation reactions of PKC isozymes versus PKD. It was found that resveratrol inhibits PKD autophosphorylation in a concentration-dependent manner, but has only negligible effects against the autophosphorylation reactions of representative members of each PKC isozyme subfamily (cPKC-α, -β_1, and -γ, nPKC-Δ and -ε, and aPKC-ζ). Resveratrol was comparably effective against PKD autophosphorylation and PKD phosphorylation of the exogenous substrate syntide-2.	The inhibitory potency of resveratrol against PKD may contribute to the cancer chemopreventive action of resveratrol.	186
Investigation of the sulfation of resveratrol in the human liver and duodenum.	A radiometric assay for resveratrol sulfation was developed. It employed 3′-phosphoadenosine-5′-phosphosulfate-(^{35}S) as the sulfate donor and the rates of resveratrol sulfation (mean $\pm$ SD, pmol/min/mg cytosolic protein) were 90 $\pm$ 21 (liver, n = 10) and 74 $\pm$ 60 (duodenum, n = 10, p = 0.082). Resveratrol sulfotransferase followed Michaelis-Menten kinetics and Km (mean $\pm$ SD; μM) was 0.63 $\pm$ 0.03 (liver, n = 5) and 0.50 $\pm$ 0.26 (duodenum, n = 5, p = 0.39) and Vmax (mean $\pm$ SD, pmol/min/mg cytosolic protein) were 125 $\pm$ 31 (liver, n = 5) and 129 $\pm$ 85 (duodenum, n = 5, p = 0.62). Resveratrol sulfation was inhibited by the flavonoid quercetin, by mefenamic acid and salicylic acid. IC_{50} of resveratrol sulfation for quercetin was 12 $\pm$ 2 pM (liver) and 15 $\pm$ 2 pM (duodenum), those for mefenamic acid were 24 $\pm$ 3 nM (liver) and 11 $\pm$ 0.6 nM (duodenum), and those for salicylic acid were 53 $\pm$ 9 μM (liver) and 66 $\pm$ 4 μM (duodenum).	The potent inhibition of resveratrol sulfation by quercetin suggests that compounds present in the diet may inhibit the sulfation of resveratrol, thus improving its bioavailability.	187

Table 5. Evaluation of resveratrol with *in vitro* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Incorporation into model membranes and inhibition of protein kinase C α (PKCα) activity.	Differential scanning calorimetry measured the effect of resveratrol on the gel to liquid-crystalline phase transition of multilamellar vesicles made of phosphatidylcholine/phosphatidylserine and the temperature at which the fluid lamellar to H(II) inverted hexagonal transition took place in multilamellar vesicles made of 1,2-dielaidoyl-*sn*-phosphatidylethanolamine. This effect on 1,2-dielaidoyl-*sn*-phosphatidylethanolamine polymorphism was confirmed through ^{31}P-NMR, which showed that an isotropic peak appeared at high temperature instead of the H(II)-characteristic peak of 42 μM of resveratrol. The ability of resveratrol to inhibit PKCα when activated by phosphatidylcholine/phosphatidylserine vesicles was tested.	The study reports that resveratrol is able to incorporate itself into model membranes in a location that is inaccessible to the fluorescence quencher, acrylamide. These results indicate that the inhibition of PKCα by resveratrol can be mediated, at least partially, by membrane effects exerted near the lipid-water interface.	188
Mechanism of protein kinase C (PKC) inhibition.	Various systems were employed to determine inhibition by resveratrol: Ca^{2+}/phosphatidylserine-stimulated activity of a purified rat brain PKC isozyme mixture by competition with ATP; lipid-dependent activity of PKC isozymes with divergent regulatory domains, cofactor-independent catalytic domain fragment (CDF) of PKC generated by limited proteolysis. The effects of resveratrol were examined on PKC-catalyzed phosphorylation of the cofactor-independent substrate protamine sulfate, which is a polybasic protein that activates PKC by a novel mechanism.	The results indicate that resveratrol has a broad range of inhibitory potencies against purified PKC that depend on the nature of the substrate and the cofactor dependence of the phosphotransferase reaction.	189
Inhibition of cytochrome P450 1A1.	To investigate the mechanism of anticarcinogenic activity of resveratrol, the effects on cytochrome P450 (P450) were determined in human liver microsomes and *Escherichia coli* membranes coexpressing human P450 1A1 or P450 1A2 with human NADPH-P450 reductase (bicistronic expression system).	Resveratrol slightly inhibited ethoxyresorufin *O*-deethylation (EROD) activity in human liver microsomes. Resveratrol exhibited potent inhibition of human P450 1A1 in a dose-dependent manner for EROD and for methoxyresorufin *O*-demethylation (MROD). The inhibition of human P450 1A2 by resveratrol was not very strong. Resveratrol showed over 50-fold selectivity for P450 1A1 over P450 1A2. The activities of human NADPH-P450 reductase were not significantly changed by resveratrol. In a human P450 1A1/reductase bicistronic expression system, resveratrol inhibited human P450 1A1 activity in a mixed-type inhibition (competitive-noncompetitive). These results suggest that resveratrol is a selective human P450 1A1 inhibitor.	190
Identification of antioxidants in plant extracts.	Test materials were assessed for potential to scavenge stable 1,2-diphenyl-2-picrylhydrazyl (DPPH) free radicals, reduce TPA-induced free radical formation in cultured HL-60 human leukemia cells, and inhibit responses observed with a xanthine/xanthine oxidase assay system. Based on secondary analyses performed to assess inhibition of 7,12-dimethylbenz(*a*)anthracene-induced preneoplastic lesion formation with a mouse mammary organ culture model, various plants were selected and subjected to bioassay-guided fractionation. Various compounds were identified.	Approximately 700 plant extracts were evaluated, and 28 were found to be active in the DPPH free radical scavenging assay. The hydroxystilbenes piceatannol and resveratrol inhibited carcinogen-induced preneoplastic lesion formation in the mouse mammary gland organ culture model.	35

(Continued on next page)

Table 5. Evaluation of resveratrol with *in vitro* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Screen resveratrol-binding proteins to determine different biological activities, such as inhibiting lipid peroxidation, scavenging free radicals, inhibiting platelet aggregation, and anticancer activity.	Synthesized biotinylated resveratrol, purified by liquid chromatography and immobilized it into streptavidin-coated microplate wells. 3-(4,5-Demethylthiazol-)-2,5-diphenyl tetrazolium bromide assay showed little change in the anticancer activity of biotinylated resveratrol *in vitro*. A random library of phage-displayed peptides was screened for binding to immobilized resveratrol to isolate resveratrol-binding proteins. Several peptides were found to bind to resveratrol specifically, which was proven by enzyme-linked immunosorbent assay.	Through amino acid sequence analysis of the selected peptides and human proteins using the BLAST program, the results showed that resveratrol has an affinity for various proteins such as breast cancer-associated antigen, breast cancer resistance protein, death-associated transcription factor, and human cyclin-dependent kinase. These results demonstrated that the study provided a feasible method for the study of binding proteins of natural compounds using a phage-displayed random peptide library.	191
Evaluation of isolated mixed polyphenolic fractions to determine the potency of, and potential interactions between, individual fractions and some of the purified bioactive polyphenols that comprise these fractions on human DNA topoisomerase II catalytic activity.	Treatments that combined anthocyanin-rich fractions (TP-2; 0.5 or 2.0 μg of dried material/mL), fractions containing catechins, procyanidin dimers, and flavanones (TP-4; 0.25 μg of dried material/mL), and/or fractions enriched with procyanidin oligomers and polymers (TP-6; 0.15 or 0.5 μg of dried material/mL) showed additive effects toward catalytic inhibition of the enzyme. Epicatechin gallate ($IC_{50} = 0.029$ μM), myricetin (0.39 μM), procyanidin B2 (PB2, 4.5 μM), and resveratrol (65.7 μM), constituents of the most bioactive mixed fraction from grape cell culture (TP-4), each individually provided potent catalytic inhibition of topoisomerase II.	The mixed fractions provided potent catalytic inhibition of topoisomerase II. In addition, potentiating interactions between the PB2 and the other polyphenolic constituents and between myricetin and resveratrol were clearly demonstrated. A synergistic interaction between myricetin and resveratrol was also confirmed with isobolographic analysis at a molar ratio of 1:70.	192
Exploration of the structure-activity relationship of resveratrol in DNA strand scission and characterization of the substrate specificity for Cu(II) and DNA binding.	When pBR322DNA was incubated with resveratrol or its analogues differing in the number and positions of hydroxyl groups in the presence of Cu(II), the ability of 4-hydroxystilbene analogues to induce DNA strand scission is much stronger than that of 3-hydroxy analogues. The high binding affinity with both Cu(II) and DNA was also observed by 4-hydroxystilbene analogues. The reduction of Cu(II), which is essential for activation of molecular oxygen, proceeded by addition of resveratrol to the solution of the Cu(II)-DNA complex, while such reduction was not observed with the addition of isoresveratrol, in which the 4-hydroxy group of 1 is changed to the 3-position.	The results show that the 4-hydroxystilbene structure is a major determinant of generation of reactive oxygen species that was responsible for DNA strand scission.	193
Investigation of the molecular targets of resveratrol in early signaling cascades.	Resveratrol inhibits type II PtdIns 4-kinase but not PtdIns 3-kinase activity *in vitro*. It directly binds to the enzyme with a Kd of 7.2 μM. Kinetic studies showed that resveratrol competes with PtdIns binding.	Inhibition of PtdIns 4-kinase activity by resveratrol/phenylarsine oxide reduced Jurkat cell adhesion to matrigel/fibronectin coated surfaces, suggesting a role for type II PtdIns 4-kinase in lymphocyte infiltration to the sites of inflammation.	194
Investigation of the mutagenicity of resveratrol in plasmid DNA.	Plasmid bluescript SK(+) DNA was treated with increasing concentrations of resveratrol in the presence and absence of copper ions, transformed into competent DH5α cells and sequenced. Mutations were located that were caused by resveratrol treatment by comparing the sequences of treated plasmids versus control (untreated plasmid). The results showed a decrease in the transformation efficiency of the plasmid after resveratrol treatment, and although all types of mutations were recorded, point mutations (deletions/substitutions) were found to be the predominant ones. Resveratrol alone resulted in deletion of mainly guanine bases. Because copper ions are known to be found in the nucleus, bound to guanine bases in chromatin, the results suggested mobilization of such endogenous copper by resveratrol resulting in prooxidant DNA cleavage at the site.	Concentration of copper is reportes to be elevated in various malignancies and the present studies might explain the reported anticancer activity of resveratrol in various cancer cell lines.	195

Table 5. Evaluation of resveratrol with *in vitro* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigation of antioxidants in the treatment of 5-aminolevulinic acid (ALA)-induced oxidative stress.	This study showed the antioxidant efficacy of several compounds including melatonin, quercetin, resveratrol, and *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK), a melatonin oxidation product, in terms of their ability to limit DNA damage induced by ALA/Fe2+ in an *in vitro* system. Damage was measured by plasmid DNA strand breaks and detection of 8-oxo, 7-8-dihydro,2′-deoxyguanosine (8-oxodGuo) by high-performance liquid chromatography coupled with electrochemical detection. All compounds tested showed a dose-dependent protective action against free radical damage.	The results suggested that these could be the first studies showing the possible use of these antioxidants in oxidative stress promoted by ALA or other pro-oxidants.	196
Investigated the binding of resveratrol to plasma proteins, human serum albumin (HSA), and hemoglobin (Hb) systematically by fluorescence quenching technique, synchronous fluorescence, UV-Vis absorption spectroscopy, circular dichroism (CD) spectroscopy, and molecular modeling method.	The fluorescence data showed that the binding of resveratrol to HSA or Hb is a static quenching procedure and each protein has only one binding site for the drug. The binding constant of resveratrol to HSA is larger than that of resveratrol to Hb at corresponding temperature, which indicates that the affinity of HSA toward the drug is higher than that of Hb. CD spectroscopy indicates that the secondary structures of the proteins are changed in the presence of resveratrol with the reduction of α-helices, which decreased about 18.75% for HSA and 9.43% for Hb at the drug to proteins molar ratio of 2. Thermodynamic analysis and molecular modeling suggest that hydrophobic interaction plays a major role in the binding of resveratrol to HSA, and hydrogen bonding is the main binding force in the binding of resveratrol to Hb.	The study of molecular modeling showed that resveratrol is located in the hydrophobic cavity between subdomain IB and IIA of HSA (the entrance of site I), or located in the central cavity of Hb (partial to the subunit A).	197
Investigated genetic evidence and *in vitro* enzymatic measurements indicating that the deacetylase Sir2/SIRT1, an enzyme promoting stress-resistance and aging, is a target of resveratrol.	Downregulation of insulin-like pathways—of which phosphoinositide 3-kinase (PI3K) is a key mediator—promotes longevity and is an attractive strategy to fight cancer. The study showed that resveratrol inhibits, *in vitro* and in cultured muscle cell lines, class IA PI3K and its downstream signaling in the same concentration range at which it activates sirtuins.	This study showed class IA PI3K as a target of resveratrol that may contribute to longevity-promoting and anticancer properties and identified resveratrol as a natural class-specific PI3K inhibitor.	198

In addition to data obtained with cell culture or *in vivo* models, the following references contain data derived from *in vitro* systems: 40, 80, 178, 214–216, 219–224, 226–229, 231, 234–240, 242, 243, 245–249, 251, 253, 254, 256–263, 266–277, 279–283, 284, 286, 287, 289–293, 295–299, 300–304, 306–327, 329, 330, 334, 340, 341, 343, 346–350, 408, 426, 449, 453, 456, 457, 464, 466, 468, 471, 472, 475–477, 482, 483, 485, 509, 510.

Table 6. Evaluation of resveratrol with cell culture model systems.

Model	What was measured	Effect	Ref.
U937 cell growth.	Inhibition of cell cycle progression.	Cell growth was impaired due to reduced cell proliferation, without significant induction of apoptosis. There was an antiproliferative effect and duplication in the DNA of the resveratrol-treated U937 cells.	201
Prostate cancer cells LNCaP, DU145, and PC-3.	The role of phosphoglycerate mutase B using two-dimensional sodium dodecyl sulfate–polyacrylamide gel electrophoresis (2D-SDS-PAGE) followed by mass spectrometric analysis of the prostate cells.	Identified the role of phosphoglycerate mutase B on resveratrol-treated human prostate cells at the transcription level. There was an effect on metabolic enzymes in cancer cells, but did not affect normal cells.	202
DU145 and LNCaP prostate cancer cells.	Inhibition of epidermal growth factor (EGF) for up to 4 h resulted in brief activation of MAPK followed by inhibition of resveratrol-induced signal transduction, p53 phosphorylation, and apoptosis.	Resveratrol-induced apoptosis in DU145 and LNCaP prostate cancer cells occurs through different PKC-mediated and MAPK-dependent pathways.	203
DU145 prostate cancer cells.	Using resveratrol and the ethanol extract of propolis, a natural honeybee hive product, a comparison between the activity of these micronutrients and vinorelbine bitartrate (Navelbine), a semi synthetic drug normally used in the therapy of prostate cancer, was conducted. Several biochemical parameters were tested using the MTT assay, cell membrane integrity (lactate dehydrogenase release), cell redox status (nitric oxide formation, reactive oxygen species production, reduced glutathione levels), COMET assay with special attention on the presence of apoptotic DNA damage (TUNEL test), and possible mitochondrial transmembrane potential alteration ($\Delta\psi$).	Studies demonstrated the anticancer activity of resveratrol and propolis extract in human prostate cancer, exerting their cytotoxicity through two different types of cell death: necrosis and apoptosis, respectively. The data obtained suggest the possible use of these micronutrients both in alternative to classic chemotherapy, and in combination with very low dosage of vinorelbine (5 μM).	204
Colon carcinoma cells.	In colon cancer cells that resist resveratrol-induced apoptosis, the polyphenol also induces a redistribution of death receptors into lipid rafts. This effect sensitizes these tumor cells to death receptor-mediated apoptosis. In resveratrol-treated cells, tumor necrosis factor (TNF), anti-CD95 antibodies and TNF-related apoptosis-inducing ligand (TRAIL) activate a caspase-dependent death pathway that escapes Bcl-2–mediated inhibition.	Resveratrol does not enhance the number of death receptors at the surface of tumor cells but induces their redistribution into lipid rafts and facilitates the caspase cascade activation in response to death receptor stimulation. The cholesterol sequestering agent nystatin prevents resveratrol-induced death receptor redistribution and cell sensitization to death receptor stimulation. Thus, whatever its ability to induce apoptosis in a tumor cell, resveratrol induces redistribution of death receptors into lipid rafts. This redistribution sensitizes the cells to death receptor stimulation.	205
Using HepG2 cells, investigated the potential of resveratrol to trigger tumor cell apoptosis through various pathways. Resveratrol induced apoptosis through the activation of the mitochondrial pathway.	This study showed that resveratrol-induced HepG2 cell apoptosis and mitochondrial dysfunction was dependent on the induction of the mitochondrial permeability transition (MPT), because resveratrol caused the collapse of the mitochondrial membrane potential ($\delta\psi^m$) with the concomitant release of cytochrome c (Cyt.c). In addition, resveratrol induced a rapid and sustained elevation of intracellular (Ca^{2+}), which compromised the mitochondrial $\delta\psi^m$ and triggered the process of HepG2 cell apoptosis. In permeabilized HepG2 cells, the group further demonstrated that the effect of the resveratrol was indeed synergistic with that of Ca^{2+} and Ca^{2+} is necessary for resveratrol-induced MPT opening. Calcium-induced calcium release from mitochondria (mCICR) played a key role in mitochondrial dysfunction and cell apoptosis: (1) mCICR inhibitor, ruthenium red (RR), prevent MPT opening and Cyt.c release; and (2) RR attenuated resveratrol-induced HepG2 cell apoptotic death. Furthermore, resveratrol promotes MPT opening by lowering Ca^{2+}-threshold.	These data suggest that modifying mCICR and Ca^{2+} threshold to modulate MPT opening may be a potential target to control cell apoptosis induced by resveratrol.	206

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the molecular mechanism of resveratrol on preventing cardiac fibroblasts from proliferative and hypertrophic response induced by angiotensin II.	Cell proliferation and cytotoxicity were detected by methyl thiazolyl tetrazolium (MTT) and lactate dehydrogenase (LDH) release assay, respectively. Hypertrophic response of cardiac fibroblasts was measured by mRNA expression of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Resveratrol (25, 50, 75, and 100 μM) inhibited cardiac fibroblasts proliferation in a dose- and time-dependent manner compared with angiotensin II group ($P < 0.01$), and the inhibitory effects were blocked by pretreatment with *N*(G)-nitro-l-arginine methyl ester (l-NAME) and 1H-[1,2,4]-oxadiazole-[4,3-a]-quinoxalin-1-one (ODQ). Resveratrol increased nitric oxide (NO) and nitric oxide synthase (NOS) levels in culture medium, increased intracellular cyclic GMP (cGMP) level in cardiac fibroblasts, and decreased ANP and BNP levels in culture medium. The mRNA expression of ANP and BNP was suppressed by resveratrol.	The study suggests that resveratrol inhibited cardiac fibroblasts proliferation induced by angiotensin II, and the inhibitory effect might be associated with the activation of NO-cGMP signaling pathway.	207
Resveratrol is thought to have considerable potential for therapy of osteoporosis. Investigated the ability of resveratrol to exhibit bone-protective effects equivalent to those exerted by hormone replacement therapy and decrease the risk of breast cancer in the *in vivo* and *in vitro* models.	Forkhead proteins were found to be essential for both effects of resveratrol. The bone-protective effect was attributable to induction of bone morphogenetic protein-2 through Src kinase-dependent estrogen receptor activation and FOXA1 is required for resveratrol-induced estrogen receptor-dependent bone morphogenetic protein-2 expression. The tumor-suppressive effects of resveratrol were the consequence of Akt inactivation-mediated FOXO3a nuclear accumulation and activation.	This study suggests resveratrol could be highly effective in management of postmenopausal osteoporosis without an increased risk of breast cancer.	208
This study demonstrated a role for mitogen-activated protein kinase phosphatase-5 (MKP5) in mediating antiinflammatory activities of curcumin, resveratrol, and [6]-gingerol.	This research group utilized the cytokines tumor necrosis factor-α (TNFα) and interleukin (IL)-1β to increase p38-dependent nuclear factor κ-B (NFκB) activation and expression of proinflammatory genes cyclooxygenase-2 (COX-2), IL-6 and IL-8 in normal prostatic epithelial cells. MKP5 overexpression decreased cytokine-induced NF-κB activation, COX-2, IL-6 and IL-8 in normal prostatic epithelial cells, suggesting potent anti-inflammatory activity of MKP5. Pretreatment of cells with a p38 inhibitor mimicked the results observed with MKP5 over-expression, further implicating p38 inhibition as the main activity of MKP5. Curcumin upregulated MKP5, subsequently decreasing cytokine-induced p38-dependent proinflammatory changes in normal prostatic epithelial cells. Resveratrol and [6]-gingerol also upregulated MKP5 in normal prostate epithelial cells. Moreover, it was found that PCa cell lines DU 145, PC-3, LNCaP and LAPC-4 retained the ability to up-regulate MKP5 following curcumin, resveratrol, and [6]-gingerol exposure, suggesting utility of these phytochemicals in prostate cancer treatment.	This study showed direct anti-inflammatory activity of MKP5 in prostate cells and suggest that upregulation of MKP5 by phytochemicals may contribute to their chemopreventive actions by decreasing prostatic inflammation.	209
Investigated the effect of resveratrol on the production of nitric oxide (NO) and prostaglandin (PGE_2) by lipopolysaccharide (LPS)-activated C6 microglia.	Exposure of cultured rat C6 astroglioma cells to LPS increased their release of NO and PGE_2 and their inducible expression of NO synthase and cyclooxygenase-2, all of which were significantly inhibited by resveratrol pretreatment. Further studies revealed that resveratrol suppressed LPS-induced nuclear translocation and activation of nuclear factor κB (NF-κB).	These results demonstratee a potent suppressive effect of resveratrol on proinflammatory responses of microglia by modulation of NF-κB activity, suggesting a therapeutic potential for this compound in neurodegenerative diseases accompanied by microglial activation.	210

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Androgen receptor (AR)-positive LNCaP and estrogen receptor α (ERα)-expressing PC-3 prostate tumor cells were used to analyze whether the antiproliferative activity of resveratrol takes place by inhibition of the AR- or ERα-dependent PI3K pathway.	Although resveratrol treatment (up to 150 μM) decreased AR and ERα protein levels, it did not affect AR and ERα interaction with p85-PI3K. Immunoprecipitation and kinase assays showed that resveratrol inhibited AR- and ERα-dependent PI3K activities in LNCaP and PC-3, respectively. Consistently, lower PI3K activities correlated with decreased phosphorylation of downstream targets protein kinase B/AKT (PKB/AKT) and glycogen synthase kinase-3 (GSK-3). GSK-3 dephosphorylation could be responsible for the decreased cyclin D1 levels observed in both cell lines. Importantly, resveratrol markedly decreased PKB/AKT phosphorylation in primary cultures from human prostate tumors, suggesting that the mechanism proposed here could take place *in vivo*.	Resveratrol could have antitumor activity in androgen-sensitive and androgen-nonsensitive human prostate tumors by inhibiting survival pathways such as that mediated by PI3K.	211
Cultured human lung cancer cells (A549).	Using resveratrol as the prototype stilbenoid, this group synthesized various analogues and evaluated their growth inhibitory effects in cultured human cancer cells. One of the stilbenoids, 3,4,5-trimethoxy-4′-bromo-*cis*-stilbene (BCS), was more effective than its corresponding *trans*-isomer and resveratrol on the inhibition of cancer cell growth. Prompted by the strong growth inhibitory activity of BCS compared to its *trans*-isomer and resveratrol in A549, the mechanism of action was investigated. BCS induced arrest at the G_2/M phase of the cell cycle at early times and subsequently increased in the sub-G_1 phase DNA contents in a time-dependent manner, indicating induction of apoptosis. Morphological observation with round-up shape and DNA fragmentation was also revealed the apoptotic phenomena. BCS treatment elevated the expression levels of the proapoptotic protein p53, the cyclin-dependent kinase inhibitor p21, and the release of cytochrome c in the cytosol. The downregulation of checkpoint protein cyclin B1 by BCS was well correlated with the cell cycle arrest at G_2/M.	These data suggest the potential of BCS to serve as a cancer chemotherapeutic or chemopreventive agent by virtue of arresting the cell cycle and induction of apoptosis of human lung cancer cells.	212
ER-α and ER-β binding ability with quinone reductase (QR) expression in breast cancer cells.	Used three phytoestrogens, biochanin A, genistein, and resveratrol, as they upregulate QR expression in breast cancer cells. It was reported that regulation can occur at the transcriptional level preferentially through ER-β transactivation at the electrophile response element of the QR gene promoter. By chromatin immunoprecipitation analysis, showed binding of ER-α and ER-β to the QR promoter, with increased ER-β binding in the presence of resveratrol. Antisense technology was used to determine whether such protection was dependent on ER-β or QR.	The protective ability of resveratrol is partially dependent on the presence of ER-β and QR. Phytoestrogen-mediated induction of QR may represent an additional mechanism for breast cancer protection, although the effects may be specific for a given phytoestrogen.	213
LNCaP and LAPC-4 prostate cancer cell lines.	Quercetin and resveratrol caused an increase in expression of c-Jun as well as its phosphorylated form in a dose-dependent manner in prostatic cell lines using a transient transfection assay. Gel shift assays showed that induced c-Jun has specific DNA binding activity. Transient transfections demonstrated that c-Jun repressed prostate-specific antigen promoter activity and transcriptional activity of the androgen receptor (AR) promoter.	These results support a mechanism in which overexpressed c-Jun mediates an inhibitory effect on the function of AR.	214

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Human ovarian cancer cells A2780/CP70 and OVCAR-3.	Investigated the effect of resveratrol on hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) expression.	This study demonstrated that resveratrol inhibited HIF-1α and VEGF expression through multiple mechanisms. First, resveratrol inhibited AKT and mitogen-activated protein kinase activation, which played a partial role in the downregulation of HIF-1α expression. Second, resveratrol inhibited insulin-like growth factor 1-induced HIF-1α expression through the inhibition of protein translational regulators, including M_r 70,000 ribosomal protein S6 kinase 1, S6 ribosomal protein, eukaryotic initiation factor 4E-binding protein 1, and eukaryotic initiation factor 4E. Finally, it was found that resveratrol substantially induced HIF-1α protein degradation through the proteasome pathway. These data suggest that resveratrol may inhibit human ovarian cancer progression and angiogenesis by inhibiting HIF-1α and VEGF expression and thus provide a novel potential mechanism for the anticancer action of resveratrol.	215
The expression of 2059 cancer-related genes in a renal cell carcinoma (RCC) cell line RCC54 treated with resveratrol.	Biological functions of 633 genes were annotated based on biological process ontology and clustered into functional categories. Twenty-nine highly differentially expressed genes in resveratrol treated RCC54 were identified and the potential implications of some gene expression alterations in RCC carcinogenesis were identified.	The findings from this study support the hypothesis that resveratrol induces differential expression of genes that are directly or indirectly related to the inhibition of RCC cell growth and induction of RCC cell death. In addition, it is apparent that the gene expression alterations due to resveratrol treatment depend strongly on resveratrol concentration. This study provides a general understanding of the overall genetic response of RCC54 to resveratrol treatment and yields insights into the understanding of the cancer preventive mechanism of resveratrol in RCC.	216
Used sensitizer for anticancer drug-induced apoptosis by inducing cell cycle arrest, which in turn resulted in survivin depletion.	Analysis of cell cycle and apoptosis revealed that pretreatment with resveratrol resulted in cell cycle arrest in S phase and apoptosis induction preferentially out of S phase upon subsequent drug treatment. Likewise, cell cycle arrest in S phase by cell cycle inhibitors enhanced drug-induced apoptosis. Resveratrol-mediated cell cycle arrest sensitized for apoptosis by downregulating survivin expression through transcriptional and post-transcriptional mechanisms. Similarly, downregulation of survivin expression using survivin antisense oligonucleotides sensitized for drug-induced apoptosis. Downregulation of survivin and enhanced drug-induced apoptosis by resveratrol occurred in various human tumor cell lines irrespective of p53 status.	The combined sensitizer (resveratrol)/inducer (cytotoxic drugs) concept may be a strategy to enhance the efficacy of anticancer therapy in a variety of human cancers.	217
Hep3B hepatoma, Caki-1 renal carcinoma, SK-N-MC neuroblastoma, and HEK293 cell lines.	Hypoxia-induced drug resistance is a major obstacle in the development of effective cancer chemotherapy. Examined whether drug resistance of various phenolic compounds (i.e., resveratrol) is acquired by hypoxia. The cell lines were cultured under normoxic or hypoxic conditions. Drug sensitivities to the phenolic compounds and expression of hypoxia-inducible factor-1α (HIF-1α) and the multidrug-resistance genes were examined in these cell lines.	Drug resistance was acquired 24 h after hypoxia and subsided 8 h after reoxygenation. Protein synthesis inhibitors abolished this drug resistance. A transfection study demonstrated that HIF-1α enhanced this hypoxia-induced resistance and that its dominant-negative isoform suppressed resistance acquisition. However, MDR1 and MRP1, which provide multidrug resistance to conventional anticancer agents, were not induced by hypoxia. These results suggest that HIF-1α-dependent gene expression participates in the cellular process of the hypoxia-induced resistance to phenolic compounds.	218

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Human lymphoblastoid cell line TK6 and its p53-knockout counterpart (NH32).	The proapoptotic ability of (*Z*)-3,5,4′-tri-*O*-methyl-resveratrol (R3) was investigated using these cell lines. R3 induced the stimulation of caspase-3. Although R3 induced growth inhibition and apoptosis of both cell lines, two distinct mechanisms were observed.	The p53-knockout NH32 cells were shown to override the G_2/M phase checkpoint with development of hyperdiploid cells, whereas TK6 cells accumulated at G_2/M. As p53 function is often altered in human cancer cells, these results show that the proapototic effects of R3 against tumor cells are independent of their p53 status.	219
Leukemia B-cell lines and B-cell chronic lymphocytic leukemia (B-CLL) cells from patients.	Resveratrol induces apoptosis of leukemic B-cells and simultaneously inhibits the production of endogenous nitric oxide (NO) through inducible NO synthase (iNOS) downregulation. In addition these results were observed with not only acetate derivatives of polyphenols, particularly the pentaacetate of viniferin (resveratrol dimer), but also with a synthetic flavone (a diaminomethoxyflavone) in both leukemia B-cell lines and B-cell chronic lymphocytic leukemia (B-CLL) cells from patients. Moreover, flavopiridol, another flavone already known for its proapoptotic properties in B-CLL cells, was found to downregulate both iNOS expression and NO production.	Inhibition of the NO pathway during apoptosis of leukemia B-cells appears a common mechanism for several compounds belonging to two distinct families of phytoalexins, the flavones and grape-derived polyphenols.	220
Human breast cancer MCF-7 cells.	The mechanism of resveratrol to induce apoptosis in MCF-7 cells was dependent on mitogen-activated protein kinase (MAPK, ERK1/2) activation and was associated with serine phosphorylation and acetylation of p53. Treatment of MCF-7 cells with resveratrol in the presence of 17β-estradiol (E_2) further enhanced MAPK activation, but E_2 blocked resveratrol-induced apoptosis, as measured by nucleosome ELISA and DNA fragmentation assays. E_2 inhibited resveratrol-stimulated phosphorylation of serines 15, 20, and 392 of p53 and acetylation of p53 in a concentration- and time-dependent manner. These effects of E_2 on resveratrol action were blocked by ICI 182,780 (ICI), an inhibitor of the nuclear estrogen receptor-α (ER). ICI 182,780 did not block the actions of resveratrol, alone. Electrophoretic mobility studies of p53 binding to DNA and of p21 expression indicated that E_2 inhibited resveratrol-induced, p53-directed transcriptional activity.	These results suggest that E_2 inhibits p53-dependent apoptosis in MCF-7 cells by interfering with post-translational modifications of p53, which are essential for p53-dependent DNA binding and consequent stimulation of apoptotic pathways.	221
CYP1A1 and 1B1 in UW228-3 medulloblastoma cells.	The status of CYP1A1 and 1B1 in UW228-3 medulloblastoma cells without and with resveratrol treatments were elucidated in this study with the ethoxyresorufin *O*-deethylation assay, followed by RT-PCR, immunocytochemical staining and Western blot hybridization. CYP1A1/1B1 enzymatic activity was low in UW228-3 cells but became several fold higher upon resveratrol treatments. CYP1A1 was undetectable and CYP1B1 was expressed in normally cultured cells. Accompanied by the increased fraction of apoptosis, enhanced CYP1A1 and downregulated CYP1B1 were observed in resveratrol-treated cells in time- and dose-related fashions.	The results demonstrate that in the medulloblastoma cell system, CYP1A1 upregulation is paralleled with resveratrol-induced differentiation and apoptosis, while CYP1B1 may not be an essential element in metabolic activation of resveratrol in those cells. CYP1A1 and 1B1 are resveratrol response genes and potential chemosensitive markers of medulloblastoma cells.	222

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Various human breast cancer cells and a wild-type cell line, astrocytoma N 1321N1 was used as the control.	Purpose of study was to identify the role of p53-dependent or p53-independent pathways in the induction of apoptosis in human breast cancer cells by resveratrol. A number of human breast cancer cell lines, as well as astrocytoma N 1321N1, were investigated for induction of apoptosis by resveratrol using both microscopic evaluation and DNA fragmentation assays. Concurrently, the p53 gene status (wild-type or mutant) of each cell line was established by Western blot using p53-specific antibody.	Apoptosis induced by resveratrol was found to occur only in breast cancer cells expressing wild-type p53 but not in mutant p53-expressing cells. The study suggests that resveratrol induces apoptosis in breast cancer cells via p53-dependent pathways.	223
Benzo(*a*)pyrene [B(*a*)P]-induced DNA adducts in human bronchial epithelial cells.	The *in vitro* effect of resveratrol on B(*a*)P-induced DNA adducts in human bronchial epithelial cells. This was compared to the effect of resveratrol on the expression of the cytochrome P450 (CYP) genes CYP1A1 and CYP1B1 and the formation of B(*a*)P metabolites. Exposure of BEAS-2B and BEP2D cells to B(*a*)P and increasing concentrations of resveratrol resulted in a dose- and time-dependent inhibition of DNA adduct formation quantified by ^{32}P-postlabeling. Supporting this result, resveratrol was shown to inhibit CYP1A1 and CYP1B1 gene expression, as measured by RT PCR. Also, a significant correlation was found between the number of DNA adducts and the mRNA levels of these genes. Using HPLC analysis, a concomitant decrease in the formation of B(*a*)P-derived metabolic products was detected.	These data suggest that resveratrol has a chemopreventive role in polycyclic aromatic hydrocarbon-induced carcinogenesis.	224
Stage 4 MYCN-amplified neuroblastoma (NB) cell lines.	Stage 4 MYCN-amplified NB cell lines, with wild-type or mutant p53, were treated with curcumin and resveratrol and analyzed for effects on proliferation, cell cycle, induction of apoptosis, and p53 function.	Observations suggest that the cytotoxicity, cell cycle arrest and apoptosis induced by curcumin and resveratrol in NB cells may be mediated via functionally activated p53.	225
Human breast tumor cell lines (HBL100, MCF7 and MBA-MB-231) and one breast cell line (MCF10a).	HBL100, MCF7, MBA-MB-231, MCF10a cells were used to study the effect of resveratrol on the transcription of a group of genes whose proteins interact in different pathways with BRCA1. BRCA1, BRCA2, ERα, ERβ, p53, p21$^{waf1/cip1}$, CBP/P300, RAD51, pS2 and K*i*67 mRNA were quantified using real-time quantitative RT-PCR.	Resveratrol modulated the expression of these genes in a pattern dependent on the status of α and β estrogen receptors. These results show that resveratrol regulates gene expression via the estrogen receptor pathway and also an undetermined pathway. Thus, resveratrol seems to have an effect on breast tumor cell lines by affecting several factors regulating the function of BRCA1.	226
Human HT-29 colon cancer cells.	Isothiocyanates, flavonoids, resveratrol, and curcumin were examined in this study. HT-29 cells were stably transfected with NF-κB luciferase construct, and stable clones were selected. HT-29 N9 cells were selected and treated with various concentrations of the natural chemopreventive agents and subsequently challenged with NF-κB stimulator lipopolysaccharide, and the luciferase activities were measured. Western blot analysis of phosphorylated IκBα was performed after treatments with the natural chemopreventive agents. The effects of these agents on cell viability and apoptosis were also evaluated by a nonradioactive cell proliferation MTS assay [3-(4,5-dimethylthiazol-2-yl)-5-(3-arboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt], Trypan blue staining, and caspase assay.	Treatments resulted in different responses in the NF-κB-luciferase assay. ITCs such as phenethyl isothiocyanate, sulforaphane, allyl isothiocyanate, and curcumin strongly inhibited LPS-induced NF-κB-luciferase activation, whereas resveratrol increased activation at lower dose, but inhibited activation at higher dose, and tea flavonoids and procyanidin dimers had little or no effect. ITCs, curcumin, (-)-epigallocatechin-3-gallate, and resveratrol reduced LPS-induced IκBα phosphorylation. Furthermore, in the MTS assay, PEITC, SUL, and curcumin also potently inhibited cell growth. Caspase-3 activity was induced by chemopreventive compounds, however, the kinetics of caspase-3 activation varied between these compounds within the 48 h time period. These results suggest that natural chemopreventive agents have differential biological functions on the signal transduction pathways in the colon and/or colon cancer.	227

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
HT-29 colon cancer cells.	HT-29 cells were transfected with AP-1-luciferase reporter gene, and one of the stable clones (C-4) was used for subsequent experiments. The HT-29 C-4 cells were treated for 1 h with various natural chemopreventive agents and challenged with AP-1 stimulators such as 12-*O*-tetradecanoylphorbol-13-acetate (TPA) or hydrogen peroxide (H_2O_2) for 6 h. The c-Jun N-terminal kinase (JNK) was examined to understand the effect of these compounds on the upstream signaling activator of AP-1. The protein expression level of endogenous cyclin D1, a gene that is under the control of AP-1, was also analyzed after treatments with the agents. In addition, cell death induced by these compounds was evaluated by MTS assay [3-(4.5-dimethylthiazol-2-yl)-5-(3-arboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt].	TPA and H_2O_2 treatments strongly induced AP-1-luciferase activity as expected. Phenethyl isothiocyanate, sulforaphane, curcumin, and resveratrol increased AP-1-luciferase activity dose-dependently and then decreased at higher doses in the presence or absence of TPA. Allyl isothiocyanate and (-)-epigallocatechin-3-gallate increased AP-1-luciferase activity dose-dependently up to 50 and 100 μM. Other tea catechins and procyanidin dimers, however, had little or no effect on AP-1-luciferase activity. The JNK activity was induced by the isothiocyanates and EGCG. Most of the chemopreventive compounds induced cell death in a dose-dependent manner, with the exception of epicatechin and the procyanidins, which had little effect. The expression of endogenous cyclin D1 protein was well correlated with those of AP-1-luciferase assay. These results suggest that natural chemopreventive compounds may have differential biological functions on the signal transduction pathways such as AP-1 in the intervention of colon cancer progression and carcinogenesis.	228
Human cancer cell lines, HeLa (cervix carcinoma), K-562 (chronic myeloid leukemia) and IM-9 (multiple myeloma).	The purpose of this study was to examine whether resveratrol can sensitize cancer cells to X-irradiation using human cancer cell lines (HeLa, K-562, and IM-9). The assays that were performed following X-irradiation (doses from 0 to 8 Gy) and/or incubation in the presence of resveratrol (concentrations ranging from 0 to 200 μM), were the following: Trypan blue exclusion test to determine cell viability, cell morphology after May-Grunwald Giemsa staining, DNA profile analysis by flow cytometry to assess cell cycle distribution and the presence of the sub-G_1 peak.	The cell lines showed different radiation sensitivity (IM-9, high radiation sensitivity, K-562, intermediate radiation sensitivity and HeLa, low radiation sensitivity) as seen by the X-irradiation dose related inhibition of cell growth and induction of apoptosis. The addition of resveratrol alone to the cell cultures induced apoptosis and inhibited cell growth from 50 (IM-9), 100 (EOL-1) or 200 μM (HeLa) resveratrol concentrations. Concomitant treatment of the cells with either resveratrol and X-irradiation induced a synergical effect at the highest dose of 200 μM. These results show that resveratrol can act as a potential radiation sensitiser at high concentrations.	229
TNF-α, IL-12, and IL-1β production from LPS activated phorbol myristate acetate (PMA) differentiated THP-1 human macrophages.	The study demonstrates that resveratrol enhanced TNF-α, IL-12, and IL-1β production from LPS activated phorbol myristate acetate (PMA) differentiated THP-1 human macrophages. Expression of CD86 on macrophages was enhanced by resveratrol alone and with LPS. When macrophages were primed with IFN-gamma, resveratrol suppressed the expression of HLA-ABC, HLA-DR, CD80, CD86 and inhibited production of TNF-α, IL-12, IL-6, and IL-1β induced by LPS.	The differential impact of resveratrol on expression of CD14 might be correlated with differential response of macrophages to LPS with or without IFN-gamma priming.	230

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
The effects of resveratrol and estradiol (E_2) on expression of exogenous reporter genes and an endogenous estrogen-regulated gene (TGFα) in MDA-MB-231 cells stably transfected with wild-type (wt) ERα or mutants with deleted or mutated AF domains.	To examine the role of the transcriptional activation function (AF) domains of ERα in resveratrol agonism, the effects of resveratrol and E_2 on expression of exogenous reporter genes and TGFα in MDA-MB-231 cells stably transfected with wtERα or mutants with deleted or mutated AF domains were compared. In reporter gene assays, cells expressing wtERα showed a superagonistic response to resveratrol. Deletion of AF-1 or mutation of AF-2 attenuated the effect of resveratrol disproportionately compared to that of E_2, while deletion of AF-2 abrogated the response to both ligands. In TGFα expression assays, resveratrol acted as a full agonist in cells expressing wtERα. Deletion of AF-1 attenuated stimulation by E_2 more severely than that by resveratrol, as did deletion of AF-2. In contrast, mutation of AF-2 left both ligands with a limited ability to induced TGFα expression.	The effect of modifying or deleting AF domains depends strongly on the ligand and the target gene.	231
Breast cancer resistance protein (BCRP/ABCG2).	In two separate BCRP-overexpressing cell lines, accumulation of the established BCRP substrates mitoxantrone and bodipy-FL-prazosin was significantly increased by the flavonoids silymarin, hesperetin, quercetin, and daidzein, and resveratrol as measured by flow cytometry, though there was no corresponding increase in the respective wild-type cell lines. These compounds also stimulated the vanadate-inhibitable ATPase activity in membranes prepared from bacteria (*Lactococcus lactis*) expressing BCRP.	Plant-derived polyphenols that interact with P-glycoprotein can also modulate the activity of the ABC transporter, BCRP/ABCG2. Given the high dietary intake of polyphenols, such interactions with BCRP, particularly in the intestines, may have important consequences *in vivo* for the distribution of these compounds as well as other BCRP substrates.	232
Transport in hepatic cells.	A new technique was used to qualitatively follow resveratrol cell uptake and intracellular distribution, based on resveratrol fluorescent properties. A time-course study and the quantification of ^{3}H-labeled resveratrol uptake were performed using human hepatic derived cells (HepG2 tumor cells) and hepatocytes.	The temperature-dependence of the kinetics of uptake as well as cis-inhibition experiments agree with the involvement of a carrier-mediated transport in addition to passive diffusion. The decrease of passive uptake resulted from resveratrol binding to serum proteins.	233
Androgen receptor (AR)-mediated transcription in human prostate cancer cells (LNCaP and PC3).	Resveratrol and genistein activated AR-driven gene expression at low concentrations, whereas they repressed the AR-dependent reporter gene activity at high concentrations. Resveratrol and genistein induced AR-driven gene expression by activating the Raf-MEK-ERK kinase pathway. The ERK1 kinase phosphorylated the AR on multiple sites*in vitro*, but this phosphorylation event did not contribute to the resveratrol-induced AR transactivation.	Due to evidence that AR pathways are involved in the development and progression of prostate cancer, these data show that the ability to modulate AR function would contribute the observed chemopreventive activity of resveratrol and genistein.	234
CYP1B1 gene expression in MCF-7 human breast carcinoma cells.	MCF-7 cells were treated with β-naphthoflavone (BNF), emodin, resveratrol, or 0.1% dimethylsulfoxide (vehicle control). Total cellular RNA was isolated and reverse transcribed. cDNA samples were quantified by a fluorescence assay and a constant amount was amplified in a real-time DNA thermal cycler. Melting curve analysis and agarose gel electrophoresis of the amplicons resulted in a single peak and a single band, respectively. The identity of the amplicon was confirmed to be CYP1B1 by sequencing analysis. The standard curve for the real-time PCR amplification of CYP1B1 cDNA was log-linear for at least four orders of magnitude. The limit of quantitation (LOQ) of the assay was 100 copies.	Method was described for the real-time PCR quantification of CYP1B1 gene expression in MCF-7 human breast carcinoma cells.	235

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Resveratrol inhibits drug-induced apoptosis in human leukemia cells.	Studies show evidence that exposure of human leukemia cells to low concentrations of resveratrol inhibits caspase activation, DNA fragmentation, and translocation of cytochrome c induced by hydrogen peroxide or anticancer drugs C2, vincristine, and daunorubicin. At these concentrations, resveratrol induces an increase in intracellular superoxide and inhibits drug-induced acidification. Blocking the activation of NADPH oxidase complex neutralized resveratrol-induced inhibition of apoptosis. The results implicate intracellular hydrogen peroxide as a common effector mechanism in drug-induced apoptosis that is inhibited by preincubation with resveratrol. Decreasing intracellular superoxide with the NADPH oxidase inhibitor diphenyliodonium reversed the inhibitory effect of resveratrol on drug-induced hydrogen peroxide production.	These data show that low concentrations of resveratrol inhibit death signaling in human leukemia cells via NADPH oxidase-dependent elevation of intracellular superoxide that blocks mitochondrial hydrogen peroxide production, thereby resulting in an intracellular environment nonconducive for death execution.	236
Analyzed the ability of resveratrol to modulate the ERα -dependent PI3K pathway using MCF-7 (human breast cancer cell).	Immunoprecipitation and kinase activity assays showed that resveratrol increased the ERα-associated PI3K activity with a maximum stimulatory effect at concentrations close to 10 μM; concentrations >50 μM decreased PI3K activity. Stimulation of PI3K activity by resveratrol was ERα-dependent as it could be blocked by the antiestrogen ICI 182,780. Resveratrol did not affect p85 protein expression but induced the proteasome-dependent degradation of the ERα. Nevertheless, the amount of PI3K immunoprecipitated by the ERα remained unchanged in presence of resveratrol, indicating that ERα availability was not limiting PI3K activity. Phosphoprotein kinase B (pPKB/AKT) followed the pattern of PI3K activity, whereas resveratrol did not affect total PKB/AKT expression. PKB/AKT downstream target glycogen synthase kinase 3 (GSK3) also showed a phosphorylation pattern that followed PI3K activity.	The study suggests a mechanism through which resveratrol could inhibit survival and proliferation of estrogen-responsive cells by interfering with an ERα-associated PI3K pathway, following a process that could be independent of the nuclear functions of the ERα.	237
Investigated whether resveratrol can sensitize non–Hodgkin's lymphoma (NHL) and multiple myeloma (MM) cell lines to paclitaxel-mediated apoptosis and to delineate the underlying molecular mechanism of sensitization.	Both resveratrol and paclitaxel negatively modulated tumor cell growth by arresting the cells at the G_2-M phase of the cell cycle. Low concentrations of resveratrol exerted a sensitizing effect on drug-refractory NHL and MM cells to apoptosis induced by paclitaxel. Resveratrol selectively downregulated the expression of antiapoptotic proteins Bcl-x^L and myeloid cell differentiation factor-1 (Mcl-1) and upregulated the expression of proapoptotic proteins Bax and apoptosis protease activating factor-1 (Apaf-1). Paclitaxel downregulated the expression of Bcl-x^L, Mcl-1, and cellular inhibitor of apoptosis protein-1 antiapoptotic proteins and upregulated Bid and Apaf-1. Combination treatment resulted in apoptosis through the formation of tBid, mitochondrial membrane depolarization, cytosolic release of cytochrome c and Smac/DIABLO, activation of the caspase cascade, and cleavage of poly(adenosine diphosphate-ribose) polymerase. Combination of resveratrol with paclitaxel had minimal cytotoxicity against quiescent and mitogenically stimulated human peripheral blood mononuclear cells. Inhibition of Bcl-x^L expression by resveratrol was critical for chemosensitization and its functional impairment mimics resveratrol-mediated sensitization to paclitaxel-induced apoptosis. Inhibition of Bcl-x^L expression by resveratrol was due to the inhibition of the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway and diminished activator protein-1-dependent Bcl-x^L expression. The findings by resveratrol were corroborated with inhibitors of the ERK1/2 pathway.	This study demonstrates that in resistant NHL and MM cell lines resveratrol and paclitaxel selectively modify the expression of regulatory proteins in the apoptotic signaling pathway and the combination, via functional complementation, results in synergistic apoptotic activity.	238

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Response of ovarian cancer cells to resveratrol.	Resveratrol inhibited growth and induced death in a panel of five human ovarian carcinoma cell lines. The response was associated with mitochondrial release of cytochrome c, formation of the apoptosome complex, and caspase activation. Surprisingly, even with these molecular features of apoptosis, analysis of resveratrol-treated cells by light and electron microscopy revealed morphology and ultrastructural changes indicative of autophagocytic, rather than apoptotic death. This suggests that resveratrol can induce cell death through two distinct pathways. Consistent with the ability of resveratrol to kill cells via nonapoptotic processes, cells transfected to express high levels of the antiapoptotic proteins Bcl-x^L and Bcl-2 were equally sensitive as control cells to resveratrol.	These findings show that resveratrol induces cell death in ovarian cancer cells through a mechanism distinct from apoptosis, therefore suggesting that it may provide leverage to treat ovarian cancer that is chemoresistant on the basis of ineffective apoptosis.	239
Resveratrol suppresses EGFR-dependent Erk1/2 activation pathways stimulated by EGF and phorbol ester (12-*O*-tetradecanoyl phorbol 13-acetate, TPA) in human prostate cancer (AI PrCa PC-3) cells.	Becaue protein kinase C (PKC) is the major cellular receptor for phorbol esters and taking into consideration that resveratrol is PKC-inhibitory, the effects of resveratrol on cellular PKC isozymes associated with the suppression of TPA-induced Erk1/2 activation were investigated. The PKC isozyme composition of PC-3 cells was defined by Western analysis of the cell lysate with a comprehensive set of isozyme-selective PKC antibiotics. PC-3 cells expressed PKCα, ε, ζ, ι, and PKD (PKCμ), as did another human AI PrCa cell line of distinct genetic origin, DU145. The effects of resveratrol on TPA-induced PKC isozyme activation were defined by monitoring PKC isozyme translocation and autophosphorylation. Under conditions where resveratrol suppressed TPA-induced Erk1/2 activation, the phytochemical produced isozyme-selective interference with TPA-induced translocation of cytosolic PKCα to the membrane/cytoskeleton and selectively diminished the amount of autophosphorylated PKCα in the membrane/cytoskeleton of the TPA-treated cells.	These results demonstrate that resveratrol abrogation of a PKC-mediated Erk1/2 activation response in PC-3 cells correlates with isozyme-selective PKCα inhibition. The results provide evidence that resveratrol may have value as an adjuvant cancer therapeutic in advanced prostate cancer.	240
Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)-induced apoptosis through p53-independent induction of p21 and p21-mediated cell cycle arrest associated with survivin depletion.	Survivin expression and apoptosis revealed that resveratrol-induced G_1 arrest was associated with downregulation of survivin expression and sensitization for TRAIL-induced apoptosis. Accordingly, G_1 arrest using the cell cycle inhibitor mimosine or induced by p21 overexpression reduced survivin expression and sensitized cells for TRAIL treatment. Likewise, resveratrol-mediated cell cycle arrest followed by survivin depletion and sensitization for TRAIL was impaired in p21- deficient cells. Also, downregulation of survivin using survivin antisense oligonucleotides sensitized cells for TRAIL-induced apoptosis.	Resveratrol is a potent sensitizer of tumor cells for tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)-induced apoptosis through p53-independent induction of p21 and p21-mediated cell cycle arrest associated with survivin depletion. Resveratrol sensitized various tumor cell lines, but not normal human fibroblasts, for apoptosis induced by death receptor ligation or anticancer drugs. Thus, this combined sensitizer (resveratrol)/inducer (e.g., TRAIL) strategy may be a novel approach to enhance the efficacy of TRAIL-based therapies in a variety of human cancers.	241

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Human breast cancer cell line MCF-7.	Resveratrol treatment of MCF-7 cells resulted in a dose-dependent inhibition of the cell growth and the cells accumulated at the S phase transition of the cell cycle at low concentrations, but high concentrations do not induce S phase accumulation. The antiproliferative effects of resveratrol were associated with a marked inhibition of cyclin D and cyclin-dependent kinase (Cdk) 4 proteins, and induction of p53 and Cdk inhibitor $p21^{WAF1/CIP}$. Growth suppression by resveratrol was also due to apoptosis, as seen by the appearance of a sub-G_1 fraction and chromatin condensation. In addition, the apoptotic process involves activation of caspase-9, a decrease of Bcl-2 as well as Bcl-x^L levels, and an increase of Bax levels.	Using MCF-7, this study analyzed a possible mechanism by which resveratrol could interfere with cell cycle control and induce cell death.	242
Determine the mechanism(s) by which 1,4-dihydropyridine Ca^{2+} channel blockers (DHPs) enhance the binding of neurotensin (NT) to prostate cancer PC3 cells and inhibit NT-induced inositol phosphate formation.	Earlier work indicated that these effects, which involved the G protein–coupled NT receptor NTR1, were indirect and required cellular metabolism or architecture. At the micromolar concentrations used, DHPs can block voltage-sensitive and store-operated Ca^{2+} channels, K^+ channels, and Na^+ channels, and can inhibit lipid peroxidation. By varying $[Ca^{2+}]$ and testing the effects of stimulators and inhibitors of Ca^{2+} influx and internal Ca^{2+} release, we determined that although DHPs may have inhibited inositol phosphate formation partly by blocking Ca^{2+} influx, the effect on NT binding was Ca^{2+}-independent. By varying $[K^+]$ and $[Na^+]$, it was found that these ions did not contribute to either effect. For a series of DHPs, the activity order for effects on NTR1 function followed that for antioxidant ability. Antioxidant polyphenols (luteolin and resveratrol) mimicked the effects of DHPs and showed structural similarity to DHPs. Antioxidants with equal redox ability, but without structural similarity to DHPs (such as α-tocopherol, riboflavin, and *N*-acetyl-cysteine) were without effect. A flavoprotein oxidase inhibitor (diphenylene iodonium) and a hydroxy radical scavenger (butylated hydroxy anisole) also displayed the effects of DHPs.	DHPs indirectly alter NTR1 function in live cells by a mechanism that depends on the ability of the drug to donate hydrogen but does not simply involve sulfhydryl reduction.	243
Inhibition of phorbol myristate acetate-induced matrix metalloproteinase-9 expression by inhibiting JNK and PKC Δ signal transduction.	Resveratrol was found to significantly inhibit the PMA-induced increase in MMP-9 expression and activity. These effects of resveratrol are dose dependent and correlate with the suppression of MMP-9 mRNA expression levels. PMA caused about a 23-fold increase in MMP-9 promoter activity, which was suppressed by resveratrol. Transient transfection utilizing MMP-9 constructs, in which specific transcriptional factors were mutagenized, indicated that the effects of PMA and resveratrol were mediated via an activator protein-1 and NF-κB response element. Resveratrol inhibited PMA-mediated activation of c-Jun N-terminal kinase (JNK) and protein kinase C (PKC)-Δ activation.	MMP-9 inhibitory activity of resveratrol and its inhibition of JNK and PKC-Δ may have therapeutic potential.	244

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Prostate cancer cell line (PC3).	This study compared the ability to induce both ceramide increase and growth inhibition in PC3 cells of resveratrol and three resveratrol analogues: piceatannol (3,3′,4′,5-*trans*-tetrahydroxystilbene), with an additional hydroxyl group in the 3′ position; *trans*-stilbene, the nonhydroxylated analog; and the semisynthetic 3,4′,5-trimethoxy-*trans*-stilbene (TmS), with methoxyl groups in lieu of the hydroxyl groups. Of the three stilbenoids, only piceatannol (and not stilbene or TmS) produced ceramide-associated growth inhibition.	This study demonstrates that resveratrol can exert antiproliferative/proapoptotic effects in association with the accumulation of endogenous ceramide in the androgen receptor (AR)-negative PC3. These data suggest the phenolic moiety of stilbenoids is a critical structural feature necessary to induce ceramide-associated growth inhibition.	245
Human lymphoma B (DHL-4) cells.	The effect of resveratrol on cell cycle and growth of DHL-4 cells was studied. MTT colorimetric test, Trypan blue dye exclusion assay, and cell cycle analysis showed that resveratrol has a dose-dependent antiproliferative and antiapoptotic action on DHL-4 cells.	These results confirm the potential therapeutic role of resveratrol.	246
HSP70 expression and cell death elicited by resveratrol in DU-145 human prostate cancer cells.	DU-145 cells were treated with different concentrations of resveratrol, and cell viability and membrane breakdown were measured. The possible induction of oxidative stress was evidenced both by performing a fluorescent analysis of intracellular reactive oxygen species (ROS) production, or evaluating the amount of nitrite/nitrate (NO) in culture medium. In addition, the expression of HSP70 level, evaluated by immunoblotting, was examined and compared with caspase-3 activity (fluorimetrically measured) and DNA damage, determined by single cell gel electrophoresis or COMET assay.	These data indicate that the addition of resveratrol to DU-145 cells reduces cell viability and increases membrane breakdown, in a dose-dependent manner, without interfering with ROS production or NO synthesis, unless 200 μM resveratrol is added. Furthermore, at low concentration, resveratrol is able to raise HSP70 levels but, at high concentration, the measured levels of protective HSP70 were unmodified with respect to that of the control values. The results confirm the ability of resveratrol to suppress the proliferation of human prostate cancer cells with a typical apoptotic feature, interfering with the expression of HSPs70.	247
Resveratrol inhibits the growth of human prostate carcinoma DU145 cells.	Resveratrol treatment in DU145 cells resulted in a dose-dependent inhibition of cell growth and induced apoptotic cell death. The antiproliferative effect of resveratrol was associated with the inhibition of D-type cyclins and cyclin-dependent kinase (Cdk) 4 expression, and the induction of tumor suppressor p53 and Cdk inhibitor p21. Moreover, the kinase activities of cyclin E and Cdk2 were inhibited by resveratrol without alteration of their protein levels. Resveratrol treatment also upregulated the Bax protein and mRNA expression in a dose-dependent manner; however, Bcl-2 and Bcl-x^L levels were not significantly affected. These effects were found to correlate with an activation of caspase-3 and caspase-9.	The study suggests that resveratrol has a strong potential for development as an agent for the prevention of human prostate cancer.	248

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Evaluated cellular effects of resveratrol derivatives, viniferin, gnetin H, and suffruticosol B, on proliferation and apoptosis with HL-60 cells.	Resveratrol and its derivatives reduced viability of HL-60 cells in a dose-dependent manner with IC_{50} values of 20-90 μM. Ascending orders of IC_{50}values were suffruticosol B, gnetin H, viniferin and resveratrol, respectively. HL-60 cells treated with the four stilbenes exhibited distinct morphological changes characteristics of cell apoptosis such as chromatin condensation, apoptotic bodies, and DNA fragmentations. A time-dependent histogram of the cellular DNA analyzed by flow cytometry revealed a rapid increase in subdiploid cells and a concomitant decrease in diploid cells exposed to 100 μM resveratrol for 0–24 h. Cells treated with 25 μM of resveratrol, viniferin, gnetin H, and suffruticosol B for 24 h resulted in increment of sub-G_1 population by 51, 5, 11, and 59%, respectively. Treatment of cells with 0–20 μM resveratrol for 5 h produced a concentration-dependent decrease in cytochrome P450 (CYP) 1B1 mRNA levels. Suffruticosol B also suppressed CYP1B1 gene expression.	These results demonstrated that resveratrol oligomers also strongly suppressed HL-60 cell proliferation, and induced DNA damage. In addition, CYP1B1 gene supression may suggest an involvement in the resveratrol-induced apoptosis in HL-60 cells.	249
Increasing the throughput of Caco-2 cell monolayer assays and expanding the scope of this assay to include modeling intestinal drug metabolism.	A state-of-the-art Caco-2 cell monolayer permeability assay combines multi-well plates fitted with semi-permeable inserts on which Caco-2 cells have been cultured with liquid chromatography-mass spectrometry (LC-MS) or LC-tandem mass spectrometry (LC-MS/MS) for the quantitative analysis of test compounds, and the identification of their intestinal metabolites. Application of LC-MS and LC-MS/MS for the measurement of resveratrol permeability and metabolism in the Caco-2 model was demonstrated. The apparent permeability coefficient for apical (AP) to basolateral (BL) movement of resveratrol was 2.0×10^5cm/s.	Resveratrol was not a substrate for P-glycoprotein or multidrug resistance associated proteins (MRP). No phase I metabolites were observed, but the phase II conjugates resveratrol-3-glucuronide and resveratrol-3-sulfate was identified based on LC-MS and LC-MS/MS analysis and comparison with synthetic standards. Although these data indicate that resveratrol diffuses rapidly across the intestinal epithelium, extensive phase II metabolism during absorption might reduce resveratrol bioavailability.	124
Effect on proliferation and inducing apoptosis in lung cancer cell lines (A549, EBC-1, Lu65).	Resveratrol inhibited the growth of A549, EBC-1, and Lu65 lung cancer cells by 50% (ED_{50}) at concentrations between 5–10 μM. The combined effect of resveratrol and paclitaxel was examined in these cells. Although simultaneous exposure to resveratrol plus paclitaxel did not result in significant synergy, resveratrol significantly enhanced the subsequent antiproliferative effect of paclitaxel. In addition, resveratrol as well as paclitaxel induced apoptosis in EBC-1 and Lu65 cells, as measured by TUNEL and caspase assays, as well as flow cytometry. Resveratrol enhanced the subsequent apoptotic effects of paclitaxel. The effects of resveratrol and paclitaxel were examined on levels of $p21^{waf1}$, $p27^{kip1}$, E-cadherin, EGFR, and Bcl-2 in EBC-1 cells. Resveratrol prior to paclitaxel induced $p21^{waf1}$ expression approximately 4-fold.	These results suggest that resveratrol may be a promising alternative therapy for lung cancer and that lung cancer cells exposed to resveratrol have a lowered threshold for killing by paclitaxel.	250
Resveratrol was used to treat four human medulloblastoma cell lines (Med-3, UW228-1, -2 and -3) and its effects on cell growth, differentiation, and death were examined by multiple approaches.	Expression of Fas, FasL, and caspase-3 in the cells without and with resveratrol treatments was examined by immunocytochemical staining and mRNA *in situ* hybridization, and the influence of anti-Fas antibody in cell growth and survival was determined as well. The results demonstrated that resveratrol could suppress growth, promote differentiation and commit target cells to apoptosis in time- and dose-related fashions. Fas was constitutively expressed, but FasL was undetectable in the four lines in spite of resveratrol treatment. Anti-Fas antibody neither inhibited growth nor induced apoptosis of those cell lines. Upregulated caspase-3 was found in resveratrol-treated populations and appearance of its cleaved form was closely associated with the apoptotic event.	These findings suggest that resveratrol is an effective antimedulloblastoma agent that kills medulloblastoma cells through a Fas-independent pathway.	251

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
MDA-MB-231, a highly invasive and metastatic breast cancer cell.	Accumulation of ceramide derives from both *de novo* ceramide synthesis and sphingomyelin hydrolysis. It was demonstrated that ceramide accumulation induced by resveratrol can be associated with the activation of serine palmitoyltransferase (SPT), the key enzyme of *de novo* ceramide biosynthetic pathway, and neutral sphingomyelinase (nSMase), a main enzyme involved in the sphingomyelin/ceramide pathway. However, by using specific inhibitors of SPT, myriocin and L-cycloserine, and nSMase, gluthathione and manumycin, only the SPT inhibitors could counteract the biological effects induced by resveratrol.	The study shows that resveratrol can induce growth inhibition and apoptosis in MDA-MB-231 in concomitance with a dramatic endogenous increase of growth inhibitory/proapoptotic ceramide. Resveratrol seems to exert its growth inhibitory/apoptotic effect on MDA-MB-231 by activating the *de novo* ceramide synthesis pathway.	252
Suppress the growth of endometrial cancer cells (Ishikawa cell line) through downregulation of EGF.	Ishikawa cells were treated with resveratrol (1, 10, 50, and 100 μM) for 1, 3, 5, and 7 days, and analyzed for growth signal genes (EGF and VEGF), cell cycle regulatory genes (p53 and p21), and apoptosis-related genes (Bcl-2 and Bax). Results of these experiments demonstrate that after resveratrol treatment, the growth of Ishikawa cells was inhibited in a dose-dependent manner. The gene and protein expression data suggest that resveratrol treatment significantly decreased EGF, whereas VEGF was upregulated in Ishikawa cell lines. Interestingly, protein expressions of p21 and Bax were decreased, even though their mRNA expressions did not show significant changes.	This study suggests that resveratrol can suppress proliferation of Ishikawa cells through downregulation of EGF.	253
Involvement of $p21^{WAF1/CIP1}$, pRB, Bax, and NF-κB in induction of growth arrest and apoptosis by resveratrol in human lung carcinoma A549 cells.	Resveratrol treatment of A549 cells resulted in a concentration-dependent induction of S phase arrest in cell cycle progression. This antiproliferative effect of resveratrol was associated with a marked inhibition of the phosphorylation of the retinoblastoma protein (pRB) and concomitant induction of cyclin-dependent kinase (Cdk) inhibitor $p21^{WAF1/CIP}$, which appears to be transcriptionally upregulated and is p53-dependent. In addition, resveratrol treatment resulted in induction of apoptosis as determined by fluorescence microscopy and flow cytometric analysis. These effects were found to correlate with an activation of caspase-3 and a shift in Bax/ Bcl-x^L ratio more toward apoptosis. Resveratrol treatment also inhibited the transcriptional activity of NF-κB.	These findings suggest that resveratrol has potential for development as an agent for prevention of human lung cancer.	254
Chemopreventive properties on intestinal carcinogenesis using a methylated derivative of resveratrol (*Z*-3,5,4′-trimethoxystilbene: R3).	R3 at 0.3 μM exerted an 80% growth inhibition of Caco-2 cells and arrested growth completely at 0.4 μM (R3 was 100-fold more active than resveratrol). The *cis* conformation of R3 was also 100-fold more potent than the *trans* isomer. R3 (0.3 μM) caused cell cycle arrest at the G_2/M phase transition. The drug inhibited tubulin polymerization in a dose-dependent manner ($IC_{50} = 4$ μM), and it reduced also by 2-fold ornithine decarboxylase and *S*-adenosylmethionine decarboxylase activities. This caused the depletion of the polyamines, putrescine and spermidine, which are growth factors for cancer cells. R3 inhibited partially colchicine binding to its binding site on tubulin, indicating that R3 either partially overlaps with colchicine binding or that R3 binds to a specific site of tubulin that is not identical with the colchicine binding site modifying colchicine binding by allosteric influences.	R3 is an interesting antimitotic drug that exerts cytotoxic effects by depleting the intracellular pool of polyamines and by altering microtubule polymerization. Such a drug may be useful for the treatment of neoplastic diseases.	255

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Resveratrol-induced apoptosis in human colon cancer cells (SW480), with special attention to the role of the death receptor Fas in this pathway.	The study shows that resveratrol activates various caspases and triggers apoptosis in SW480 cells. Caspase activation is associated with accumulation of the pro-apoptotic proteins Bax and Bak that undergo conformational changes and relocalization to the mitochondria. Resveratrol does not modulate the expression of Fas and Fas-ligand (FasL) at the surface of cancer cells, and inhibition of the Fas/FasL interaction does not influence the apoptotic response to the molecule. Resveratrol induces the clustering of Fas and its redistribution in cholesterol and sphingolipid-rich fractions of SW480 cells, together with FADD and procaspase-8. This redistribution is associated with the formation of a death-inducing signaling complex (DISC). Transient transfection of either a dominant-negative mutant of FADD, E8, or MC159 viral proteins that interfere with the DISC function, decreases the apoptotic response of SW480 cells to resveratrol and partially prevents resveratrol-induced Bax and Bak conformational changes.	These results indicate that the ability of resveratrol to induce the redistribution of Fas receptor in membrane rafts may contribute to the ability of the molecule to trigger apoptosis in colon cancer cells.	256
Cell growth inhibition and ability to induce apoptosis in HL60 promyelocytic leukemia cells.	A series of *cis*- and *trans*-stilbene-based resveratrols were prepared with the aim of discovering new lead compounds with clinical potential. All the synthesized compounds were tested *in vitro* for cell growth inhibition and the ability to induce apoptosis in HL60 promyelocytic leukemia cells. The tested *trans*-stilbene derivatives were less potent than their corresponding *cis* isomers, except for *trans*-resveratrol, whose *cis*-isomer was less active. The best results were obtained with the *cis*-3,5-dimethoxy derivatives of rhapontigenin (3,5,3′-trihydroxy-4′methoxy-*trans*-stilbene) and its 3′-amino derivative, respectively, which showed apoptotic activity at nanomolar concentrations. The corresponding *trans*-isomers were less active both as antiproliferative and as apoptosis-inducing agents. Some compounds were active toward resistant HL60R cells and their activity was higher than that of several classic chemotherapeutic agents.	The flow cytometry assay showed that low concentration (50 nM) of test compounds were able to recruit almost all cells in the apoptotic sub-G_0-G_1 peak, thus suggesting that the main mechanism of cytotoxicity of these compounds could be the activation of apoptosis. These data indicate that structural alteration of the stilbene motif of resveratrol can be extremely effective in producing potent apoptosis-inducing agents.	178
Antitumor effect of resveratrol oligomers against human cancer cell lines and the molecular mechanism of apoptosis induced by vaticanol C.	Vaticanol C, a resveratrol derivative which was isolated from the stem bark of *Vatica rassak* (Dipterocarpaceae), induced considerable cytotoxicity in all cell lines tested and exhibited growth suppression in colon cancer cell lines at low doses. Vaticanol C caused two cell lines (SW480 and HL60) to induce cell death at 4–7 times lower concentrations, compared with resveratrol. The growth suppression by vaticanol C was found to be due to apoptosis, which was assessed by morphological findings (nuclear condensation and fragmentation) and DNA ladder formation in the colon cancer cell lines. The apoptosis in SW480 colon cancer cells was executed by the activation of caspase-3, which was shown by Western blot and apoptosis inhibition assays. Furthermore, the mitochondrial membrane potential of apoptotic SW480 cells after 12 h treatment with vaticanol C was significantly lost, and concurrently the cytochrome c release and activation of caspase-9 were also detected by Western blot analysis. Overexpression of Bcl-2 protein in SW480 cells significantly prevented the cell death induced by vaticanol C.	These findings indicate that vaticanol C induced marked apoptosis in malignant cells mainly by affecting mitochondrial membrane potential.	257
Increase in BRCA1 and BRCA2 mRNA expression in human breast tumor cell lines (MCF7, HBL 100, and MDA-MB 231).	These studies investigated the effects of resveratrol on BRCA1 and BRCA2 expression in MCF7, HBL 100, and MDA-MB 231 cells using quantitative real-time RT-PCR, and by perfusion chromatography of the proteins. All cell lines were treated with 30 μM resveratrol.	The expression of BRCA1 and BRCA2 mRNAs were increased although no change in the expression of the proteins was found. These data indicated that resveratrol at 30 μM can increase expression of genes involved in the aggressiveness of human breast tumor cell lines.	258

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Effects of resveratrol on the activity of adenylate- and guanylate-cyclase (AC, GC) enzymes, two known cytostatic cascades in MCF-7 breast cancer cells.	Resveratrol increased cAMP levels in both time- and concentration-dependent manners. In contrast, it had no effect on cGMP levels. The stimulatory effects for resveratrol on AC were not altered either by a protein synthesis inhibitor or estrogen-receptor (ER) blockers. Likewise, cAMP formation by resveratrol was insensitive to either the broad-spectrum phosphodiesterase (PDE) inhibitor or the cAMP-specific PDE inhibitor. Instead, these PDE inhibitors significantly augmented maximal cAMP formation by resveratrol. Parallel experiments showed that either resveratrol or rolipram inhibited the proliferation of these cells in a concentration-responsive manner. Further, concurrent treatment with resveratrol and rolipram significantly enhanced their individual cytotoxic responses. The antiproliferative effects were appreciably reversed by the kinase-A inhibitors, Rp-cAMPS or KT-5720. Pretreatment with the $cPLA_2$ inhibitor arachidonyl trifluoromethyl ketone markedly antagonized the cytotoxic effects of resveratrol, but had no effect on that of rolipram.	The study demonstrates that resveratrol is an agonist for the cAMP/kinase-A system, a documented proapoptotic and cell-cycle suppressor in breast cancer cells.	259
Inhibition of proliferation of CEM-C7H2 lymphocytic leukemia cells.	Inhibition of proliferation by resveratrol of CEM-C7H2 lymphocytic leukemia cells was paradoxically associated with an enhanced cellular 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT)-reducing activity. This phenomenon was most pronounced at the subapoptotic concentration range of resveratrol.	The results of the study show that the MTT-reducing activity can be increased by resveratrol without a corresponding increase in the number of living cells and that this occurs at a concentration range of resveratrol that is not sufficient to induce apoptosis but suffices to slow down cell growth. This phenomenon appears to be restricted to proliferation inhibitors with antioxidant properties and is cell type-specific. Thus, in determining the effects of flavonoids and polyphenols on proliferation in certain cell types, this might represent a pitfall in the MTT proliferation assay.	260
A series of 43 stilbene derivatives that showed cytotoxicity against human lung carcinoma (A549) was analyzed using comparative molecular field analysis (CoMFA) for defining the hypothetic pharmacophore model.	The polyoxylated stilbenes were found to be active inhibitors of tubulin polymerization. Several *cis*-stilbenes are structurally similar to combretastatins. However, the *trans*-stilbenes are assumed to be close to resveratrol. With several synthesized compounds that were evaluated for antitumor cytotoxicity against human lung tumor cells (A549), the stilbene derivatives were subjected to CoMFA. To perform systematic molecular modeling of these compounds, a conformational search was carried out based on the precise dihedral angle analysis of the lead compound. The X-ray crystallographic structure of combretastatin A-1 was also used for defining the active conformers of the compounds. After determining the energy-minimized conformers of the lead compound, CoMFA was performed using five different alignments.	The three dimensional (3D)-quantitative structure-activity relationship study resulted in reasonable cross-validated, conventional r^2 values equal to 0.640 and 0.958, respectively.	261

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Phytoestrogen regulation of a vitamin D_3 (VDR) receptor promoter and 1,25-dihydroxyvitamin D_3 actions in human breast cancer cells (T47D and MCF-7).	These studies examined regulation of VDR promoter region by two phytoestrogens, resveratrol and genistein. The group transiently transfected a VDR promoter luciferase construct into the estrogen receptor (ER) positive human breast cancer cell lines T47D and MCF-7, and treated with resveratrol or genistein. Both phytoestrogens upregulated the transcription of the VDR promoter, as measured by reporter gene activity, approximately two-fold compared to vehicle treated cells. Cotreatment with the antiestrogen tamoxifen in T47D cells and transfection in an estrogen receptor negative breast cancer cell line demonstrated that the effects of phytoestrogens on the VDR promoter are dependent on estrogen receptor. Resveratrol and genistein also increased VDR protein expression as detected by Western blotting.	Treatment with resveratrol had no effect on cell number or cell cycle profile, while treatment with genistein increased cell number. Because resveratrol could upregulate VDR without increasing breast cancer cell growth, the group hypothesized that resveratrol mediated increase in VDR expression would sensitize breast cancer cells to the effects of 1,25-dihydroxyvitamin $D_3$and vitamin D_3 analogues. In support of this hypothesis, both T47D and MCF-7 cells pretreated with resveratrol exhibited increased VDR mediated transactivation of a vitamin D_3responsive promoter compared to cells pretreated with vehicle. In addition, cotreatment with resveratrol enhanced the growth inhibitory effects of 1,25-dihydroxyvitamin D_3 and the vitamin D_3 analog EB1089. These data support the concept that dietary factors, such as phytoestrogens, may impact on breast cancer cell sensitivity to vitamin D_3 analogues through regulation of the VDR promoter.	262
Activity of resveratrol against fresh acute myeloid leukemia (AML) cells and its mechanism of action.	Because interleukin 1β (IL-1β) plays a key role in proliferation of AML cells, the effect of resveratrol was first tested on the AML cell lines OCIM2 and OCI/AML3, both of which produce IL-1β and proliferate in response. Resveratrol inhibited proliferation of both cell lines in a dose-dependent fashion by arresting the cells at S phase, thus preventing their progression through the cell cycle; IL-1β partially reversed this inhibitory effect. Resveratrol significantly reduced production of IL-1β in OCIM2 cells. It also suppressed the IL-1β-induced activation of transcription factor NF-κB, which modulates an array of signals controlling cellular survival, proliferation, and cytokine production. Incubation of OCIM2 cells with resveratrol resulted in apoptotic cell death. Because caspase inhibitors Ac-DEVD-CHO or z-DEVD-FMK partially reversed the antiproliferative effect of resveratrol, the group tested its effect on the caspase pathway and found that resveratrol induced the activation of the cysteine protease caspase-3 and subsequent cleavage of the DNA repair enzyme poly(adenosine diphosphate [ADP]-ribose) polymerase. Resveratrol suppressed colony-forming cell proliferation of fresh AML marrow cells from five patients with newly diagnosed AML in a dose-dependent fashion.	Having shown resveratrol is an effective *in vitro* inhibitor of AML cells, the data suggest this compound may have a role in future therapies for AML.	263
Inhibition of cell transformation by resveratrol and its derivatives.	To develop more effective agents with fewer side effects for the chemoprevention of cancer, the group investigated the effect of resveratrol and its structurally related derivatives on epidermal growth factor (EGF)-induced cell transformation. The results provided the first evidence that one of the resveratrol derivatives exerted a more potent inhibitory effect than resveratrol on EGF-induced cell transformation, but had less cytotoxic effects on normal nontransformed cells. Compared to resveratrol, this compound also caused cell cycle arrest in the G_1 phase, but did not induce p53 activation and apoptosis. Furthermore, this compound markedly inhibited EGF-induced phosphatidylinositol-3 kinase (PI-3K) and Akt activation.	These data suggested that the higher antitumor effect of the compound compared to resveratrol, may act through a different mechanism by mainly targeting PI-3K/Akt signaling pathways.	264

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Resveratrol-induced modification of polyamine metabolism is accompanied by induction of c-Fos.	The objective of the study was to investigate the effect of resveratrol on polyamine metabolism in the human cell line Caco-2. The group demonstrated that inhibition of ornithine decarboxylase (ODC) was due to attenuated ODC protein and mRNA levels. The resveratrol analogue, piceatannol, also diminished ODC activity, protein and mRNA levels, whereas (-)-epigallocatechin gallate exerted only weak effects on ODC. The transcription factor c-Myc was attenuated by resveratrol treatment and to a lesser extent by piceatannol and EGCG. *S*-Adenosylmethionine decarboxylase was concomitantly inhibited by resveratrol and piceatannol treatment, whereas EGCG did not affect its activity. In addition, resveratrol, piceatannol and EGCG enhanced spermidine/spermine N^1-acetyltransferase activity. Intracellular levels of spermine and spermidine were not affected, whereas putrescine and N^8-acetylspermidine concentrations increased after incubation with resveratrol. These events were paralleled by an increase of the activator protein-1 constituents c-Fos and c-Jun. Whereas DNA-binding activity of c-Jun remained unchanged, DNA-binding activity of c-Fos was significantly enhanced by resveratrol and piceatannol, but inhibited by EGCG.	The data suggest that growth arrest by resveratrol is accompanied by inhibition of polyamine synthesis and increased polyamine catabolism. c-Fos seems to play a role in this context. Effects of piceatannol on polyamine synthesis were similar, but not as potent as those exerted by resveratrol.	265
Resveratrol-induced G_2 arrest through the inhibition of CDK7 and $p34^{CDC2}$ kinases in colon carcinoma HT29 cells.	These studies present an explanation for the antitumor effect of resveratrol. Based on flow cytometric analysis, resveratrol inhibited the proliferation of HT29 colon cancer cells and resulted in their accumulation in the G_2 phase of the cell cycle. Western blot analysis and kinase assays demonstrated that the perturbation of G_2 phase progression by resveratrol was accompanied by the inactivation of $p34^{CDC2}$ protein kinase and an increase in the tyrosine phosphorylated (inactive) form of $p34^{CDC2}$. Kinase assays revealed that the reduction of $p34^{CDC2}$ activity by resveratrol was mediated through the inhibition of CDK7 kinase activity, while CDC25A phosphatase activity was not affected. In addition, resveratrol-treated cells were shown to have a low level of CDK7 kinase-Thr^{161}-phosphorylated $p34^{CDC2}$.	These results demonstrated that resveratrol induced cell cycle arrest at the G_2 phase through the inhibition of CDK7 kinase activity, suggesting that its antitumor activity might occur through the disruption of cell division at the G_2/M phase.	266
Investigation of apoptosis in esophageal cancer cells (EC-9706) induced by resveratrol, and the relation between this apoptosis and expression of Bcl-2 and Bax.	With *in vitro* experiments, the MTT assay was used to determine the cell growth inhibitory rate. Transmission electron microscope and the TUNEL staining method were used to quantitatively and qualitively detect the apoptosis status of esophageal cancer cell line EC-9706 before and after the resveratrol treatment. Immunohistochemical staining was used to detect the expression of apoptosis-regulated gene Bcl-2 and Bax.	Resveratrol inhibited growth of the esophageal cancer cell line EC-9706 in a dose-and time-dependent manner. Resveratrol induced EC-9706 cells to undergo apoptosis with typically apoptotic characteristics, including morphological changes of chromatin condensation, chromatin crescent formation, nucleus fragmentation, and apoptotic body formation. TUNEL assay showed that after the treatment of EC-9706 cells with resveratrol for 24 to 96 h, the AIs were apparently increased with treated time. Immunohistochemical staining showed that after the treatment of EC-9706 cells with resveratrol for 24 to 96 h, the PRs of Bcl-2 proteins were apparently reduced with treatment time and the PRs of Bax proteins were apparently increased with treatment time.	267

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Examined whether resveratrol has any effect on growth and gene expression in human ovarian cancer PA-1 cells.	The studies show that resveratrol inhibits cell growth and induces apoptosis in PA-1 human ovarian cancer cells. The group also investigated the effect of resveratrol on changes of global gene expression during resveratrol-induced growth inhibition and apoptosis in PA-1 cells using a human cDNA microarray with 7448 sequence-verified clones. Out of the 7448 genes screened, 118 genes were founded to be affected in their expression levels by more than 2-fold after 24-h treatment with 50 μM resveratrol. Resveratrol treatment of PA-1 cells at the final concentration of 50 μM for 6, 12, 24, and 48 h and gene expression patterns were analyzed by microarray. Clustering of the genes modulated more than 2-fold at three of the above times points divided the genes into two groups. Within these groups, there were specific subgroups of genes whose expression were substantially changed at the specified time points.	One of the most highly up-regulated genes found in this study was NAD(P)H quinone oxidoreductase 1 (NQO-1), which has recently been shown to be involved in p53 regulation. Although the precise role of genes whose expression levels were found to fluctuate after resveratrol treatment remain to be elucidated, gene expression in human ovarian cancer cells following resveratrol exposure, as offered by this study, may provide clues for the mechanism of resveratrol action.	268
The effects of resveratrol at both the molecular (TGFα gene activation) and the cellular (cell growth) levels in breast cancer cells stably transfected with wild-type (wt) ER (D351) and mutant (mut) ER (D351Y).	TGFα mRNA induction was used as a specific marker of estradiol (E_2) responsiveness. Resveratrol caused a concentration-dependent (10^8—10^4 M) stimulation of TGFα mRNA, indicating that it acts as an estrogen agonist in these cell lines. The pure antiestrogen ICI 182,780 (ICI) blocked resveratrol-induced activation of TGFα, consistent with action through an ER-mediated pathway. Further studies that combined treatments with E_2 and resveratrol showed that resveratrol does not act as an antagonist in the presence of various (10^{11}—10^8 M) concentrations of E_2. To determine whether resveratrol can be classified as a type I or type II estrogen, resveratrol was examined with the D351G ER in the TGFα assay and found that resveratrol belongs to the type I estrogens. Both resveratrol and E_2 had concentration-dependent growth inhibitory effects in cells expressing wtER and D351Y ER. Although the pure antiestrogen ICI blocked the growth inhibitory effects of E_2, it did not block the inhibitory effects of resveratrol, suggesting that the antiproliferative effects of resveratrol also involve ER-independent pathways. Resveratrol differentially affected the levels of ER protein in these 2 cell lines: Resveratrol downregulated wtER levels while significantly upregulating the amount of mutD351Y ER. Cotreatment with ICI resulted in strongly reduced ER levels in both cell lines. Gene array studies revealed resveratrol-induced up-regulation of more than 80 genes, among them a profound activation of $p21^{CIP1/WAF1}$, a gene associated with growth arrest. The $p21^{CIP1/WAF1}$ protein levels measured by Western blotting confirmed resveratrol-induced significant upregulation of this protein in both cell lines.	Resveratrol acts as an ER agonist at low doses but also activates ER-independent pathways, some of which inhibit cell growth.	269

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Activation of p53-directed genes that are involved in apoptosis mechanism(s) or whether resveratrol modifies the androgen receptor and its coactivators directly or indirectly and induces cell growth inhibition. These were conducted using androgen-sensitive prostate cancer cells (LNCaP).	The study demonstrates by DNA microarray, RT-PCR, Western blot and immunofluorescence analyses that treatment of androgen-sensitive prostate cancer cells (LNCaP) with 10^5 M RE for 48 h downregulates prostate-specific antigen (PSA), AR coactivator ARA 24 and NF-kB p65. Altered expression of these genes is associated with an activation of p53-responsive genes such as p53, PIG 7, $p21^{Waf1-Cip1}$, p300/CBP and Apaf-1. The effect of RE on p300/CBP plays a central role in its cancer preventive mechanisms in LNCaP cells.	The results implicate activation of more than one set of functionally related molecular targets. Key molecular targets have been identified that are associated with AR and p53 target genes. These findings suggest the need for further extensive studies on AR co-activators, such as p300, its central role in post-translational modifications such as acetylation of p53 and/or AR by resveratrol in a time- and dose-dependent manner at different stages of prostate cancer that will fully elucidate the role of resveratrol as a chemopreventive agent for prostate cancer in humans.	270
Induction of apoptosis in human melanoma cells (A375 and SK-mel28).	This study examined the effect of resveratrol on growth of two human melanoma cell lines. It was found that resveratrol inhibited growth and induced apoptosis in both cell lines, with the amelanotic cell line A375 being more sensitive. The potential involvement of different MAP kinases in the action of resveratrol was also examined. Although resveratrol did not alter the phosphorylation of p38 or JNK MAP kinases in either cell line, it induced phosphorylation of ERK1/2 in A375, but not in SK-mel28 cells.	These results suggest that *in vivo* studies of the effect of resveratrol on melanoma are warranted and that it might have effectiveness as either a therapeutic or chemopreventive agent against melanoma.	271
Effect of resveratrol on signal transduction pathways involved in paclitaxel-induced apoptosis in human neuroblastoma SH-SY5Y cells.	Resveratrol was able to significantly reduce paclitaxel-induced apoptosis in the human neuroblastoma (HN) SH-SY5Y cell line, acting on several cellular signaling pathways that are involved in paclitaxel-induced apoptosis. Resveratrol reverses phosphorylation of Bcl-2 induced by paclitaxel and concomitantly blocks Raf-1 phosphorylation, also observed after paclitaxel exposure, thus suggesting that Bcl-2 inactivation may be dependent on the activation of the Raf/Ras cascade. Resveratrol also reverses the sustained phosphorylation of JNK/SAPK, which specifically occurs after paclitaxel exposure.	The study demonstrates that the toxic action of paclitaxel on neuronal-like cells is not only related to the effect of the drug on tubulin, but also to its capacity to activate several intracellular pathways leading to inactivation of Bcl-2, thus causing cells to die by apoptosis, and resveratrol significantly reduces paclitaxel-induced apoptosis by modulating the cellular signaling pathways which commit the cell to apoptosis.	272
Induction of downregulation in survivin expression and apoptosis in HTLV-1-infected cell lines.	These studies investigated the effect of resveratrol in adult T cell leukemia. Observations showed that resveratrol induced growth inhibition in all five human T cell lymphotrophic virus-1-infected cell lines examined, with 50% effective doses of 10.4–85.6 μM. In the resveratrol-treated cells, induction of apoptosis was confirmed by annexin V-based analyses and morphological changes. The most surprising observation was that resveratrol treatment resulted in a gradual decrease in the expression of survivin, an antiapoptotic protein, during cell apoptosis.	These findings indicate that resveratrol inhibits the growth of human T cell lymphotrophic virus-1–infected cell lines, at least in part, by inducing apoptosis mediated by downregulation in survivin expression. In view of the accumulating evidence that survivin may be an important determinant of a clinical response in adult T cell leukemia, these data suggest that resveratrol merits further investigation as a potential therapeutic agent for this incurable disease.	273

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Action of some phenolic compounds (curcumin, yakuchinone B, resveratrol and capsaicin) in four human tumor cell lines: acute myeloblastic leukemia (HL-60), chronic myelogenic leukemia (K-562), breast adenocarcinoma (MCF-7) and cervical epithelial carcinoma (HeLa).	The phenolics exhibited growth inhibition as assessed by Trypan blue dye exclusion. It was evident from the results of the MTT reduction assay and [^{3}H]thymidine incorporation into nuclear DNA that the phenolics were cytotoxic and inhibited cell proliferation. Dose-response studies indicated curcumin to be most cytotoxic toward HL-60, K-562, and MCF-7 but did not show much activity in HeLa cells. On the other hand, yakuchinone B, although less active than curcumin, displayed cytotoxicity toward all four cell lines. Resveratrol was cytotoxic only in leukemic cells, while capsaicin was marginally cytotoxic. All these phenolics did not elicit any cytotoxic activity as judged by the above parameters toward lymphocytes purified from normal human blood. When cells treated with phenolics were stained with propidium iodide and examined under a fluorescent microscope, characteristic apoptotic features such as chromatin condensation and nuclear fragmentation were observed. Scoring of cells with apoptotic and non-apoptotic features showed positive correlation of apoptotic index with dose of phenolic, and fragmented DNA extracted free of genomic DNA displayed on gel electrophoresis a typical ladder pattern.	The actions of the phenolics as inducers of apoptosis in tumor cells suggest their potential use in a strategy for cancer control.	274
Comparative antiproliferative and apoptotic effects of resveratrol, ε-viniferin and vine-shoots derived polyphenols (vineatrols) on chronic B cell malignancies (B-cell chronic lymphocytic leukemia, B-CLL or hairy cell leukemia, HCL) and normal peripheral blood-derived mononuclear cells (PBMC) as control.	Resveratrol, its dimer ε-viniferin and two preparations of vineatrol (a grape-derived polyphenol fraction isolated from vine-shoot extracts) were compared for their effects on the proliferation and survival of normal and leukemic human lymphocytes. Two different batches of vineatrol (vineatrol 10 and 25%) were obtained by HPLC fractionation and contained 10 and 25% *trans*-resveratrol, respectively. The different polyphenols were added to cultures of leukemic cells from chronic B cell malignancies or PBMC cells as a control. The different polyphenols displayed antiproliferative effect on the leukemic cells, as estimated by the observed inhibition of ^{3}H-thymidine uptake and the reduction of cell recovery. Vineatrol 10% was the most potent whereas vineatrol 25% and resveratrol displayed comparable activity; ε-viniferin only exhibited slight effects. The same order of potency was observed for their capacity to induce apoptosis in leukemic B cells. In contrast, the survival of PBMC cells was little affected in the presence of these polyphenolic compounds and higher concentrations were required in order to elicit cell death. Polyphenol-driven apoptosis in chronic leukemic B cells was shown to correlate with an activation of caspase 3, a drop in the mitochondrial transmembrane potential, a reduction in the expression of the anti-apoptotic protein Bcl-2, as well as a reduction in the expression of the inducible nitric oxide synthase (iNOS).	These data indicate that vine-shoots may be a convenient and natural source of material for the purification of resveratrol and other polyphenolic compounds of putative therapeutic interest.	275

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Inhibit of cell proliferation in hepatoblastoma HepG2 and colorectal tumor SW480 cells. Analysis of the biochemical mechanism of resveratrol.	In order to determine if the amount of resveratrol taken up during food or drink consumption is sufficient to ensure the whole body relevance of *in vitro* described beneficial effects, the ratio between plasma level of resveratrol and its cell bioabsorption was evaluated. The study reports a higher uptake of resveratrol in the human hepatic derived HepG2 cells than in colorectal derived SW480 cells. In contrast, resveratrol is conjugated in these cells and derivatives are released in large amounts in the cell medium. Based on present knowledge, resveratrol appears to be a promising bioactive natural molecule with potential applications in phytotherapy, pharmacology or in nutriprotection (nutraceutic food) area.	The results show that resveratrol strongly inhibits cell proliferation at the micromolar range in a time- and dose-dependent manner. Resveratrol appears to block the cell cycle at the transition S to G_2/M as there is no inhibition of ^{3}H-thymidine incorporation observed, while there is an increase of the cell number in S phase.	276
Inhibition of cell proliferation using two *in vitro* assay systems, i.e., binding to human estrogen receptor α and stimulation of MCF-7 cell proliferation. L5178Y mouse lymphoma and Chinese hamster V79 cells were used.	Resveratrol was analyzed for genotoxic potential. Resveratrol induced cellular toxicity, micronuclei, and metaphase chromosome displacement in L5178Y mouse lymphoma cells. The induction of micronuclei was observed in Chinese hamster V79 cells. Determination of kinetochore signals in micronuclei and cell cycle analysis suggested that resveratrol did not cause a direct disturbance of mitosis. In support of this notion, cell-free tubulin polymerization studies indicated no direct effect of resveratrol on microtubule assembly.	According to an estimation of daily intake and bioavailability, concentrations that were found genotoxic *in vitro* might be reached in human exposure. On the other hand, the estrogenic acitivity might be beneficial.	277
Elucidation of rapid phytoestrogen action on ER-positive and -negative breast cancer cells using various estrogenic compounds.	As a preliminary step toward elucidating rapid phytoestrogen action on breast cancer cells, the effect of 17β-estradiol (E_2), genistein, daidzein, and resveratrol was investigated for their activation status of signaling proteins that regulate cell survival and invasion, the cell properties underlying breast cancer progression. The effect of these estrogenic compounds on the activation, via phosphorylation, of Akt/protein kinase B (Akt) and focal adhesion kinase (FAK) were analyzed in ER-positive and -negative human breast cancer cell lines. E_2, genistein and daidzein increased whereas resveratrol decreased both Akt and FAK phosphorylation in nonmetastatic ER-positive T47D cells. In metastatic ER-negative MDA-MB-231 cells, all estrogenic compounds tested increased Akt and FAK phosphorylation. The inhibitory action of resveratrol on cell survival and proliferation is ER dependent.	All estrogenic compounds tested, including resveratrol, may exert supplementary ER-independent nongenomic effects on cell survival and migration in breast cancer cells.	278
Evaluation of the potential role of resveratrol on pancreatic cancer cell proliferation using two human pancreatic cancer cell lines, PANC-1 and AsPC-1.	Resveratrol inhibited proliferation of both PANC-1 and AsPC-1 in a concentration- and time-dependent manner as measured by ^{3}H-thymidine incorporation. Cell number of both PANC-1 and AsPC-1 was also significantly decreased following 48 and 72 h of treatment with 100 μmol resveratrol. The growth inhibition induced by resveratrol was accompanied by apoptotic morphologic changes, characterized by cell rounding and cell membrane blebbing suggesting apoptosis. Propidium iodide staining of DNA, measured by flow cytometry, showed a dramatic increase in the fraction of sub-G_0/G_1 cells following resveratrol treatment in both PANC-1 and AsPC-1.	The substantial apoptosis inducted by resveratrol on these two cell lines was confirmed by the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling assay. These findings suggest that resveratrol may have a potent antiproliferative effect on human pancreatic cancer with induction of apoptosis. Resveratrol may be of value for the management and prevention of human pancreatic cancer.	279

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Antiproliferation effect of resveratrol in two human liver cancer cell lines, Hep G2 and Hep 3B.	The results showed that resveratrol inhibited cell growth in p53-positive Hep G2 cells only. This anticancer effect was a result of cellular apoptotic death induced by resveratrol via the p53-dependent pathway. The group demonstrated that the resveratrol-treated cells were arrested in the G_1 phase and were associated with the increase of p21 expression. Resveratrol-treated cells had enhanced Bax expression but they were not involved in Fas/APO-1 apoptotic signal pathway. In contrast, the p53-negative Hep 3B cells treated with resveratrol did not show the antiproliferation effect nor did they show significant changes in p21 or Fas/APO-1 levels.	The study demonstrated that resveratrol effectively inhibited cell growth and induced programmed cell death in hepatoma cells on a molecular basis. These results implied that resveratrol might also be a new potent chemopreventive drug candidate for liver cancer as it played an important role to trigger p53-mediated molecules involved in the mechanism of p53-dependent apoptotic signal pathway.	280
Tested antiproliferative activity and induction of apoptosis using MCF-7 and MDA-MB-231 human breast cancer cells.	Using human breast cancer cell lines MCF-7 and MDA-MB-231, a possible mechanism by which resveratrol could interfere with cell cycle control and induce cell death was analyzed. The results showed that although resveratrol inhibited cell proliferation and viability in both cell lines, apoptosis was induced in a concentration- and cell-specific manner. In MDA-MB-231, resveratrol reduced the expression and kinase activities of positive G_1/S and G_2/M cell cycle regulators and inhibited ribonucleotide reductase activity in a concentration dependent manner, without a significant effect on the low expression of tumor suppressors p21, p27, and p53. These cells died by a nonapoptotic process in the absence of a significant change in cell cycle distribution. In MCF-7, resveratrol produced a significant and transient increase in the expression and kinase activities of positive G_1/S and G_2/M regulators. Simultaneously, p21 expression was markedly induced in presence of high levels of p27 and p53. These opposing effects resulted in cell cycle blockade at the S-phase and apoptosis induction in MCF-7 cells.	The antiproliferative activity of resveratrol could take place through the differential regulation of the cell cycle leading to apoptosis or necrosis. This could be influenced, among other factors, by the concentration of this molecule and by the characteristics of the target cell.	281
Induction of apoptosis in human HCT116 colon carcinoma cells.	The expression, subcellular localization, and importance of Bax for resveratrol-provoked apoptosis were assessed in human HCT116 colon carcinoma cells and derivatives with both Bax alleles inactivated. Low to moderate concentrations of resveratrol induced co-localization of cellular Bax protein with mitochondria, collapse of the mitochondrial membrane potential, activation of caspases 3 and 9, and finally, apoptosis. In the absence of Bax, membrane potential collapse was delayed, and apoptosis was reduced but not absent. Resveratrol inhibited the formation of colonies by both HCT116 and HCT116 Bax / cells.	Resveratrol, at physiological doses, can induce a Bax-mediated and a Bax-independent mitochondrial apoptosis. Both can limit the ability of the cells to form colonies.	282

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Cytostatic effects on peripheral blood human lymphocytes.	Resveratrol had no detectable effects on resting lymphocytes. With the mitogen phytohemagglutin (PHA), however, resveratrol elicited concentration- and time-dependent responses in lymphocytes. Resveratrol prevented cell entry into the cell cycle, resulting in 99% suppression at 100 μM. The arrested lymphocytes following 24 h treatment with 50 μM resveratrol had minimal RNA content, the feature characteristic of G_0 cells, and were blocked at the stage past the induction of cyclins D2 and D3 and prior to induction of cyclin E. Prolonged treatment (72 h) of PHA-stimulated lymphocytes with 100 μM resveratrol showed a pronounced decrease in the expression of pRb, cyclins E and B, and reduction in $p34^{cdc2}$ and PCNA. The activation-induced apoptosis was also reduced in the presence of $\geq$50 μM resveratrol.	These data suggest that studies designed to test resveratrol efficacy as a chemopreventive agent should include evaluation of its immunomodulatory effect revealed by suppression of lymphocyte stimulation as well as its effect on apoptosis of stimulated lymphocytes.	283
Inhibition of neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE) activity of the neuroblastoma cell line SK-N-SH.	The long-term incubation of the cells for 4 days with quercetin, resveratrol, and a combination of both substances in concentrations lower than necessary for inhibition of NEP and ACE activity induced the cellular enzyme activity of NEP and ACE associated with an inhibition of cellular proliferation. The long-term treatment of neuroblastoma cells with quercetin and resveratrol enhanced the differentiation state of the cells.	Taking into account the significance of NEP and ACE for the degradation of amyloid β peptides, the effect of quercetin and resveratrol as constituents of red wine for neuroprotective activity is suggested.	284
Induction of apoptosis using prostate cancer cells (LNCaP and DU 145) and the significance of the three hydroxyl groups on resveratrol to the measured effect.	Hormone-sensitive LNCaP cells and hormone-insensitive DU 145 cells were treated with resveratrol, tri-methoxy-resveratrol, or diethylstilbestrol (the positive control for toxicity and apoptosis). Cell viability was determined by using a MTS assay. Apoptosis was determined by the appearance of apoptotic morphology, annexin V-FITC-positive intact cells, and caspase activation.	Resveratrol and diethylstilbestrol decreased viability in LNCaP cells, but only resveratrol-treated cells expressed apoptotic morphology, annexin V-FITC-positive cells, and caspase activation. Tri-methoxy-resveratrol had no effect on DU 145 cell-viability and was less toxic to LNCaP cells than resveratrol. Resveratrol was toxic to cells regardless of whether the cells were hormone-responsive or -unresponsive. This finding suggests that the hormone responsive status of the cell is not an important determinant of the response to resveratrol. Furthermore, the hydroxyl-groups on resveratrol are required for cell toxicity. Finally, resveratrol but not diethylstilbestrol induced caspase-mediated apoptosis.	285
Investigation of the effects of resveratrol on DNA binding via esterification reactions with 2-hydroxyamino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (N-OH-PhIP) - a metabolite of a mammary gland carcinogen present in cooked meats.	Treatment of primary cultures of human mammary epithelial cells with 50 μM resveratrol led to a decrease in PhIP-DNA adducts ranging from 31 to 69%. Using substrate-specific assays and mammary gland tissue cytosols, resveratrol inhibited PhIP-DNA adduct formation by *O*-acetyltransferase and sulfotransferase catalysis. Cytosols from tumor tissue and breast reduction tissue were similarly affected. Resveratrol also suppressed *O*-acetyltransferase and sulfotransferase activities from the breast cancer cell lines MCF-7 and ZR-75-1. It was also observed that resveratrol stimulated ATP-dependent cytosolic activation of N-OH-PhIP in all human samples but not in mouse liver samples.	The data suggest that *O*-acetyltransferases and sulfotransferases may represent anti-oncogenic targets for resveratrol.	286

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Inhibition of the growth and the induction of apoptosis of both normal and leukemic hematopoietic cells.	Resveratrol inhibited the proliferation and induced the apoptosis of all tested lymphoid and myeloid leukemia cells. Prior to apoptosis, resveratrol-induced caspase activity in a dose-dependent manner and cell cycle arrest in G_2/M-phase, correlating with a significant accumulation of cyclins A and B. Leukemia cell death with resveratrol required both caspase-dependent and -independent proteases, as it was significantly inhibited by simultaneous addition of z-VAD-FMK and leupeptin to these cultures. While resveratrol did not affect nonactivated normal lymphocytes, it decreased the growth and induced the apoptosis of cycling normal human peripheral blood lymphocytes at lower concentrations than those required for most leukemia cells. Resveratrol also induced the apoptosis of early normal human $CD34^+$ cells and decreased the number of colonies generated by these precursor cells in a dose-dependent manner.	These data suggest the complexity of resveratrol-mediated signaling pathways and revealed the high antiproliferative and proapoptotic activities of resveratrol in normal cycling hemopoietic cells.	287
Cytotoxic and antimutagenic effects of resveratrol, ε-viniferin, viniferin, gnetin H, suffruticosols A and B, were determined against five different cancer cell lines, C6 (mouse glioma), HepG2 (liver hepatoma), HT-29 (colon), HeLa (cervical), MCF-7 (breast), and mutagenicity of *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine (MNNG) in *Salmonella typhimurium* TA100.	Resveratrol showed significant cytotoxic activity against HepG2 (liver hepatoma) and HT-29 (colon) human cancer cell lines. In contrast, *trans*-ε-viniferin and *cis*-viniferin, and gnetin H exhibited marked cytotoxic activity against HeLa (cervical) and MCF-7 (breast) human cancer cell lines. However, suffruticosol A and B had a reduced cytotoxic effect against all cancer cells except C6.	The six stilbenes showed cytotoxic activity in a dose-dependent manner, and were especially potent against the C6 (mouse glioma) cancer cell. These stilbenes exerted antimutagenic activity in a dose-dependent fashion. Of them, resveratrol exhibited the strongest antimutagenic effect against MNNG, while the other five resveratrol oligomers also mediated moderate antimutagenic activity.	288
Induction of serine phosphorylation of p53 causes apoptosis in a mutant p53 prostate cancer cell line (DU 145).	The effect of resveratrol was determined in the androgen insensitive DU 145 prostate cancer cell line. Induction of apoptosis and activation of apoptosis related signal transduction pathways were measured. DU 145 cells were treated with resveratrol and apoptosis was measured by determining nucleosome content. Activation of mitogen activated protein kinase (MAPK) (extracellular signal-regulated kinase 1/2), p53 content and serine-15 phosphorylation of p53 were measured by immunoblot. Electrophoretic mobility shift assay of p53 binding to DNA, and measurement of p21 and glyceraldehyde-3-phosphate dehydrogenase messenger RNA were also done.	Resveratrol induced apoptosis in DU 145 cells. It activated MAPK and caused increased abundance of p53 and serine-15 phosphorylated p53. Resveratrol induced serine-15 phosphorylation of p53 was blocked by PD 98059, a MAPK kinase inhibitor, implicating MAPK activation in the phosphorylation of p53. PD 98059 also inhibited resveratrol induced apoptosis. These results suggest that apoptosis induction by resveratrol in DU 145 cells requires serine-15 phosphorylation of p53 by MAPK. Inhibition of MAPK dependent serine-15 phosphorylation resulted in reduced p53 binding to a p53 specific oligonucleotide on electrophoretic mobility shift assay. Pifithrin-α, a p53 inhibitor, blocked resveratrol induced serine-15 phosphorylation of p53 and p53 binding to DNA. Resveratrol caused a p53 stimulated increase in p21 messenger RNA. Transfection of additional wild-type p53 into DU 145 cells induced apoptosis, which was further enhanced by resveratrol treatment. Resveratrol causes apoptosis in DU 145 prostate cancer cells. This action depends on the activation of MAPK, increase in cellular p53 content, serine-15 phosphorylation of p53 and increased p53 binding to DNA.	289

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Inhibition of cell proliferation in human colorectal tumor SW480 cell line.	The mechanism by which resveratrol inhibits cell proliferation was studied in human colorectal tumor SW480 cell line. Resveratrol strongly inhibits cell proliferation at the micromolar range in a time- and dose-dependent manner. Resveratrol appears to block the cell cycle at the transition $\rightarrow$ G_2/M as inhibition of [^{3}H]-thymidine incorporation is not observed, while there is an increase of the cell number in S phase. During this inhibition process, resveratrol increases the content of cyclins A and B1 as well as cyclin-dependent kinases Cdk1 and Cdk2. Moreover, resveratrol promotes Cdk1 phosphorylation.	Resveratrol exerts a strong inhibition of SW480 human colorectal tumor cell proliferation modulates cyclin and cyclin-dependent kinase activities.	290
Differentiation induced by butyrate in Caco-2 colon cancer cells.	The aim of this study was to determine whether resveratrol modulates the effects of butyrate on Caco-2, a colonic adenocarcinoma cell line. The growth inhibitory effect of resveratrol was more powerful than that of butyrate. Butyrate did not intensify the inhibition of proliferation exerted by resveratrol. Although the polyphenol enhanced the differentiation-inducing effect of butyrate, it did not elevate alkaline phosphatase activity or E-cadherin protein expression, markers of epithelial differentiation, when applied alone. Butyrate-induced transforming growth factor-β1 secretion was inhibited by resveratrol. Treatment with the combination of resveratrol and butyrate attenuated levels of $p27^{Kip1}$, whereas resveratrol enhanced the effect butyrate had on the induction of $p21^{Waf1/Cip1}$ expression.	These data demonstrate a possible combined chemopreventive effect of two substances naturally occurring in the colonic lumen after ingestion of fibers and resveratrol-containing food.	291
Inducer of differentiation in human myeloid leukemias (HL-60, NB4, U937,THP-1, ML-1, Kasumi-1) and fresh samples from 17 patients with acute myeloid leukemia.	This group studied the *in vitro* biological activity of resveratrol by examining its effect on proliferation and differentiation in myeloid leukemia cell lines (HL-60, NB4, U937,THP-1, ML-1, Kasumi-1) and fresh samples from 17 patients with acute myeloid leukemia. Resveratrol alone inhibited the growth in liquid culture of each of the six cell lines. Resveratrol enhanced the expression of adhesion molecules (CD11a, CD11b, CD18, CD54) in each of the cell lines except for Kasumi-1. Moreover, resveratrol induced 37% of U937 cells to produce superoxide as measured by the ability to reduce nitroblue tetrazolium (NBT). The combination of resveratrol and all-*trans*-retinoic acid (ATRA) induced 95% of the NB4 cells to become NBT-positive, whereas $<$1% and 12% of the cells became positive for NBT after a similar exposure to either resveratrol or ATRA alone, respectively. In U937 cells exposed to resveratrol, the binding activity of NF-κB protein was suppressed. Eight of 19 samples of fresh acute leukemia cells reduced NBT after exposure to resveratrol.	These findings show that resveratrol inhibits proliferation and induces differentiation of myeloid leukemia cells.	292

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Induction of apoptosis in human B-cell lines derived from chronic B-cell malignancies (WSU-CLL and ESKOL), and in leukemic lymphocytes from patients with B-cell chronic lymphocytic leukemia (B-CLL).	Resveratrol displayed antiproliferative activity on both B-cell lines, as estimated by the decrease in cell recovery and inhibition of thymidine uptake. Furthermore, resveratrol induced apoptosis in the two cell lines as well as in B-CLL patients' cells, as evidenced by the increase in annexin V binding, caspase activation, DNA fragmentation and decrease of the mitochondrial transmembrane potential $\Delta \quad \psi$. The group previously reported that nitric oxide (NO), endogenously released by an iNO synthase (iNOS) spontaneously expressed in these leukemic cells, contributed to their resistance towards apoptosis. The group shows that resveratrol inhibited both iNOS protein expression and *in situ* NO release in WSU-CLL, ESKOL and B-CLL patients' cells. In addition, Bcl-2 expression was inhibited by resveratrol.	Downregulation of the two antiapoptotic proteins iNOS and Bcl-2 can contribute to the apoptotic effects of resveratrol in leukemic B cells from chronic leukemia. These data suggest that this drug is of potential interest for the therapy of B-CLL.	293
Evaluation of pterostilbene for antioxidative potential.	The peroxyl-radical scavenging activity of pterostilbene was the same as that of resveratrol, having total reactive antioxidant potentials of 237 ± 58 and 253 ± 53 μM, respectively. Both compounds were found to be more effective than Trolox as free radical scavengers. Using a plant system, pterostilbene also was shown to be as effective as resveratrol in inhibiting electrolyte leakage caused by herbicide-induced oxidative damage, and both compounds had the same activity as α-tocopherol. Pterostilbene showed moderate inhibition ($IC_{50} = 19.8$ μM) of cyclooxygenase (COX)-1, and was weakly active ($IC_{50} = 83.9$ μM) against COX-2, whereas resveratrol strongly inhibited both isoforms of the enzyme with IC_{50} values of approximately 1 μM.	Using a mouse mammary organ culture model, carcinogen-induced preneoplastic lesions were, similarly to resveratrol, significantly inhibited by pterostilbene ($ED_{50} = 4.8$ μM), suggesting antioxidant activity plays an important role in this process.	294
Impact of phenolic compounds, ellagic acid (EA) and resveratrol (RE), on target genes in prostate cancer (LNCaP) cells.	Human cDNA microarrays were used with 2400 clones consisting of 17 prosite motifs to characterize alterations in gene expression pattern in response to EA and RE. Over a 48 h exposure of androgen-sensitive LNCaP cells to EA and RE, a total of 593 and 555 genes, respectively, showed more than a two-fold difference in expression. A distinct set of genes in both EA- and RE-treated cells may represent the signature profile of phenolic antioxidant-induced gene expression in LNCaP cells. Although extensive similarity was found between effects of EA- and RE-responsive genes in prostate cancer cells, out of 246 genes with overlapping responses, 25 genes showed an opposite effect. Quantitative RT-PCR was used to verify and validate the differential expression of selected genes identified from cDNA microarrays.	In-depth analysis of the data from this study provides insight into the alterations in the p53-responsive genes, p300, Apaf-1, NF-κBp50 and p65 and PPAR families of genes, suggesting the activation of multiple signaling pathways leads to growth inhibition of LNCaP cells.	295

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Induction of prostate cancer cells (LNCaP and DU145) entry into S phase and inhibition of DNA synthesis.	The studies revealed that, in androgen-sensitive LNCaP cells, the effect of resveratrol on DNA synthesis varied dramatically depending on the concentration and the duration of treatment. In cells treated for 1 h, resveratrol showed only an inhibitory effect on DNA synthesis, which increased with increasing concentration ($IC_{50} = 20\ \mu M$). However, when treatment duration was extended to 24 h, a dual effect of resveratrol on DNA synthesis was observed. At 5 to 10 μM it caused a 2- to 3-fold increase in DNA synthesis, and at $\geq$15 μM, it inhibited DNA synthesis. The increase in DNA synthesis was seen only in LNCaP cells, but not in androgen-independent DU145 prostate cancer cells or in NIH3T3 fibroblast cells. The resveratrol-induced increase in DNA synthesis was associated with enrichment of LNCaP cells in S phase, and a concurrent decrease in nuclear $p21^{Cipl}$ and $p27^{Kip1}$ levels. Furthermore, consistent with the entry of LNCaP cells into S phase, there was a dramatic increase in nuclear Cdk2 activity associated with both cyclin A and cyclin E.	The observations indicate that LNCaP cells, treated with resveratrol, are induced to enter into S phase, but subsequent progression through S phase is limited by the inhibitory effect of resveratrol on DNA synthesis, particularly at concentrations above 15 μM. Therefore, the ability of resveratrol to exert opposing effects on two important processes in cell cycle progression, induction of S phase and inhibition of DNA synthesis, may be responsible for its apoptotic and antiproliferative effects.	296
Inhibition of gastric cancer cell (gastric adenocarcinoma SNU-1 cells) proliferation.	Low levels of exogenous reactive oxygen (H_2O_2) stimulated [^{3}H]thymidine uptake in SNU-1 cells, whereas resveratrol suppressed both synthesis of DNA and generation of endogenous O^2 but stimulated nitric oxide (NO) synthase (NOS) activity. To address the role of NO in the antioxidant action of resveratrol, the effect of sodium nitroprusside (SNP) was measured, an NO donor, on O^2 generation and on [^{3}H]thymidine incorporation. SNP inhibited DNA synthesis and suppressed ionomycin-stimulated O^2 generation in a concentration-dependent manner.	The results revealed that the antioxidant action of resveratrol toward gastric adenocarcinoma SNU-1 cells may reside in its ability to stimulate NOS to produce low levels of NO, which, in turn, exert antioxidant action. Resveratrol-induced inhibition of SNU-1 proliferation may be partly dependent on NO formation, and the group hypothesizes that resveratrol exerts its antiproliferative action by interfering with the action of endogenously produced reactive oxygen. These data are supportive of the action of NO against reactive oxygen and suggest that a resveratrol-rich diet may be chemopreventive against gastric cancer.	297
Induced activation of p53 and apoptosis using the JB6 mouse epidermal cell line.	This study determined that c-jun NH_2-terminal kinases (JNKs) are involved in resveratrol-induced p53 activation and induction of apoptosis. In the JB6 mouse epidermal cell line, resveratrol activated JNKs dose-dependently within a dose range of 10–40 μM, the same dosage responsible for the inhibition of tumor promoter-induced cell transformation. Stable expression of a dominant negative mutant of JNK1 or disruption of the Jnk1 or Jnk2 gene markedly inhibited resveratrol-induced p53-dependent transcription activity and induction of apoptosis. Furthermore, resveratrol-activated JNKs were shown to phosphorylate p53 *in vitro*, but this activity was repressed in the cells expressing a dominant negative mutant of JNK1 or in Jnk1 or Jnk2 knockout ($Jnk1^{/}$ or $Jnk2^{/}$) cells.	These data suggested that JNKs act as mediators of resveratrol-induced activation of p53 and apoptosis, which may occur partially through p53 phosphorylation.	298

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigation of S-phase arrest, apoptosis, and changes in biomarker expression in six human cancer cell lines (MCF7, SW480, HCE7, Seg-1, Bic-1, and HL60).	Resveratrol induced marked growth inhibition in five of these cell lines, with IC_{50} values of approximately 70–150 μM. However, only partial growth inhibition was seen in Bic-1 cells. After treatment with 300 μM resveratrol for 24 h, most of the cell lines were arrested in the S phase of the cell cycle. In addition, induction of apoptosis was demonstrated by the appearance of a sub-G_1 peak and confirmed using an annexin V-based assay. Cyclin B1 expression levels were decreased in all cell lines after 48 h of treatment. In SW480 cells, cyclin A, cyclin B1, and β-catenin expression levels were decreased within 24 h. There was a decrease in cyclin D1 expression after only 2 h of treatment, and this persisted for up to 48 h. This decrease was partially blocked by concurrent treatment with the proteasome inhibitor calpain inhibitor I. Using a luciferase-based reporter assay, resveratrol did not inhibit cyclin D1 promoter activity in SW480 cells. Furthermore, using a reverse transcription PCR–based assay, only a higher dose of resveratrol (300 μM) appeared to decrease cyclin D1 mRNA. Seg-1 cells expressed basal levels of cyclooxygenase-2 (cox-2), which was further induced by resveratrol. Neither basal levels nor induction of Cox-2 was detectable in the remaining cell lines. Thus, Cox-2 does not appear to be a critical target of this compound.	These studies provide support for the use of resveratrol in chemoprevention and cancer therapy trials. Cyclin D1, cyclin B1, β-catenin, and apoptotic index could be useful biomarkers to evaluate treatment efficacy.	299
Induction of apoptosis in two papillary thyroid carcinoma (PTC) and two follicular thyroid carcinoma (FTC) cell lines via a MAPK- and p53-dependent mechanism.	Two PTC and FTC cell lines were treated with resveratrol, which showed activation and nuclear translocation of MAPK (extracellular signal-regulated kinase 1/2). Cellular abundance of the oncogene suppressor protein p53, serine phosphorylation of p53, and abundance of c-fos, c-jun, and p21 mRNAs were also increased by resveratrol. Inhibition of the MAPK pathway by either H-ras antisense transfection or PD 98059, an MAPK kinase inhibitor, blocked these resveratrol-induced effects. Addition of pifithrin-α, a specific inhibitor of p53, or transfection of p53 antisense oligonucleotides caused decreased resveratrol-induced p53 and p21 expression in PTC and FTC cells. Studies of nucleosome levels estimated by ELISA and of DNA fragmentation showed that resveratrol induced apoptosis in both papillary and follicular thyroid cancer cell lines; these effects were inhibited by pifithrin-α and by p53 antisense oligonucleotide transfection. PD 98059 and H-ras antisense transfection also blocked induction of apoptosis by resveratrol.	Resveratrol acts via a Ras-MAPK kinase-MAPK signal transduction pathway to increase p53 expression, serine phosphorylation of p53, and p53-dependent apoptosis in PTC and FTC cell lines.	300
Induction of apoptosis by 3,4′-dimethoxy-5-hydroxystilbene in human promyeloid leukemic HL-60 cells.	Treatment of HL-60 cells with DMHS suppressed the cell growth in a concentration-dependent manner with an IC_{50} value of 25 μM. DMHS increased internucleosomal DNA fragmentation in a time-dependent manner. The cell death by DMHS was partially prevented by the caspase inhibitor, zVAD-fmk. DMHS caused activation of caspases such as caspase-3, -8, and -9. Immunoblot experiments revealed that DMHS-induced apoptosis was associated with the induction of Bax expression. The release of cytochrome c from mitochondria into the cytosol was increased in response to DMHS.	The results indicated that DMHS leads to apoptotic cell death in HL-60 cells through increased Bax expression and release of cytochrome c into cytosol and may be considered as a good candidate for a cancer chemopreventive agent in humans.	301
Mechanism of resveratrol-mediated suppression of tissue factor (TF) gene expression.	The mechanism was examined by which resveratrol inhibits the expression of TF in monocytes by using a monocytic cell line, THP-1, as a model cell. Northern blot analysis, gel mobility shift assays and transfection studies with various TF promoter constructs, as well as other transcription regulatory constructs, were used to elucidate the inhibitory mechanism of resveratrol. The data show that resveratrol inhibited lipopolysaccharide (LPS)-induced expression of TF in human monocytes and monocytic cell line, THP-1 in a dose dependent manner. Resveratrol did not significantly alter the binding of various transcription factors involved in TF gene expression to DNA. However, resveratrol suppressed the transcription of cloned human TF promoter. Further experiments revealed that resveratrol reduced κB- but not AP-1–driven transcriptional activity. Additional experiments showed that resveratrol suppressed the phosphorylation of p65 and its transactivation.	The results indicate that resveratrol does not inhibit the activation or translocation of NF-κB/Rel proteins but inhibits NF-κB/Rel-dependent transcription by impairing the transactivation potential of p65.	302

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Induction of apoptosis using resveratrol with 5-fluorouracil (5-FU) on the growth of hepatoma cell line H22.	The number of cells was measured by the MTT method and morphological changes of H22 cells were investigated under microscopic examination. Resveratrol inhibited the growth of H22 cells in a dose- and time-dependent manner. The synergistic anti-tumor effects of resveratrol with 5-FU increased to a greater extent than for H22 cells treated with 5-FU alone. Characteristics of apoptosis such as typical apoptotic bodies were commonly found in tumor cells in the drug-treated groups.	Resveratrol can suppress the growth of H22 cells, its antitumor activity may occur through the induction of apoptosis.	303
Induction of apoptosis using human colon cancer cell lines (SW480, DLD-1, and COLO201).	Vaticanol C (resveratrol tetramer) was characterized by nuclear changes and DNA ladder formation and tested in SW480, DLD-1, and COLO201 cells.	Vaticanol C suppressed cell growth through induction of apoptosis.	304
Inhibition of progression through the S phase of the cell cycle in colorectal cancer cell lines (Caco-2 and HCT-116) using the compound piceatannol.	Growth of Caco-2 and HCT-116 cells was analyzed by crystal violet assay, which demonstrated dose- and time-dependent decreases in cell numbers. Treatment of Caco-2 cells with piceatannol reduced proliferation rate. No effect on differentiation was observed. Determination of cell cycle distribution by flow cytometry revealed an accumulation of cells in the S phase. Immunoblotting demonstrated that cyclin-dependent kinases (cdk) 2 and 6, as well as cdc2 were expressed at steady-state levels, whereas cyclin D1, cyclin B1 and cdk 4 were downregulated. The abundance of $p27^{Kip1}$ was also reduced, whereas the protein level of cyclin E was enhanced. Cyclin A levels were enhanced only at concentrations up to 100 μM. These changes also were observed in studies with HCT-116 cells.	Piceatannol can be considered to be a promising chemopreventive or anticancer agent.	305
Radiosensitizing and antiproliferative effects tested in human cervical tumor cell lines (HeLa, Me180, A2780, and SiHa, and the mouse normal fibroblast cell line, NIH 3T3).	The group hypothesized that tumor cells may exhibit changes in the cellular response to ionizing radiation (IR) following exposure to resveratrol. Clonogenic cell survival assays were performed using irradiated HeLa and SiHa cells pretreated with resveratrol prior to IR exposure, and resulted in enhanced tumor cell killing by IR in a dose-dependent manner. Further analysis of COX-1 inhibition indicated that resveratrol pretreatment: (1) inhibited cell division as assayed by growth curves; and (2) induced an early S phase cell cycle checkpoint arrest, as demonstrated by fluorescence-activated cell sorting, as well as bromodeoxyuridine pulse-chase analysis.	These results suggest that resveratrol alters both cell cycle progression and the cytotoxic response to IR in two cervical tumor cell lines.	306
Evaluation of 12 phenols (*trans*-astringin, *trans*-piceid, *trans*-resveratroloside, *trans*-resveratrol, *trans*-piceatannol, *cis*-resveratroloside, *cis*-piceid, *cis*-resveratrol, (+)-catechin, (-)-epicatechin, epicatechin 3-*O*-gallate, and procyanidin B2 3′-*O*-gallate) for potential to inhibit cyclooxygenases and preneoplastic lesion formation in carcinogen-treated mouse mammary glands in organ culture.	At 10 μg/ml, *trans*-astringin and *trans*-piceatannol inhibited development of 7,12-dimethylbenz(*a*)anthracene-induced preneoplastic lesions in mouse mammary glands with 68.8% and 76.9% inhibition, respectively, compared with untreated glands. The latter compound was the most potent of the 12 compounds tested in this assay, with the exception of *trans*-resveratrol (87.5% inhibition). In the cyclooxygenase (COX)-1 assay, *trans*-isomers of the stilbenoids appear to be more active than *cis*-isomers: *trans*-resveratrol [50% inhibitory concentration (IC_{50}) = 14.9 μM, 96%] vs. *cis*-resveratrol (IC_{50} = 55.4 μM). In the COX-2 assay, among the compounds tested, only *trans*- and *cis*-resveratrol exhibited significant inhibitory activity (IC_{50} = 32.2 and 50.2 μM, respectively). This is the first report showing the potential cancer chemopreventive activity of *trans*-astringin. *trans*-Astringin and its aglycone *trans*-piceatannol were active in the mouse mammary gland organ culture assay but did not exhibit activity in COX-1 and COX-2 assays. *trans*-Resveratrol was active in all three of the bioassays used in this investigation.	These findings suggest that *trans*-astringin and *trans*-piceatannol may function as potential cancer-chemopreventive agents by a mechanism different from that of *trans*-resveratrol.	199

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Expression of autocrine growth modulators in human breast cancer cells (MCF-7 and MDA-MB-46).	Resveratrol maximally inhibited the growth stimulatory effect mediated by 10^{-9} M estradiol without affecting cell viability. At the molecular level, resveratrol in a dose-dependent fashion antagonized the stimulation by estradiol of an estrogen response element reporter gene construct and of progesterone receptor gene expression in MCF-7 cells. Resveratrol also inhibited the proliferation of the estrogen-receptor negative human breast carcinoma cell line MDA-MB-468. These later data suggest that resveratrol can also inhibit breast cancer cell proliferation by another mechanism besides estrogen receptor antagonism. The study shows resveratrol altered the expression of several autocrine growth modulators and their receptors in MCF-7 cells. Resveratrol at 10^{-5} M inhibited the expression of the autocrine growth stimulators transforming growth factor-α (TGF-α), PC cell-derived growth factor, and insulin-like growth factor I receptor mRNA. In addition, resveratrol significantly elevated the expression of the growth inhibitor TGF-β2 mRNA without changes in TGF-β1 and TGF-β3 expression.	Resveratrol inhibited the growth of estrogen receptor-positive MCF-7 cells cultivated in the presence of estradiol in a dose-dependent fashion. These data suggest that resveratrol inhibits proliferation by altering autocrine growth modulator pathways in breast cancer cells.	307
Thirteen stilbene-related compounds tested in the mouse hepatoma Hepa 1c1c7 cells.	The compounds were tested for their ability to be inducers of phase II detoxifying metabolic enzyme quinone reductase (QR) in the mouse hepatoma Hepa 1c1c7 cells.	Several of compounds were found to potentially induce QR activity in this cell line. In addition, substitution with 3-thiofurane ring instead of phenyl ring in the stilbene skeleton also exhibited potential induction of QR activity. This study provides primary information to design the potential inducers of QR activity in the stilbene analogues.	308
Induction of apoptosis using the HCT116 colon carcinoma cell line.	Cell death is primarily mitochondria-mediated and not receptor-mediated. No cells survived in cultures continuously exposed to 100 μM resveratrol for 120 h. When compared with 5-fluorouracil, resveratrol stimulated p53 accumulation and activity only weakly and with delayed kinetics and neither the increased levels nor the activity affected apoptosis detectably. The apoptosis agonist Bax was overproduced in response to resveratrol regardless of p53 status, yet the kinetics of Bax expression were influenced by p53. Remarkably, apoptosis was preceded by mitochondrial proliferation and signs of epithelial differentiation.	Using the human wild-type p53-expressing HCT116 colon carcinoma cell line and HCT116 cells with both p53 alleles inactivated by homologous recombination, the study shows that resveratrol at concentrations comparable to those found in some foods can induce apoptosis independently of p53. Resveratrol triggers a p53-independent apoptotic pathway in HCT116 cells that may be linked to differentiation.	309
Determination of the chemopreventive potential of resveratrol against human gastric adenocarcinoma cells (KATO-III and RF-1).	The study shows the action of resveratrol on cellular function and cellular integrity by measuring DNA synthesis, cellular proliferation, cell cycle distribution, cytolysis, apoptosis, and phosphotransferase activities of two key signaling enzymes, protein kinase C (PKC) and mitogen-activated protein kinases (ERK1/ERK2), in KATO-III and RF-1 cells. Resveratrol inhibited [^{3}H]thymidine incorporation into cellular DNA of normally proliferating KATO-III cells and of RF-1 cells whose proliferation was stimulated with carcinogenic nitrosamines. Treatment with resveratrol arrested KATO-III cells in the G_0/G_1 phase of the cell cycle and eventually induced apoptotic cell death, but had a minimal effect on cell lysis. Resveratrol treatment had no effect on ERK1/ERK2 activity but significantly inhibited PKC activity of KATO-III cells and of human recombinant PKCα.	Results indicate that resveratrol has potential as a chemopreventive agent against gastric cancer since it exerts an overall deactivating effect on human gastric adenocarcinoma cells. Resveratrol-induced inhibition of PKC activity and of PKCα, without any change in ERK1/ERK2 activity, suggests that resveratrol utilizes a PKC-mediated mechanism to deactivate gastric adenocarcinoma cells.	310

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Inhibition of cell growth and apoptosis in human cancer cells (Col2) using a resveratrol analogue, 3,5,2′,4′-tetramethoxy-*trans*-stilbene.	Prompted by the strong growth inhibitory activity of the compound compared to resveratrol in cultured Col2, a mechanistic study was performed using the analogue. It induced the accumulation of cellular DNA content in the sub-G_0 phase of the cell cycle in a time-dependent manner. The morphological changes were also consistent with an apoptotic process.	3, 5,2′,4′-Tetramethoxy-*trans*-stilbene potentiated the inhibition of cancer cell growth. This result indicated that the compound induced apoptosis of cancer cells, and may be a candidate for use as a cancer chemotherapeutic or cancer chemopreventive agent.	311
Induction of apoptosis in the lymphoma cell line BJAB and in primary, leukemic lymphoblasts.	Using BJAB cells overexpressing a dominant-negative mutant of the Fas-associated death domain (FADD) adaptor protein to block death receptor-mediated apoptosis, the study demonstrates that resveratrol- and piceatannol-induced cell death is independent of the CD95/Fas signaling pathway. To explore the antileukemic properties of both compounds in more detail, primary leukemic lymphoblasts were investigated. Piceatannol but not resveratrol is a very efficient inducer of apoptosis in this *ex vivo* assay with leukemic lymphoblasts of 21 patients suffering from childhood lymphoblastic leukemia (ALL).	Resveratrol and piceatannol are potent inducers of apoptotic cell death in BJAB Burkitt-like lymphoma cells with an ED_{50} of 25 μM. Experiments revealed that treatment of BJAB cells with both substances led to a concentration-dependent activation of caspase-3 and mitochondrial permeability transition.	312
Antiproliferative effects using human epidermoid carcinoma (A431) cells and involvement of the retinoblastoma (pRb)-E2F/DP pathway.	Immunoblot analysis demonstrated that resveratrol treatment of A431 cells results in a dose- as well as time-dependent decrease in the hyperphosphorylated form of pRb with a relative increase in hypophosphorylated pRb. This response was accompanied by downregulation of protein expression of all five E2F family members of transcription factors studied and their heterodimeric partners DP1 and DP2. This suggests that resveratrol causes a downregulation of hyperphosphorylated pRb protein with a relative increase in hypophosphorylated pRb that, in turn, compromises with the availability of free E2F. It is suggested that this series of events results in a stoppage of the cell cycle progression at the $G_1 \rightarrow S$ phase transition thereby leading to a G_0/G_1 arrest and subsequent apoptotic cell death.	Evidence is provided for the involvement of the pRb-E2F/DP pathway as an important contributor of resveratrol-mediated cell cycle arrest and apoptosis. This study shows the involvement of the pRb-E2F/DP pathway as a mechanism of the cancer-chemopreventive effects of resveratrol.	313
Inhibition of CYP1A1 expression in breast cancer cells (T47D and MCF-7).	Resveratrol inhibited TCDD-induced reporter gene activity in cells transfected with an Ah-responsive construct containing a human CYP1A1 gene promoter insert, whereas 3′-methoxy-4′-nitroflavone, a "pure" AhR antagonist, inhibited this response. Resveratrol induced transformation of the rat cytosolic AhR and, after treatment of T47D and MCF-7 cells with resveratrol, a transformed nuclear AhR complex was observed. In contrast to 3′-methoxy-4′-nitroflavone, resveratrol did not block TCDD-induced AhR transformation *in vitro* or nuclear uptake of the AhR complex in breast cancer cells. The action of resveratrol on the AhR was consistent with that of an AhR agonist; however, resveratrol did not exhibit functional AhR agonist or antagonist activities in breast cancer cells. Actinomycin D chase experiments in T47D cells showed that resveratrol and dehydroepiandrosterone both increased the rate of CYP1A1 mRNA degradation, whereas resveratrol did not affect CYP1A1-dependent activity in cells pretreated with TCDD for 18 h.	These data suggest that resveratrol inhibits CYP1A1 via an AhR-independent post-transcriptional pathway.	314

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Bcl-2 overexpression reduction and induction of apoptosis in U937/vector and U937/Bcl-2 cells by inhibition of caspase-3 activity.	U937/vector and U937/Bcl-2 cells were used, which were generated by transfection of the cDNA of the Bcl-2 gene. As compared with U937/vector, U937/Bcl-2 cells exhibited a 4-fold greater expression of Bcl-2. Treatment with 60 or 100 μM resveratrol for 24 h produced morphological features of apoptosis and DNA fragmentation in U937/vector cells, respectively. This was associated with caspase-3 activation and PLC-gamma1 degradation. In contrast, resveratrol-induced caspase-3 activation and PLC-gamma1 degradation and apoptosis were significantly inhibited in U937/Bcl-2 cells.	The effect of high intracellular levels of the antiapoptosis protein Bcl-2 on caspase-3 activation, PLC-γ1 degradation and cytochrome c release during resveratrol-induced apoptosis were determined. Bcl-2 overexpressing cells exhibited less cytochrome c release and sustained expression levels of the IAP proteins during resveratrol-induced apoptosis. In addition, these findings indicate that Bcl-2 inhibits resveratrol-induced apoptosis by a mechanism that interferes with cytochrome c release and activity of caspase-3 that is involved in the execution of apoptosis.	315
Inhibition of cell proliferation and prevention of oxidative DNA damage using a panel of cell lines of various histogenetic origin, including normal rat fibroblasts and mouse mammary epithelial cells compared to human breast, colon and prostate cancer cells.	The concentration of resveratrol inhibiting cell growth by 50% (IC_{50}) ranged from about 20 to 100 μM. At such concentrations, a significant increase was observed in the apoptotic index in most of the cell lines analyzed. There was a reduction in the percentage of cells in the G_2/M phase which was most frequently associated with an increase of cells in the S phase of the cell cycle. Resveratrol was able to prevent the increase in reactive oxygen species (ROS) following exposure to oxidative agents. Resveratrol also reduced nuclear DNA fragmentation, as assessed by single cell gel electrophoresis (comet test).	The results suggest that resveratrol can act as an antimutagenic/anticarcinogenic agent by preventing oxidative DNA damage which plays a pivotal role in the carcinogenic activity of many genotoxic agents.	316
Cytostatic and antiestrogenic properties using human endometrial adenocarcinoma (Ishikawa) cells.	Treatment of cultured Ishikawa cells with resveratrol did not significantly increase the levels of an estrogen-inducible marker enzyme, alkaline phosphatase. When alkaline phosphatase was induced by treatment of 17β-estradiol (E_2), resveratrol exhibited a dose-dependent decrease in activity. When Ishikawa cells were treated with resveratrol as a single agent, estrogen-inducible progesterone receptor (PR) was not enhanced, and PR expression induced by treatment with E_2 was inhibited by resveratrol in a dose-dependent fashion at both the mRNA and protein levels. Resveratrol mediated suppression of a functional activity of PR as demonstrated by downregulation of α_1-integrin expression induced by E_2 plus progesterone. With transient transfection experiments conducted with Ishikawa cells, antiestrogenic effects were confirmed by dose-dependent inhibition of E_2-induced estrogen response element-luciferase transcriptional activity. Because resveratrol antagonized estrogenic effects in Ishikawa cells, competitive binding analyses were performed to examine the potential of displacing [^{3}H]E_2 from human estrogen receptor (ER). Resveratrol showed no discernable activity with ER-α, but with ER-β, E_2 was displaced with an IC_{50} of 125 μM. However, mRNA and protein expression of ER-α but not ER-β were suppressed by resveratrol in Ishikawa cells, in the concentration range of 5–15 μM. In the presence or absence of E_2, resveratrol inhibited Ishikawa cell proliferation in a time-dependent manner with cells accumulating in the S phase of the cycle $\leq$48 h. This effect was reversible. Analysis of some critical cell cycle proteins revealed a specific increase in expression of cyclins A and E but a decrease in cyclin-dependent kinase 2.	These data suggest resveratrol exerts an antiproliferative effect in Ishikawa cells, and the effect may be mediated by both estrogen-dependent and -independent mechanisms.	317

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigate the effect of resveratrol on the human colonic adenocarcinoma cell line Caco-2 and the colon carcinoma cell line HCT-116.	The compound inhibited cell growth and proliferation of Caco-2 cells in a dose-dependent manner as assessed by crystal violet assay, [^{3}H]thymidine and [^{14}C]leucine incorporation. Apoptosis was determined by measuring caspase-3 activity, which increased significantly after treatment with resveratrol. Perturbed cell cycle progression from the S to G_2 phase was observed for concentrations up to 50 μmol/L, whereas higher concentrations led to reversal of the S phase arrest. These effects were specific for resveratrol; they were not observed after incubation with the stilbene analogs stilbenemethanol and rhapontin. Levels of cyclin D1 and cyclin-dependent kinase (cdk) 4 proteins were decreased, as revealed by immunoblotting. Resveratrol enhanced the expression of cyclin E and cyclin A. The protein levels of cdk2, cdk6 and proliferating cell nuclear antigen were unaffected. Similar results were obtained for HCT-116 cells, indicating that cell cycle inhibition by resveratrol is independent of cyclooxygenase inhibition. The phosphorylation state of the retinoblastoma protein in Caco-2 cells was shifted from hyperphosphorylated to hypophosphorylated at 200 μM, which may account for reversal of the S phase block at concentrations exceeding 50 μM.	These findings suggest that resveratrol exerts chemopreventive effects on colonic cancer cells by inhibition of the cell cycle.	318
Induction of apoptotic cell death investigation using CD95-sensitive leukemia lines, B-lineage leukemic cells that are resistant to CD95-signaling, and leukemia lines derived from patients with pro-B t(4;11), pre-B, and T-cell ALL.	Multiple dose treatments of the leukemic cells with resveratrol resulted in cell death with no statistically significant cytotoxicity against normal peripheral blood mononuclear cells under identical conditions. Resveratrol treatment did not increase CD95 expression or trigger sensitivity to CD95-mediated apoptosis in the ALL lines. Inhibition of CD95-signaling with a CD95-specific antagonistic antibody indicated that CD95-CD95 ligand interactions were not involved in initiating resveratrol-induced apoptosis. However, in each ALL line, resveratrol induced progressive loss of mitochondrial membrane potential as measured by the dual emission pattern of the mitochondria-selective dye JC-1. The broad spectrum caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone failed to block the depolarization of mitochondrial membranes induced by resveratrol, further indicating that resveratrol action was independent of upstream caspase-8 activation via receptor ligation. However, increases in caspase-9 activity ranged from 4- to 9-fold in the eight cell lines after treatment with resveratrol.	This study shows that resveratrol induces extensive apoptotic cell death not only in CD95-sensitive leukemia lines, but also in B-lineage leukemic cells that are resistant to CD95-signaling. This investigated using leukemia lines derived from patients with pro-B t(4;11), pre-B, and T-cell ALL. These results suggest a general mechanism of apoptosis induction by resveratrol in ALL cells that involves a mitochondria/caspase-9-specific pathway for the activation of the caspase cascade and is independent of CD95-signaling.	319
Evaluation of the effects of resveratrol on invasion of the human hepatoma cell line HepG2.	Cell invasion was assessed using a Boyden chamber assay. Activation of the HGF signal transduction pathways was evaluated by Western blot with phospho-specific antibodies. Urokinase expression was measured by RT-PCR and zymography. Resveratrol decreased hepatocyte growth factor-induced cell scattering and invasion. It also decreased cell proliferation without evidence for cytotoxicity or apoptosis. Resveratrol did not decrease the level of the hepatocyte growth factor receptor c-met and did not impede the hepatocyte growth factor–induced increase in c-met precursor synthesis. Resveratrol did not decrease hepatocyte growth factor-induced c-met autophosphorylation, or Akt-1 or extracellular-regulated kinases-1 and -2 activation. Resveratrol did not decrease urokinase expression and did not block the catalytic activity of urokinase.	The results demonstrate that resveratrol decreases hepatocyte growth factor-induced HepG2 cell invasion by an unidentified post-receptor mechanism.	320
Suppression of hepatoma cells (rat ascites hepatoma cell line of AH109A cells) invasion independently of antiproliferative action.	Resveratrol (100 and 200 μM) inhibited the proliferation of hepatoma cells, although it exerted little influence up to 50 μM. Resveratrol suppressed the invasion of the hepatoma cells even at a concentration of 25 μM. Sera from rats orally given resveratrol restrained only the invasion of AH109A cells. Resveratrol and resveratrol-loaded rat serum suppressed reactive oxygen species-potentiated invasive capacity.	These results suggest that the antiinvasive activity of resveratrol is independent of the anti-proliferative activity, and that the antioxidative property of resveratrol may be involved in its anti-invasive action.	321

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Modulation in cyclin-dependent kinase (cdk) inhibitor-cyclin-cdk machinery, WAF-1/p21-mediated G_1-phase arrest of the cell cycle and induction of apoptosis of human epidermoid carcinoma (A431) cells.	Resveratrol treatment of A431 cells resulted in a dose-dependent (a) inhibition of cell growth as shown by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, (b) G_1-phase arrest of the cell cycle as shown by DNA cell cycle analysis, and (c) induction of apoptosis as assessed by ELISA. The immunoblot analysis revealed that resveratrol treatment causes a dose- and time-dependent (a) induction of WAF1/p21; (b) decrease in the protein expression of cyclin D1, cyclin D2, and cyclin E; and (c) decrease in the protein expression of cdk2, cdk4, and cdk6. Resveratrol treatment was also found to result in a dose- and time-dependent decrease in kinase activities associated with all of the cdks examined.	Taken together, the study suggests that resveratrol treatment of the cells causes an induction of WAF1/p21 that inhibits cyclin D1/D2-cdk6, cyclin D1/D2-cdk4, and cyclin E-cdk2 complexes, thereby imposing an artificial checkpoint at the $G_1 \rightarrow S$ transition of the cell cycle. This series of events results in a G_1-phase arrest of the cell cycle, which is an irreversible process that ultimately results in the apoptotic death of cancer cells. This study shows the involvement of each component of cdk inhibitor-cyclin-cdk machinery during cell cycle arrest and apoptosis of cancer cells by resveratrol.	322
Effect of synthetic resveratrol on the growth of estrogen receptor (ER)-positive (KPL-1 and MCF-7) and -negative (MKL-F) human breast cancer cell lines.	Resveratrol, at low concentrations, caused cell proliferation in ER-positive cell lines. At high concentrations, it caused suppression of cell growth in all three cell lines. Growth suppression was due to apoptosis as seen by the appearance of a sub-G_1 fraction. The apoptosis cascade upregulated Bax and Bak protein, downregulated Bcl-x^L protein, and activated caspase-3. Resveratrol antagonized the effect of linoleic acid and suppressed the growth of both ER-positive and -negative cell lines.	The study shows that resveratrol could be a promising anticancer agent for both hormone-dependent and hormone-independent breast cancers, and may mitigate the growth stimulatory effect of linoleic acid in the Western-style diet.	323
Expression of the cytochrome P450 1A1 (CYP1A1) and 1B1 (CYP1B1), microsomal epoxide hydrolase (mEH), and glutathione *S*-transferase P1 (GSTP1) genes were tested to determine involvement in the metabolism of polycyclic aromatic hydrocarbons in the human bronchial epithelial cell line BEP2D.	Expression of the genes was measured by quantitative reverse transcriptase-polymerase chain reaction. The cells were treated either with benzo(*a*)pyrene or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the presence or absence of resveratrol. Resveratrol inhibited both the constitutive and the induced expression of CYP1A1 and CYP1B1 in a dose-dependent manner. The expression of the mEH gene was increased in response to resveratrol and no change in the expression of GSTP1 was found. The altered gene expression in response to resveratrol was reflected in a reduced overall level of benzo(*a*)pyrene metabolism.	These data indicate that resveratrol may exert lung cancer chemopreventive activity through altering the expression of genes involved in the metabolism of polycyclic aromatic hydrocarbons, resulting in altered formation of carcinogenic benzo(*a*)pyrene metabolites in human bronchial epithelial cells.	324
Antiapoptotic effect of *trans*-resveratrol on paclitaxel (an anticancer drug)-induced apoptosis in the human neuroblastoma SH-SY5Y cell line.	Paclitaxel induces apoptosis in human neuroblastoma cell line SH-SY5Y. The addition of resveratrol to SH-SY5Y cultures exposed to paclitaxel significantly reduces cellular death. The neuroprotective action of resveratrol is due neither to its antioxidant capacity nor to interference with the polymerization of tubulin induced by paclitaxel. Resveratrol is able to inhibit the activation of caspase-7 and degradation of poly-(ADP-ribose)-polymerase which occur in SH-SY5Y exposed to paclitaxel.	Resveratrol exerts its antiapoptotic effect by modulating the signal pathways that commit these neuronal-like cells to apoptosis.	325

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Using a mouse JB6 epidermal cell line, elucidation of the potential signaling components underlying resveratrol-induced p53 activation and induction of apoptosis were investigated.	In a mouse JB6 epidermal cell line, resveratrol activated extracellular-signal-regulated protein kinases (ERKs), c-Jun NH_2-terminal kinases (JNKs), and p38 kinase, and induced serine 15 phosphorylation of p53. Stable expression of a dominant negative mutant of ERK2 or p38 kinase, or their respective inhibitors, PD98059 or SB202190, repressed the phosphorylation of p53 at serine 15. In contrast, overexpression of a dominant negative mutant of JNKI had no effect on the phosphorylation. Most importantly, ERKs and p38 kinase formed a complex with p53 after treatment with resveratrol. Strikingly, resveratrol-activated ERKs and p38 kinase, but not JNKs, phosphorylated p53 at serine 15 *in vitro*. Furthermore, pretreatment of the cells with PD98059 or SB202190 or stable expression of a dominant negative mutant of ERK2 or p38 kinase impaired resveratrol-induced p53-dependent transcriptional activity and apoptosis, whereas constitutively active MEK1 increased the transcriptional activity of p53.	These data strongly suggest that both ERKs and p38 kinase mediate resveratrol-induced activation of p53 and apoptosis through phosphorylation of p53 at serine 15.	326
Effect of cell transformation and gene expression using a resveratrol analog, 3,4,5,4′-tetrahydroxystilbene (R-4). WI38VA and WI38 cells were used.	RNase protection assay showed that R-4 significantly induced the expression of p53, GADD45 and Bax genes and concomitantly suppressed the expression of Bcl-2 gene in WI38VA, but not in WI38 cells. A large increase in p53 DNA binding activity and the presence of p53 in the Bax promoter binding complex suggested that p53 was responsible for the Bax gene expression induced by R-4 in transformed cells. Within 4 h of treatment with R-4, the Bax to Bcl-2 protein ratio in WI38 and WI38VA cells was a difference of three orders of magnitude. While R-4 prominently induced the p53/Bax proapoptotic genes, it also concomitantly suppressed the expression of Cox-2 in WI38VA cells.	R-4 inhibited the growth of SV40 virally transformed WI38 cells (WI38VA), but had no effect on normal WI38 cells. R-4 induced apoptosis in WI38VA cells, but not in WI38 cells. The study suggests that the induction of p53 gene by R-4 in transformed cells may play a key role in the differential growth inhibition and apoptosis of transformed cells.	327
Reverse inhibition and progression through S and G_2 phases of the cell cycle in human leukemia U937 cells.	Resveratrol induces arrest in the S phase at low concentrations, but high concentrations do not induce S phase accumulation in U937 cells. Removal of resveratrol from the culture medium stimulates U937 cells to reenter the cell cycle synchronously, as judged by the expression patterns of cyclin E, A and by fluorescent activated cell sorting analysis. These data demonstrate that resveratrol causes S phase arrest and reversible cell cycle arrest.	The report shows that resveratrol induces antiproliferation and arrests the S phase in human histiocytic lymphoma U937 cells. Resveratrol is an important cell cycle blocker.	328
Investigation catechin, epicatechin, quercetin, and resveratrol on the growth of prostate cancer cell lines (LNCaP, PC3, and DU145).	A dose- and time-dependent inhibition of cell growth by polyphenols was found at nanomolar concentrations. The proliferation of LNCaP and PC3 cells was preferentially inhibited by catechin, epicatechin, and quercetin, whereas resveratrol was the most potent inhibitor of DU145 cell growth. Possible mechanisms of action were investigated: (1) The competition of polyphenols for androgen binding in LNCaP cells revealed significant interaction only in the case of high concentrations of quercetin, at least at five orders of magnitude higher than the concentrations needed for cell growth inhibition. All other phenols showed low interactions. (2) Oxygen species production after mitogen stimulation and H_2O_2 sensitivity of these cell lines did not correlate with the observed antiproliferative effects, ruling out such a mode of action. (3) NO production revealed two different patterns: LNCaP and DU145 cells produced high concentrations of NO, whereas PC3 cells produced low concentrations. Phorbol ester stimulation of cells did not reveal any additional effect in LNCaP and DU145 cells, whereas it enhanced the secretion of NO in PC3 cells. Polyphenols decreased NO secretion. This effect correlates with their antiproliferative action and the inhibition of inducible NO synthase.	It is proposed that the antiproliferative effect of polyphenols is mediated through the modulation of NO production. The data show a direct inhibitory effect of low concentrations of antioxidant wine phenols on the proliferation of human prostate cancer cell lines mediated by the production of NO, further suggesting potential beneficial effects of wine and other phenol-containing foods or drinks for the control of prostate cancer cell growth.	329

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Arrest in the S-phase prior to Fas-independent apoptosis in CEM-C7H2 lymphocytic leukemia cells.	Resveratrol induced arrest in the S-phase and apoptosis in the T cell-derived T-ALL lymphocytic leukemia cell line CEM-C7H2 which is deficient in functional p53 and p16. Expression of transgenic p16/INK4A reduced the percentage of apoptotic cells. Antagonist antibodies to Fas or FasL, or constitutive expression of crmA did not diminish the extent of resveratrol-induced apoptosis. Furthermore, a caspase-8-negative, Fas-resistant Jurkat cell line was sensitive to resveratrol-induced apoptosis which could be strongly inhibited in the Jurkat as well as in the CEM cell line by z-VAD-fmk and z-IETD-fmk. The almost complete inhibition by z-IETD-fmk and the lack of inhibition by crmA suggested caspase-6 to be the essential initiator caspase. Western blots revealed the massive conversion of procaspase-6 to its active form, while caspase-3 and caspase-2 were proteolytically activated to a much lesser extent.	Resveratrol causes arrest in the S-phase prior to Fas-independent apoptosis in CEM-C7H2 acute leukemia cells.	330
Effect of resveratrol on estrogen receptors α and β.	Resveratrol was shown to bind ER in cytosolic extracts from MCF-7 and rat uteri. However, the contribution of ERα vs. ERβ in this binding is unknown. Thus, resveratrol differs from other phytoestrogens that bind ERβ with higher affinity than ERα. Resveratrol acts as an estrogen agonist and stimulates ERE-driven reporter gene activity in CHO-K1 cells expressing either ERα or ERβ. The estrogen agonist activity of resveratrol depends on the ERE sequence and the type of ER. Resveratrol-liganded ERβ has higher transcriptional activity than E_2-liganded ERβ at a single palindromic ERE. This indicates that those tissues that uniquely express ERβ or that express higher levels of ERβ than ERα may be more sensitive to the estrogen agonist activity of resveratrol. For the natural, imperfect EREs from the human c-fos, pS2, and progesterone receptor (PR) genes, resveratrol shows activity comparable to that induced by E_2. Resveratrol exhibits E_2 antagonist activity for ERα with select EREs. In contrast, resveratrol shows no E_2 antagonist activity with ERβ.	These data indicate that resveratrol differentially affects the transcriptional activity of ERα and ERβ in an ERE sequence-dependent manner. The study reports that resveratrol binds ERβ and ERα with comparable affinity, but with 7000-fold lower affinity than estradiol (E_2).	331
Investigation of gap-junctional intercellular communication (GJIC) in WB-F344 rat liver epithelial cells.	Seventeen to 50 μM resveratrol increased GJIC significantly by a factor of 1.3 compared with solvent vehicle controls, when the WB-F344 cells were exposed to resveratrol for 6 h. Most tumor promoters, including the phorbol ester TPA and the insecticide DDT, block GJIC. Resveratrol at 17-50 μM also significantly prevented downregulation of GJIC by TPA and DDT, by a factor of 2.7 and 1.8, respectively. This recovery of GJIC from TPA inhibition was partly correlated with hindered hyperphosphorylation of Cx43.	Resveratrol was found to enhance GJIC and counteract the effects of tumor promoters on GJIC, and this is likely a mechanism that contributes to the antipromotional and anticarcinogenic properties of resveratrol.	332

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigation of pharmacological effects using Caco-2 human colon cancer cells.	The study investigated the effects of resveratrol on the growth and polyamine metabolism of Caco-2 human colon cancer cells. Treatment of the Caco-2 cells with 25 μM resveratrol caused a 70% growth inhibition. The cells accumulated at the S/G_2 phase transition of the cell cycle. No signs of cytotoxicity or apoptosis were detected. Resveratrol caused a significant decrease of ornithine decarboxylase (ODC) activity.	ODC inhibition resulted in the reduction of the intracellular putrescine content, indicating that polyamines might represent one of several targets involved in the antiproliferative effects of resveratrol.	333
Investigation of inflammatory and antioncogenic properties of resveratrol.	Because the transcription factor NF-κB is involved in inflammatory diseases and oncogenesis, resveratrol was tested to see if it could modulate NF-κB activity.	Resveratrol was shown to be a potent inhibitor of both NF-κB activation and NF-κB-dependent gene expression through its ability to inhibit IκB kinase activity, the key regulator in NF-κB activation, likely by inhibiting an upstream signaling component. In addition, resveratrol blocked the expression of mRNA-encoding monocyte chemoattractant protein-1, a NF-κB-regulated gene. Relative to cancer chemopreventive properties, resveratrol induced apoptosis in fibroblasts after the induced expression of oncogenic H-Ras.	334
Inhibition of cell proliferation in rat hepatoma Fao cell line and human hepatoblastoma HepG2 cell line.	The ability of resveratrol to inhibit cell proliferation was studied in rat hepatoma Fao cell line and human hepatoblastoma HepG2 cell line. The results show that resveratrol strongly inhibits cell proliferation at the micromolar range in a time- and dose-dependent manner. Concentrations higher than 50 μM become toxic. Fao cells are more sensitive than HepG2 cells. The presence of ethanol lowers the threshold of resveratrol effect. Resveratrol appears to prevent or to delay the entry to mitosis since no inhibition of [^{3}H]thymidine incorporation is observed, while there is an increase of cell number in S and G_2/M phases.	Resveratrol shows a strong inhibition of hepatic cell proliferation where alcohol may act as an enhancing agent.	335
Induction of Fas signaling-independent apoptosis in THP-1 human monocytic leukemia cells.	Resveratrol inhibits the growth of THP-1 human monocytic leukemia cells in a dose-dependent manner with a median effective dose of 12 μM. It did not induce differentiation of THP-1 cells and had no toxic effect on THP-1 cells that had been induced to differentiate into monocytes/macrophages by phorbol myristate acetate. A significant fraction of resveratrol-treated cells underwent apoptosis as judged by flow cytometric analysis of DNA content, DNA fragmentation and caspase-specific cleavage of poly(ADP-ribosyl) polymerase. Resveratrol treatment had no effect on the expression of Fas receptor or Fas ligand (FasL) in THP-1 cells, nor did it induce clustering of Fas receptors. In addition, THP-1 cells were resistant to activating anti-Fas antibody, and neutralizing anti-Fas and/or anti-FasL antibodies had no protective effect against resveratrol-induced inhibition of THP-1 cell growth. The effect of resveratrol on THP-1 cells was reversible after its removal from the culture medium.	These results suggest that (1) resveratrol inhibits the growth of THP-1 cells, at least in part, by inducing apoptosis, (2) resveratrol-induced apoptosis of THP-1 cells is independent of the Fas/FasL signalling pathway, and (3) resveratrol does not induce differentation of THP-1 cells and has no toxic effect on differentiated THP-1 cells. Resveratrol may be a potential chemotherapeutic agent for the control of acute monocytic leukemia.	336

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Suppression of cyclooxygenase-2 (COX-2) promoter-dependent transcriptional activity in human colon cancer DLD-1 cells by 14 chemopreventive agents, which include resveratrol, with a resorcin-type structure.	A β-galactosidase reporter gene system in human colon cancer DLD-1 cells was constructed, and measured COX-2 promoter-dependent transcriptional activity in the cells. Interferon gamma suppressed this COX-2 promoter activity, while 12-*O*-tetradecanoylphorbol-13-acetate and transforming growth factor α (TGFα) exerted enhancing effects. The influence of 14 compounds on COX-2 promoter activity was tested.	The compounds, all having a common resorcin moiety, were found to effectively suppress the COX-2 promoter activity with and without TGFα-stimulation in DLD-1 cells. Because all these compounds have a resorcin moiety as a common structure, a resorcin-type structure may play an active role in the inhibition of COX-2 expression in colon cancer cells.	200
Inhibition of cell proliferation is tested using prostate cancer cells (LNCaP) and the expression of a prostate specific gene, PSA.	A 4-day treatment with resveratrol reduced the levels of intracellular and secreted PSA by approximately 80%, as compared to controls. To test whether this decrease was coordinated with changes in androgen receptor (AR) expression, levels of AR were assayed by Western blot analysis, using the cognate antibody, or by binding with the radioactive ligand methyltrienolone [^{3}H]R1881.	With either assay, little or no change in AR expression could be detected between control and resveratrol-treated cells. Thus, it would appear that the prostate tumor marker PSA is downregulated by resveratrol by a mechanism independent of changes in AR.	337
Effect of resveratrol and grapevine polyphenols on cultured human liver myofibroblasts.	Resveratrol profoundly affects myofibroblast phenotype—it induced morphological modifications. Resveratrol markedly reduced proliferation of myofibroblasts in a dose-dependent manner. Resveratrol also decreased the expression of α smooth muscle actin (α-SMA) without affecting vimentin or β-cytoplasmic actin expression. It decreased myofibroblast migration in a monolayer wounding assay. In addition, resveratrol inhibited the messenger RNA (mRNA) expression of type I collagen. Resveratrol decreased the secretion of matrix metalloproteinase 2 (MMP-2).	Resveratrol can deactivate human liver myofibroblasts. Neither *trans*-piceid nor *trans*-piceatannol reproduces resveratrol effects on liver myofibroblasts. Although *trans*-resveratrol decreases the proliferation of skin fibroblast and vascular smooth muscle cells, it does not affect their expression of α-SMA, which indicates some cell specificity.	338
Growth and proliferation of human oral squamous carcinoma cell (SCC-25).	Resveratrol, quercetin, the combination of the two, and diluted red wine, were tested for dose-dependent inhibition in human oral squamous carcinoma cell (SCC-25) growth and DNA synthesis.	Resveratrol induced significant dose-dependent inhibition in human oral squamous carcinoma cell (SCC-25) growth and DNA synthesis. Quercetin exhibited a biphasic effect, stimulation and minimal inhibition in cell growth and DNA synthesis. Combining of resveratrol with quercetin resulted in a gradual and significant increase in the inhibitory effect of the two compounds. Diluted red wine had a significantly more inhibitory effect on cell growth, DNA synthesis and changes in cell morphology than each compound alone or in combination. Resveratrol by itself or a combination of resveratrol and quercetin are effective inhibitors of SCC-25 growth and DNA synthesis. The presence of other wine phenolic phytochemicals enhances significantly the effect of resveratrol and quercetin on inhibition of cancer cell growth and DNA synthesis.	339

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Suppression of phorbol ester (PMA)-mediated induction of COX-2 in human mammary and oral epithelial cells.	Human mammary and oral epithelial cells were treated with PMA and tested for inhibition of COX-2 mRNA, COX-2 protein, and prostaglandin synthesis.	Treatment of cells with PMA induced COX-2 mRNA, COX-2 protein, and prostaglandin synthesis. Nuclear runoffs revealed increased rates of COX-2 transcription after treatment with PMA. These effects were inhibited by resveratrol. Resveratrol inhibited PMA-mediated activation of protein kinase C and the induction of COX-2 promoter activity by c-Jun. Phorbol ester-mediated induction of AP-1 activity was blocked by resveratrol.	79
Inhibition of the expression and function of the androgen receptor (AR) in prostate cancer cells (LNCaP).	Effects of resveratrol were tested on androgen-stimulated growth and gene expression in LNCaP cells. The group transfected a construct containing a 6-kb PSA promoter fragment in front of a luciferase reporter gene into LNCaP cells with or without Mib to test whether resveratrol can directly affect androgen-mediated transcriptional activity of the *PSA* gene. Northern or western analyses were performed to see whether different classes of the androgen-regulated genes are affected.	Resveratrol represses different classes of androgen up-regulated genes at the protein or mRNA level including prostate-specific antigen, human glandular kallikrein-2, AR-specific coactivator ARA70, and the cyclin-dependent kinase inhibitor p21. This inhibition is likely attributable to a reduction in AR contents at the transcription level, inhibiting androgen-stimulated cell growth and gene expression.	340
Effects of resveratrol on the increased proliferation of human AHTO-7 osteoblastic cell line induced by conditioned media (CM) from a panel of carcinoma cell lines [pancreas (BxPC3, Panc-1), breast (ZR75-1), renal (ACHN), colon (SW620, Colo320DM) and prostate cancer (PC3, DU145 and LNCaP)].	A tamoxifen-sensitive mechanism was used to test the ability of resveratrol to modulate AHTO-7 proliferation. Resveratrol was tested for its proliferative response of AHTO-7 cells to CM from carcinoma in the panel of carcinoma cell lines.	Resveratrol was found to modulate AHTO-7 proliferation in a tamoxifen-sensitive mechanism at lower concentrations, but failed to induce the osteoblast differentiation marker alkaline phosphatase (ALP) in contrast to vitamin D_3. The proliferative response of AHTO-7 cells to CM from carcinoma cell lines was diminished upon pretreatment with resveratrol. Highest inhibition was demonstrated for BxPC3, Panc-1, ZR75-1 and ACHN carcinoma cell line supernatants whereas the effect on SW620, Colo320DM, PC3, DU145, LNCaP CM was less pronounced. Direct addition of resveratrol affected only supernatants of cell lines exhibiting growth stimulatory activity for normal WI-38 lung fibroblasts. Resveratrol inhibited proliferation of DU145 and LNCaP cells, altered cell cycle distribution of all prostate cancer cell lines, but did not inhibit the production of osteoblastic factors by these lines. In sum, resveratrol failed to induce ALP activity as marker of osteoblast differentiation in human osteoblastic AHTO-7 cells, however, inhibited their response to osteoblastic carcinoma-derived growth factors in concentrations significantly lower than those to reduce growth of cancer cells, thus effectively modulating tumor-osteoblast interaction.	341
Induction of apoptosis in human promyelocytic leukemia (HL-60) cells.	Resveratrol was tested to determine if it reduces viability and DNA synthesis capability in cultured HL-60 cells.	The growth inhibitory and antiproliferative properties of resveratrol appear to be attributable to its induction of apoptotic cell death as determined by morphological and ultrastructural changes, internucleosomal DNA fragmentation, and increased proportion of the subdiploid cell population. Resveratrol treatment resulted in a gradual decrease in the expression of antiapoptotic Bcl-2.	342

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Ability to control growth and cell cycle transition in MDA-MB-435 and MCF-7 breast carcinoma cells. Effect on a panel of MDA-MB-435 cells transfected with nm23-H1 and nm23-H2 genes.	Resveratrol was tested in MDA-MB-435 and MCF-7 breast carcinoma cells lines to determine ability to control growth and cell cycle transition. In addition, resveratrol was tested to determine its effect on a panel of MDA-MB-435 cells transfected with nm23-H1 and nm23-H2 genes. The responses of these cells to resveratrol were assessed by measuring proliferation, cell cycle phase distribution, and changes in expression of several genes.	The data revealed that resveratrol exerted a greater inhibitory effect on the MDA-MB-435 cells. A diminution of percentage of cells in G_1 phase and a corresponding accumulation of cells in S phase of the cell cycle was observed. These studies have shown that resveratrol reduced growth of all cell types. Overexpression of both wild-type and catalytically inactive nm23-H1 but not nm23-H2 reduced the proportion of cells in G_1 phase compared to the control cells. Little change in expression of PCNA, Rb, p53, and Bcl-2 was observed in the five cell types treated with resveratrol, compared to untreated cells. Noted exceptions included reduced expression of Rb protein and increased expression of p53 in two of the cells, and increased expression of Bcl-2 in one treated with resveratrol. Resveratrol upregulated expression of cathepsin D by 50-100% in all cell lines except one.	343
Inhibition of carcinogen-induced preneoplastic lesion formation in mouse mammary organ culture and tumorigenesis in the two-stage mouse skin model. Cancer chemopreventive potential on the three major stages of carcinogenesis.	Anti-initiation activity was determined by inhibition of the hydroperoxidase function of cyclooxygenase (COX), and induction of phase II drug-metabolizing enzymes. Antipromotion activity was determined by inhibition of production of arachidonic acid metabolites catalyzed by either COX-1 or COX-2, and chemical carcinogen-induced neoplastic transformation of mouse embryo fibroblasts. Antiprogression activity was determined by induction of human promyelocytic leukemia (HL-60) cell differentiation. Treatment of mouse skin with resveratrol to determine the effect of 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative stress.	Resveratrol reduced the generation of hydrogen peroxide, and normalized levels of myeloperoxidase and oxidized-glutathione reductase activities. It also restored glutathione levels and superoxide dismutase activity. Based on the reverse transcriptase-polymerase chain reaction, resveratrol selectively inhibited TPA-induced expression of c-fos and transforming growth factor-β1 (TGF-β1), but did not affect other TPA-induced gene products including COX-1, COX-2, c-myc, c-jun, and tumor necrosis factor-α. These data indicate that resveratrol may interfere with reactive oxidant pathways and/or modulate the expression of c-fos and TGF-β1 to inhibit tumorigenesis in mouse skin. Resveratrol inhibited the *de novo* formation of inducible nitric oxide synthase (iNOS) in mouse macrophages stimulated with lipopolysaccharide.	80
Investigation of the effects of resveratrol on growth, induction of apoptosis, and modulation of prostate-specific gene expression using cultured prostate cancer cells that mimic the initial (hormone-sensitive) and advanced (hormone-refractory) stages of prostate carcinoma cell lines (LNCaP, DU-145, PC-3, and JCA-1).	Androgen-responsive LNCaP and androgen-nonresponsive DU-145, PC-3, and JCA-1 cells were cultured with different concentrations of resveratrol. Cell growth, cell cycle distribution, and apoptosis were determined.	Addition of resveratrol led to a substantial decrease in growth of LNCaP and in PC-3 and DU-145 cells, but only had a modest inhibitory effect on proliferation of JCA-1 cells. Flow cytometric analysis showed resveratrol to partially disrupt G_1/S transition in all three androgen-nonresponsive cell lines, but had no effect in the androgen-responsive LNCaP cells. In contrast to the androgen-nonresponsive prostate cancer cells however, resveratrol causes a significant percentage of LNCaP cells, to undergo apoptosis and significantly lowers both intracellular and secreted prostate-specific antigen (PSA) levels without affecting the expression of the androgen receptor (AR).	344

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Resveratrol-induced activation of the mitogen-activated protein kinases, ERK1 and ERK2, in human neuroblastoma SH-SY5Y cells.	Phosphorylation of the mitogen-activated protein (MAP) kinases, extracellular signal-regulated kinase 1 (ERK1) and extracellular signal-regulated kinase 2 (ERK2), induced by resveratrol has been studied *in vitro* on undifferentiated and differentiated (induction by retinoic acid) SH-SY5Y human neuroblastoma cells.	In undifferentiated cells, resveratrol induced phosphorylation of ERK1 and ERK2. A wide range of resveratrol concentrations were able to induce phosphorylation of ERK1 and ERK2, while higher concentrations inhibited MAP kinases phosphorylation. In retinoic acid (RA) differentiated cells, resveratrol induced an evident increase in ERK1 and ERK2 phosphorylation. This study demonstrates that resveratrol may have a biological effect on neuron-like cells.	345
Antiestrogenic activity and inhibition of the growth of human breast cancer cells (MCF-7).	The effect of resveratrol on the growth of human breast cancer cells was examined.	Resveratrol inhibits the growth of estrogen receptor (ER)-positive MCF-7 cells in a dose-dependent fashion. Detailed studies with MCF-7 cells demonstrate that resveratrol antagonized the growth-promoting effect of 17β-estradiol (E_2) in a dose-dependent fashion at both the cellular (cell growth) and the molecular (gene activation) levels. Resveratrol abolished the growth-stimulatory effect mediated by concentrations of E_2. The antiestrogenic effect of resveratrol was demonstrated at the molecular level. Resveratrol, in a dose-dependent fashion, antagonized the stimulation by E_2 of progesterone receptor gene expression in MCF-7 cells. Expression of transforming growth factor-α and insulin-like growth factor I receptor mRNA was inhibited while the expression of transforming growth factor β2 mRNA was significantly elevated in MCF-7 cells cultivated in the presence of resveratrol. The results show that resveratrol, a partial ER agonist, acts as an ER antagonist in the presence of estrogen leading to inhibition of human breast cancer cells.	346
Effect of resveratrol and quercetin on human oral squamous carcinoma cells (SCC-25) growth and proliferation.	Resveratrol and quercetin were incubated with human oral squamous carcinoma cells SCC-25. Cell growth was determined by counting the number of viable cells with a hemocytometer. Cell proliferation was measured by means of incorporation of [^{3}H]thymidine.	Resveratrol induced significant dose-dependent inhibition in cell growth as well as in DNA synthesis. Quercetin exhibited a biphasic effect, stimulation and minimal inhibition in cell growth and DNA synthesis. Combining resveratrol and quercetin resulted in a gradual and significant increase in the inhibitory effect of quercetin on cell growth and DNA synthesis. Resveratrol or a combination of resveratrol and quercetin, in concentrations equivalent to that present in red wines, are effective inhibitors of oral squamous carcinoma cell (SCC-25) growth and proliferation.	347
Suppression of cell transformation and induction of apoptosis through a p53-dependent pathway. JB6 P^+ mouse epidermal cell line C1 41 and its stable p53-luciferase reporter plasmid transfect, C1 41 p53 cells were used.	Inhibition of resveratrol on TPA- or EGF-induced cell transformation was investigated in JB6 C1 41 cells. The levels of p53 protein after resveratrol treatment were measured by Western blot for immunoprecipitation with specific antibodies against p53.	Resveratrol suppresses tumor promoter-induced cell transformation and induces apoptosis, transactivation of p53 activity and expression of p53 protein in the same cell line and at the same dosage. Also, resveratrol-induced apoptosis occurs only in cells expressing wild-type p53 (p53+/+), but not in p53-deficient (p53-/-) cells, while there is no difference in apoptosis induction between normal lymphoblasts and sphingomyelinase-deficient cell lines. These results demonstrate that resveratrol induces apoptosis through activation of p53 activity, suggesting that its anti-tumor activity may occur through the induction of apoptosis.	348

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Induction of apoptotic cell death in HL60 human leukemia cell line.	Resveratrol-treated tumor cells exhibit a dose-dependent increase in externalization of inner membrane phosphatidylserine and in cellular content of subdiploid DNA, indicating loss of membrane phospholipid asymmetry and DNA fragmentation. Resveratrol-induced cell death is mediated by intracellular caspases as observed by the dose-dependent increase in proteolytic cleavage of caspase substrate poly (ADP-ribose) polymerase (PARP) and the ability of caspase inhibitors to block resveratrol cytotoxicity. Resveratrol treatment enhances CD95L expression on HL60 cells, as well as T47D breast carcinoma cells, and that resveratrol-mediated cell death is specifically CD95-signaling dependent. On the contrary, resveratrol treatment of normal human peripheral blood lymphocytes (PBLs) does not affect cell survival for up to 72 h, which correlates with the absence of a significant change in either CD95 or CD95L expression on treated PBLs.	These data show specific involvement of the CD95-CD95L system in the anticancer activity of resveratrol and highlight the chemotherapeutic and chemopreventive potential.	349
Inhibitor of ribonucleotide reductase using L1210-R2 murine lymphoblastic leukemia cells.	The ability of resveratrol to destroy the tyrosyl radical was correlated with its strong dose-dependent inhibitory effects on enzyme activity, as assayed in soluble extracts of murine leukemia cells containing high protein R2 expression and high cytidine diphosphate reductase activity suitable for sensitive and reproducible assays. The antiproliferative properties of resveratrol and its inhibitory effects on DNA synthesis were evaluated by [^{3}H]thymidine incorporation.	Resveratrol is an inhibitor of ribonucleotide reductase and DNA synthesis in mammalian cells, which might have further applications as an antiproliferative or a cancer chemopreventive agent in humans.	350
C3H10T1/2 CL8 mouse embryo fibroblasts were used to determine the ability of resveratrol to block eicosanoid production and chemically induced cellular transformation.	Cyclooxygenase metabolites were investigated by using HPLC analysis. COX-1 and -2 activities were determined by measuring arachidonic acid metabolites production. Two-stage transformation assays with C3H10T1/2 cells were performed.	Resveratrol is capable of inhibiting eicosanoid production catalyzed by both COX-1 and –2, and transformation of chemically-initiated 10T1/2 cells.	351
Investigation of resveratrol to determine if it is a phytoestrogen using MCF-7 MDA-MB-231 and T47D cells.	Diethylstilbestrol, a synthetic estrogen and structurally similar to resveratrol, was examined to determine whether resveratrol might be a phytoestrogen. At concentrations comparable to those required for its other biological effects, resveratrol inhibited the binding of labeled estradiol to the estrogen receptor and it activated transcription of estrogen-responsive reporter genes transfected into human breast cancer cells. This transcriptional activation was estrogen receptor-dependent, required an estrogen response element in the reporter gene, and was inhibited by specific estrogen antagonists. In some cell types (e.g., MCF-7 cells), resveratrol functioned as a superagonist (i.e., produced a greater maximal transcriptional response than estradiol) whereas in others it produced activation equal to or less than that of estradiol. Resveratrol also increased the expression of native estrogen-regulated genes, and it stimulated the proliferation of estrogen-dependent T47D breast cancer cells.	Resveratrol is a phytoestrogen and that it exhibits variable degrees of estrogen receptor agonism in different test systems.	352

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Determination of the underlying molecular mechanisms and to identify a possible role of transcription factor peroxisome proliferator-activated receptor γ (PPARγ) with resveratrol.	Cell growth was determined by bromodeoxyuridine incorporation and crystal violet staining. Protein levels were examined by Western blot analysis. Spermine/spermidine acetyltransferase (SSAT) activity was determined by a radiochemical assay. PPARγ ligand-dependent transcriptional activity was measured by a luciferase assay. A dominant-negative PPARγ mutant was transfected in Caco-2 cells to suppress PPARγ-mediated functions. Resveratrol inhibited cell growth of both Caco-2 and HCT-116 cells in a dose- and time-dependent manner ($P < 0.001$). In contrast to Caco-2-wild type cells ($P < 0.05$), resveratrol failed to increase SSAT activity in dominant-negative PPARγ cells. PPARγ involvement was further confirmed via ligand-dependent activation ($P < 0.01$) as well as by induction of cytokeratin 20 ($P < 0.001$) after resveratrol treatment. Coincubation with SB203580 abolished SSAT activation significantly in Caco-2 ($P < 0.05$) and HCT-116 ($P < 0.01$) cells. The involvement of p38 mitogen-activated protein kinase (MAPK) was further confirmed by a resveratrol-mediated phosphorylation of p38 protein in both cell lines. Resveratrol further increased the expression of PPARγ coactivator PGC-1α ($P < 0.05$) as well as SIRT1 ($P < 0.01$) in a dose-dependent manner after 24 hours of incubation.	p38 MAPK and transcription factor PPARγ can be considered as molecular targets of resveratrol in the regulation of cell proliferation and SSAT activity, respectively, in a cell culture model of colon cancer.	353
Analyze cellular effects of resveratrol in metabolically active H4IIE rat hepatoma cells in comparison to metabolically poorly active C6 rat glioma cells.	Resveratrol is rapidly taken up by both cell types and acts as a potent intracellular antioxidant. On the other hand, resveratrol in higher concentrations is relatively toxic to both cell lines as measured by the neutral red accumulation assay. In H4IIE cells, resveratrol concentrations rapidly decline to very low levels during the first hours of incubation due to formation of resveratrol glucuronides. The first resveratrol effect found at 3 h after the start of resveratrol treatment was the induction of mild DNA damage as detected by the comet assay. Cell death was caused via induction of apoptosis as detected by caspase activation, oligonucleosomal DNA fragmentation and formation of apoptotic nuclei. Following DNA damage, resveratrol led to an activation of caspases 2 and 8/10 at 6 h and consequently of caspase 3 at 12 h, but failed to activate caspase 9. In contrast to H4IIE cells, resveratrol is not metabolized in C6 glioma cells and accumulates to concentrations that are assumed to drive the cell into necrosis.	This study suggests that the mode of cell death caused by resveratrol and the usefulness of resveratrol for cancer prevention and treatment critically depends on the metabolic capacity of the tumor cell to be eradicated.	354
Investigated the involvement of the mitogen activated protein kinase (MAPK)/p53 signal transduction mechanism in resveratrol-induced growth inhibition using a human osteosarcoma cell line.	The research group demonstrated that resveratrol reduces cell viability and growth of SJSA1 osteosarcoma cells. Morphological profiles and 4,6-diamidino-2-phenylindole nuclear staining of resveratrol-treated cells indicated marked nuclear fragmentation. Cleavage of the (116-kDa) poly(ADP-ribose) polymerase protein into an 89-kDa fragment (a proapoptotic marker system) was substantially augmented by resveratrol treatment. Resveratrol-dependent growth impairment was preceded by enhanced phosphorylation of extracellular signal-regulated kinase (ERK)1/2 (at Thr202/Tyr204). Likewise, resveratrol increased the phosphorylation of p53 tumor suppressor protein (at Ser15). The effects of resveratrol on ERKs and on p53 phosphorylation were abrogated by either the MAPK inhibitor PD98059 or the p53 inhibitor pifithrine-α.	The study indicated that resveratrol antiproliferative effects on osteosarcoma cells are mediated by the activation of the ERKs/p53 signaling pathway and therefore identified new targets for strategies to treat and/or prevent osteosarcoma.	355

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Cell surface resveratrol receptor on the extracellular domain of hetero-dimeric $\alpha V\beta 3$ integrin in MCF-7 human breast cancer cells.	This receptor is linked to induction by resveratrol of extracellular-regulated kinases 1 and 2 (ERK1/2)- and serine-15-p53-dependent phosphorylation leading to apoptosis. The integrin receptor is near the Arg-Gly-Asp (RGD) recognition site on the integrin; an integrin-binding RGD peptide inhibits induction by resveratrol of ERK1/2- and p53-dependent apoptosis. Antibody (Ab) to integrin $\alpha V\beta 3$, but not to $\alpha V\beta 5$, inhibits activation by resveratrol of ERK1/2 and p53 and consequent apoptosis in estrogen receptor-α (ERα) positive MCF-7, and ERα-negative MDA-MB231 cells. Resveratrol is displaced from the purified integrin by an RGD, but not RGE, peptide, and by $\alpha V\beta 3$ integrin-specific Ab. Resveratrol action is blocked by siRNA$\beta 3$, but not by siRNAαV. [^{14}C]-Resveratrol binds to commercially purified integrin $\alpha V\beta 3$ and to $\alpha V\beta 3$ prepared from MCF-7 cells; binding of [^{14}C]-resveratrol to the $\beta 3$, but not to the αV monomer, is displaced by unlabeled resveratrol	The study concluded that binding of resveratrol to integrin $\alpha V\beta 3$, principally to the $\beta 3$ monomer, is essential for transduction of the stilbene signal into p53-dependent apoptosis of breast cancer cells.	356
Investigated the effect of resveratrol on cell fate in immortalized human keratinocytes HaCaT cells.	The results indicated that resveratrol potentiates the production of significant amounts of 8-oxo-7,8-dihydro-2′-deoxyguanosine in UVA-irradiated genomic DNA. Moreover, the combination of resveratrol with UVA significantly enhanced the induction of DNA strand breaks and cell death in HaCaT keratinocytes.	The conclusion is a potential hazardous effect of topical application of resveratrol, particularly on regions exposed to sunlight.	357
Investigated the mechanism of the antiproliferative effect of resveratrol in A431-transformed keratinocytes harbouring mutant p53.	The research group showed that resveratrol in A431-transformed keratinocytes harbouring mutant p53 was accompanied by G_1 cell cycle arrest, which coincides with a marked inhibition of G_1 cell cycle regulatory proteins, including cyclins A and D_1 and cyclin-dependent kinase (CDK)6 and p53-independent induction of p21WAF1. Cell cycle arrest was also associated with the accumulation of hypophosphorylated Rb and p27KIP1. Resveratrol inhibited mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK)1 > extracellular signal-regulated protein kinase (ERK)1/2 signalling, downregulated c-Jun, and suppressed activating protein (AP)-1 DNA-binding and promoter activity. In addition, the inhibition of MEK1 > ERK1/2 signaling appears to be independent of retinoblastoma protein (pRb) hypophosphorylation in A431 cells, as PD098059 did not suppress pRb phosphorylation.	The results demonstrated that resveratrol affects multiple cellular targets in A431 cells, and that the downregulation of both AP-1 and pRb contributes to its antiproliferative activity in these cells.	358
Evaluated the chemopreventive/ antiproliferative potential of resveratrol against prostate cancer and its mechanism of action.	Treatment with resveratrol (0–50 μmol/L for 24 h) resulted in a significant decrease in cell viability, decrease of clonogenic cell survival, inhibition of androgen (R1881)-stimulated growth, and induction of apoptosis in androgen-responsive human prostate carcinoma (LNCaP) cells. Interestingly, at similar concentrations, resveratrol treatment did not affect the viability or rate of apoptosis in normal human prostate epithelial cells. Furthermore, the data showed that resveratrol-treatment resulted in significant dose-dependent inhibition in the constitutive expression of phosphatidylinositol 3′-kinase and phosphorylated (active) Akt in LNCaP cells. Resveratrol treatment for LNCaP cells was also found to result in a significant loss of mitochondrial membrane potential, inhibition in the protein level of antiapoptotic Bcl-2, and increase in proapoptotic members of the Bcl-2 family, i.e., Bax, Bak, Bid, and Bad.	The data suggested that resveratrol causes an inhibition of phosphatidylinositol 3′-kinase/Akt activation that, in turn, results in modulations in Bcl-2 family proteins in such a way that the apoptosis of LNCaP cells is promoted. Based on these studies, it is suggested that resveratrol could be developed as an agent for the management of prostate cancer.	359
Explored the SAR of resveratrol-related *trans*-stilbene derivatives.	Synthesized a series of 3,5-dimethoxy analogues in which a variety of substituents were introduced at positions 2′, 3′, 4′, and 5′ of the stilbene scaffold, and a second group of derivatives (2-phenylnaphthalenes and terphenyls) that incorporate a phenyl ring as a bioisosteric replacement of the stilbene alkenyl bridge. The new compounds were thoroughly characterized with respect to their apoptosis-inducing activity and their effects on the cell cycle. One of the new derivatives, 13g, behaved differently from the others, as it was able to block the cell cycle in the G_0-G_1 phase and also to induce differentiation in acute myelogenous leukemia HL60 cells.	The study showed that compared to resveratrol, the synthetic terphenyl 13 g showed a more potent apoptotic and differentiating activity. Moreover, it was active on both multidrug resistance and Bcr-Abl–expressing cells that were resistant to resveratrol.	360

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the protective effect of resveratrol on β-amyloid-induced cytoxicity in cultured rat astroglioma C6 cells.	Preincubation of C6 cells with resveratrol concentration-dependently protected the cells from the growth inhibition induced by β-amyloid treatment. β-Amyloid treatment led to increased nitric oxide (NO) synthesis and inducible nitric oxide synthase (iNOS) expression; however, cells pretreated with resveratrol showed a dose-dependent inhibition of NO production and iNOS expression following β-amyloid treatment. Resveratrol also attenuated β-amyloid-induced prostaglandin E2 (PGE2) release, which was associated with the inhibition of cyclooxygenase (COX)-2 expression. Furthermore, β-amyloid treatment induced nuclear translocation of nuclear factor-κB (NF-κB), which was suppressed by resveratrol pretreatment.	These results indicated that modulation of NF-κB activity is involved in the neuroprotective action of resveratrol against NF-κB-amyloid-induced toxicity.	361
Investigated the effects of resveratrol on the proliferation, apoptosis, mitochondrial membrane potential, and cell morphology of human liver cancer cell line HepG2.	Evaluated by MTT assay the changes in HepG2 cell growth and proliferation in response to resveratrol treatment, and resveratrol-induced apoptosis of HepG2 cells was investigated by flow cytometry. Inverted microscope and electron microscope were employed for observing morphological changes of the treated cells. The whole-cell mitochondrial membrane potential was measured in separate experiments using two fluorimetric probes, rhodamine123 and TMRE, respectively. HepG2 cells treated with rhodamine123 were analyzed by flow cytometry and cells treated with TMRE by confocal microscope. The MTT assay showed that low concentrations of resveratrol produced no significant effect on the growth of HepG2 cells, whereas at high concentrations, resveratrol could obviously inhibit the cell growth in a time- and dose-dependent manner. Resveratrol also induced apoptosis of HepG2 cells, and after a 24-hour treatment, resveratrol caused sharp increment of the mitochondria membrane potential.	Resveratrol is capable of inhibiting the proliferation of HepG2 cells and inducing cell apoptosis by depolarizing mitochondrial membrane potential.	362
Investigated several synthesized resveratrol derivatives to determine if these show higher efficacy than resveratrol as an anticancer agent. Used PC-3 and LNCaP human prostate cancer cells.	Compounds C, F, and G evidenced higher inhibitory activity than resveratrol with regard to the growth of PC-3 and LNCaP human prostate cancer cells. Moreover, four derivatives of resveratrol evidenced potent growth inhibitory activity (IC_{50} 0.01–0.04 μM) in LNCaP cells. The levels of activity in these derivatives were 25–100 times stronger than that associated with resveratrol (IC_{50} 1.0 μM).	The results suggested that compounds C, D, F, and G might function as anticancer agents on prostate tumors. This study also contains a discussion regarding the structure-activity relationships of several resveratrol derivatives.	363
Investigated the mechanism of resveratrol-induced apoptosis upstream of mitochondria.	The results from this study suggest that caspase-2 activation occurs upstream of mitochondria in resveratrol-treated cells. The upstream activation of caspase-2 is not dependent on its antioxidant property or NF-κB inhibition. The activated caspase-2 triggers mitochondrial apoptotic events by inducing conformational changes in Bax/Bak with subsequent release of cytochrome c, apoptosis-inducing factor, and endonuclease G. Caspase-8 activation seems to be independent of these events and does not appear to be mediated by classical death receptor processing or downstream caspases. Both caspase-2 and caspase-8 contribute toward the mitochondrial translocation of Bid, as neither caspase-8 inhibition nor caspase-2 inhibition could prevent translocation of Bid DsRed into mitochondria. Caspase-2 inhibitors or antisense silencing of caspase-2 prevented cell death induced by resveratrol and partially prevented processing of downstream caspases, including caspase-9, caspase-3, and caspase-8.	Studies using mouse embryonic fibroblasts deficient for both Bax and Bak indicate the contribution of both Bax and Bak in mediating cell death induced by resveratrol and the existence of Bax/Bak-independent cell death possibly through caspase-8- or caspase-2-mediated mitochondria-independent downstream caspase processing.	364

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effect of resveratrol on the expression and enzyme activity of aromatase.	By assaying on MCF-7 cells stably transfected with CYP19 (MCF-7aro cells), resveratrol inhibited the aromatase activity with an IC_{50} value of 25 μM. Kinetic analysis indicated that both competitive and noncompetitive inhibition might be involved. The administration of 10 nmol/L testosterone-a substrate of aromatase-produced a 50% increase in the MCF-7aro cell number. This cell proliferation specifically induced by testosterone was significantly reduced by 10 μM resveratrol. In addition, 50 μM resveratrol significantly reduced the CYP19-encoding mRNA abundance in SK-BR-3 cells. The transcriptional control of CYP19 gene is tissue specific, and promoter regions I.3 and II have previously been shown to be responsible for CYP19 expression in breast cancer cells. Luciferase reporter gene assays revealed that resveratrol could repress the transcriptional control dictated by the promoter regulation.	The present study illustrated that pharmacological dosage of resveratrol inhibited aromatase at both the enzyme and mRNA levels.	365
Investigated the effect of Yuccaols and resveratrol on the vascular endothelial growth factor (VEGF)-induced proliferation, migration, and PAF biosynthesis in KS cells.	The results indicated that Yuccaols (25 μM) were more effective than resveratrol (25 μM) in inhibiting the VEGF-induced KS cell proliferation. Western blot analysis revealed that Yuccaols reduced the VEGF-induced phosphorylation of p38 and p42/44, thus indicating a possible interference with the mechanism underlying the VEGF-stimulated cell proliferation. Furthermore, Yuccaols completely inhibited the VEGF-stimulated PAF biosynthesis catalyzed by the acetyl-CoA:lyso-PAF acetyltransferase and enhanced its degradation through the PAF-dependent CoA-independent transacetylase (250% of control). In addition, Yuccaol C abrogated the PAF-induced cell motility whereas Yuccaol A and Yuccaol B reduced the cell migration from 7.6 μm/h to 6.1 μm/h and 5.6 μm/h, respectively.	These results indicate that the anti-inflammatory properties attributed to *Yucca schidigera* can be ascribed to both resveratrol and Yuccaols and provide the first evidences of the anti-tumor and antiinvasive properties of these novel phenolic compounds.	366
Investigated the elucidation of the molecular mechanisms activated by resveratrol and propolis ethanol extract; using vinorelbine bitartrate, a drug widely used in prostate cancer therapy, as a reference drug.	The combined treatments between the micronutrients and vinorelbine have been studied to test a possible vinorelbine dose reduction, avoiding its side effects without altering its cytotoxic action. In this investigation, SEM and TEM analyses were performed to examine the morphological modifications induced; the observations confirmed necrotic cell features after treatment with resveratrol, and apoptotic modifications after propolis. Cell cycle progression was measured to study a correlation with p21 and p53, two well-known cell cycle checkpoints. The levels of HSP27 and HSP70, two chaperones also exerting antioxidant/antiapoptotic functions, were also analyzed. The data indicate that the two micronutrients modulate cell cycle distribution, increasing p53 levels, without the induced HSPs being able to rescue DU145 from death.	The results suggest that chemotherapy based on resveratrol and propolis, alone or in combination with vinorelbine, are potentially useful tools for prostate cancer therapy; the increase in cell cycle control and the modulation of HSPs expression reinforce this suggestion.	367

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effectiveness of resveratrol as a chemopreventive agent in the digestive tract.	Knockdown of proapoptotic Bak by RNA interference reduced the apoptotic response to a similar extent as Bax deficiency in the parental cells and completely abolished apoptosis in Bax-null cells. Notably, although negative for resveratrol-induced, mitochondria-mediated apoptosis, Bax+Bak double-deficient cells were sensitized by resveratrol to ligand-induced, death receptormediated apoptosis. Thus, in contrast to NSAIDs, resveratrol may remain effective as a proapoptotic chemopreventive as long as Bax and Bak have not both been inactivated during clonal selection.	This study reports that resveratrol efficiently provokes apoptosis in human colorectal carcinoma cells deficient for Bax, although at a reduced rate compared to the parental cells, through the activation of the mitochondrial death pathway	368
Investigated the anticancer effects of resveratrol using the following cell lines: v-Src-transformed mouse fibroblasts (NIH3T3/v-Src), human breast (MDA-MB-231), pancreatic (Panc-1), and prostate carcinoma (DU145) cell lines at the G0-G1 phase or at the S phase of human breast cancer (MDA-MB-468) and pancreatic cancer (Colo-357) cells.	This study showed that resveratrol inhibits Src tyrosine kinase activity and thereby blocks constitutive signal transducer and activator of transcription 3 (Stat3) protein activation in malignant cells. Analyses of resveratrol-treated malignant cells harboring constitutively active Stat3 reveal irreversible cell cycle arrest of v-Src–transformed mouse fibroblasts (NIH3T3/v-Src), human breast (MDA-MB-231), pancreatic (Panc-1), and prostate carcinoma (DU145) cell lines at the G0-G1 phase or at the S phase of human breast cancer (MDA-MB-468) and pancreatic cancer (Colo-357) cells, and loss of viability due to apoptosis. By contrast, cells treated with resveratrol, but lacking aberrant Stat3 activity, show reversible growth arrest and minimal loss of viability. Moreover, in malignant cells harboring constitutively active Stat3, including human prostate cancer DU145 cells and v-Src–transformed mouse fibroblasts (NIH3T3/v-Src), resveratrol treatment represses Stat3-regulated cyclin D1 as well as Bcl-xL and Mcl-1 genes, suggesting that the antitumor cell activity of resveratrol is in part due to the blockade of Stat3-mediated dysregulation of growth and survival pathways.	This study identified Src-Stat3 signaling as a target of resveratrol, further defining the mechanism of antitumor cell activity of resveratrol and raising its potential application in tumors with an activated Stat3 profile.	369
Investigated the chemopreventive activity of resveratrol against esophageal cancer using human esophageal HET-1A cells.	This study showed that time-dependent benzo[*a*]pyrene (BaP)-DNA binding was associated with upregulation of CYP1B1, but not CYP1A1, mRNA and protein in human esophageal HET-1A cells. The dietary flavonoid 5,7-dimethoxyflavone significantly inhibited B*a*P-DNA binding and downregulated B*a*P-induced CYP1B1 mRNA and protein. 3′,4′-Dimethoxyflavone was an even more potent inhibitor of CYP1B1 expression, while resveratrol had no effect.	Dietary methoxylated flavones inhibited B*a*P-induced CYP1B1 transcription in a cell-specific manner and hold promise as chemopreventive agents in esophageal carcinogenesis.	370
Investigated the molecular basis of resveratrol-evoked apoptosis in four (Bax+/, Bax/, p53+/+, and p53-/-) HCT116 colon cancer cell lines.	This study showed that resveratrol induced apoptosis in all the cells in a dose-dependent manner; however, Bax+/ and p53+/+ cells were more susceptible than their knockout counterparts (Bax/ and p53-/-, respectively). Using Bax+/ cells as a model, proteomic analysis revealed four resveratrol-responsive events: fragmentation of lamin A/C protein; increase in concentration of a more basic isoelectric variant of the ribosomal protein P0; and decrease in concentration of dUTPase as well as stathmin 1. Lamin A cleavage in response to resveratrol treatment was confirmed using Western blot analysis. Caspase-6 was activated, which was evidenced by cleavage and accumulation in active form of caspase-6 as well as upregulation of the protease activity. Resveratrol-elicited lamin A cleavage and apoptosis were entirely abrogated by the peptide inhibitors of caspase-6. Likewise, partial knockdown of caspase-6 expression using small interfering RNA resulted in significant inhibition of resveratrol-elicited lamin A cleavage and apoptosis. Furthermore, the lower apoptosis sensitivity of the knockout cells (Bax/ and p53-/-) correlated with the relatively reduced processing of caspase-6 and lamin A cleavage.	These data highlight the critical role of caspase-6 and its cleavage of lamin A in apoptotic signaling triggered by resveratrol in the colon carcinoma cells, which can be activated in the absence of Bax or p53.	371

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated estrogenic and/or antiestrogenic activity of urolithins A and B (hydroxy-6H-dibenzo[b,d]pyran-6-one derivatives) Both urolithins and other known phytoestrogens (genistein, daidzein, resveratrol, and enterolactone) were assayed to evaluate the capacity to induce cell proliferation on the estrogen-sensitive human breast cancer MCF-7 cells as well as the ability to bind to α- and β-estrogen receptors.	Both urolithins A and B showed estrogenic activity in a dose-dependent manner even at high concentrations (40 μM), without antiproliferative or toxic effects, whereas the other phytoestrogens inhibited cell proliferation at high concentrations. Overall, urolithins showed weaker estrogenic activity than the other phytoestrogens. However, both urolithins displayed slightly higher antiestrogenic activity (antagonized the growth promotion effect of 17-β-estradiol in a dose-dependent manner) than the other phytoestrogens. The IC_{50} values for the ERα and ERβ binding assays were 0.4 and 0.75 μM for urolithin A; 20 and 11 μM for urolithin B; 3 and 0.02 for genistein; and 2.3 and 1 for daidzein, respectively; no binding was detected for resveratrol and enterolactone. Urolithins A and B entered into MCF-7 cells and were metabolized to yield mainly urolithin-sulfate derivatives.	These results, together with previous studies regarding absorption and metabolism of dietary ellagitannins and ellagic acid in humans, suggest that the gut microflora metabolites urolithins are potential endocrine-disrupting molecules, which could resemble other described "enterophytoestrogens" (microflora-derived metabolites with estrogenic/antiestrogenic activity).	372
Evaluated the effect of resveratrol on the expression of ErbB2 in a human breast cancer cell line, MCF-7.	Low concentrations of resveratrol (1–10 nM) reduced the basal expression level of ErbB2 in MCF-7 cells cultured in an estrogen-free medium. When cells were cultured in a medium containing estrogen, resveratrol increased the ErbB2 protein levels in a dose-dependent manner. Resveratrol increased the luciferase reporter gene activity in cells transfected with the -756bp flanking region of the human erbB2 gene. Resveratrol increased the nuclear levels of AP-2α and AP-2γ, and the induction of the luciferase reporter gene by resveratrol was inhibited by a mutation of two AP-2 binding sites in the promoter region of the human erbB2 gene.	Blocking ERK, p38 kinase or PI3-kinase activity had no effect on the resveratrol-inducible transactivation of the erbB2 gene and the ErbB2 expression level.	373
Investigated 5,7-dimethoxyflavone (5,7-DMF) and 3′,4′-DMF, compared to resveratrol, to determine chemopreventive activity, utilizing benzo[*a*]pyrene (B*a*P) and BEAS-2B cells (human bronchial epithelial cells).	Exposure of BEAS-2B cells to [^{3}H]B*a*P (1 μM) showed increasing binding to DNA up to 72 h of exposure, about 20-fold higher than at 0.5 h exposure. B*a*P-exposure also increased both CYP1A1/1B1 and microsomal epoxide hydrolase (mEH) enzyme activities with a maximum 10-fold increase at 48 h. B*a*P induced CYP1A1 protein and mRNA levels maximally after 48 h. In contrast, although CYP1B1 mRNA was rapidly induced, its protein expression showed a very poor response. Simultaneous treatment with B*a*P and either 5,7-DMF, 3′,4′-DMF or resveratrol for 48 h inhibited B*a*P-DNA binding by $\geq$ 75%, with 3′,4′-DMF being the most effective. 5,7-DMF affected CYP1A1 mRNA levels only modestly, whereas 3′,4′-DMF was a potent inhibitor. The catalytic activity of CYP1A1/1B1 was reduced over 95% after exposure to either 5,7-DMF, 3′,4′-DMF or resveratrol, most effectively by 3′,4′-DMF. B*a*P-induced mEH activity was not affected by treatment with 5,7-DMF, but significantly inhibited by 3′,4′-DMF. In contrast, mEH activity was notably increased by resveratrol. Western blotting showed all three polyphenols dramatically reducing B*a*P-induced CYP1A1 protein expression. Both 5,7-DMF and 3′,4′-DMF demonstrated very high, about 40-fold, accumulation in BEAS-2B cells.	This study shows that B*a*P exposure results in a high level of DNA-binding in BEAS-2B cells, which is mainly mediated by induction of CYP1A1 protein, just as in the human lung. Two methoxylated dietary flavonoids with highly specific effects on B*a*P bioactivation, block this DNA binding and CYP1A1 protein expression as effectively as resveratrol, thus making them potential chemopreventive agents for B*a*P-induced lung carcinogenesis.	374

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the activity of resveratrol on human metastatic breast cancer using MCF-7 tumor cells.	Cell growth, cell cycle perturbation, and apoptosis were evaluated by Trypan blue dye exclusion assay, flow cytometric analysis, and confocal fluorescence microscopy. TRAP assay and Western blot analysis, respectively, detected levels of telomerase activity and levels of hTERT in intracellular compartments of MCF-7 cells treated with resveratrol. Resveratrol has a direct inhibitory effect on cell proliferation. The results demonstrated that the drug induces apoptosis in MCF-7 cells, in a time- and concentration-related manner. Our results also show that the growth-inhibitory effect of resveratrol on malignant cells is mainly due to its ability to induce S-phase arrest and apoptosis in association with reduced levels of telomerase activity. In particular, TRAP assay and Western blot analysis respectively showed that resveratrol treatment down-regulates the telomerase activity of target cells and the nuclear levels of hTERT, the reverse transcriptase subunit of the telomerase complex.	In this study, resveratrol showed direct antiproliferative and proapoptotic effects on the experimental breast cancer model. Studies on telomerase function and intracellular hTERT distribution point out that this agent is endowed with additional suppressive functions on critical tumor biological properties. These results support the potential role of resveratrol in chemoprevention/chemotherapy of breast cancer.	375
Investigated the ability of resveratrol to rapidly induce S phase cell cycle arrest of human malignant B cells including myeloma cells in dose- and time-dependent manners, followed by S phase cell cycle arrest through ATM/Chk pathway.	Resveratrol-induced apoptosis occurs in association with the activation of caspase-3 and the loss of mitochondrial transmembrane potentials. In addition, resveratrol induces the phosphorylation of p38 MAP kinase, and specific inhibition of p38 MAP kinase abolishes the resveratrol-induced apoptosis, indicating that activation of the p38 MAP kinase pathway is required for inducing apoptosis in malignant B cells.	These results suggest that resveratrol may have potential as a novel therapeutic agent for the patients with B cell malignancies including multiple myeloma.	376
Investigated the ability of polyphenols (in the absence of added copper) to cause DNA breakage in cells. This research group has previously shown that resveratrol-Cu(II) is capable of causing DNA degradation in cells.	Incubation of lymphocytes with neocuproine inhibited the DNA degradation confirming that Cu(I) is an intermediate in the DNA cleavage reaction. It was shown that polyphenols generate oxidative stress in lymphocytes, which is inhibited by scavengers of reactive oxygen species and neocuproine.	These results support the hypothesis that anticancer mechanism of plant polyphenols involve mobilization of endogenous copper, possibly chromatin bound copper, and the consequent prooxidant action.	377
Evaluated the effects and possible mechanism of resveratrol in enhancing radiosensitivity of human non–small cell lung cancer NCI-H838 cells.	NCI-H838 cells were irradiated with or without resveratrol pretreatment. The surviving fraction and sensitizer enhancement ratio (SER) were estimated by using a colony formation assay and linear-quadratic model. The cell-cycle distribution was evaluated by using propidium iodide staining and flow cytometry. An ELISA-based assay with immobilized oligonucleotide was performed to assess the DNA binding activity of NF-κB. Resveratrol had no direct growth-inhibitory effect on NCI-H838 cells treated for 24 h with doses up to 25 μM. Pretreatment with resveratrol significantly enhanced cell killing by radiation, with an SER up to 2.2. Radiation activated NF-κB, an effect reversed by resveratrol pretreatment. Resveratrol resulted in a decrease of cells in the G_0/G_1 phase and an increase in the S phase.	The results demonstrate that resveratrol enhances the radiosensitivity of NCI-H838 cells accompanied by NF-κB inhibition and S-phase arrest.	378

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated resveratrol to determine if it regulates cathepsin D (CD) in MCF-7, T47D (ER^+) breast cancer cells as well as in Hs578t (cancer) and MCF-10A (normal) ER cell lines.	Resveratrol (10^{-6} M) increased CD and IGF-II secretion in ER^+ but not ER cells. Resveratrol treatment (10^4 M) inhibited CD in ER^+ but not in ER cells. Transfection of ER cells with proIGF-II increased CD secretion. Resveratrol (10^{-6} M) modulates CD secretion through IGF-II while resveratrol (10^4 M) inhibits CD in ER^+ but not ER cells.	This study shows that regulation of cathepsin D by resveratrol represents a novel mechanism by which resveratrol may protect against breast cancer.	379
Investigated apurinic/apyrimidinic endonuclease-1/redox factor-1 (APE/Ref-1) and resveratrol using different melanoma cells.	APE/Ref-1 is a multifunctional protein involved in DNA base excision repair and redox regulation of many transcription factors. In different melanoma cell lines, this research group found that both nucleus and cytoplasm exhibited higher levels of Ref-1 compared with normal melanocytes. Similar increases of Ref-1 expression, detected by immunohistofluorescence, were also evident in nevi and malignant melanoma biopsies compared with normal skin, which were predominantly localized in the nucleus. Using recombinant adenovirus Adref-1, encoding full-length Ref-1, APE/Ref-1 in human melanocytes was transiently overexpressed, which protected these cells from UVB-induced apoptosis and increased foci formation in culture. Ref-1 overexpression also protected melanoma cells from cisplatin- or H_2O_2-induced apoptosis, whereas increased apoptosis was observed with Ref-1 antisense construct infection. These observations suggested that intracellular Ref-1 levels played an important role in sensitization of melanoma cells to apoptosis. Electrophoretic mobility shift assay results showed that in both cultured primary and metastatic melanomas DNA-binding activities of activator protein-1 and nuclear factor-κB (NF-κB) were significantly diminished or shifted when anti-APE/Ref-1 antibody was added to deplete APE/Ref-1 from the binding complexes. Induced NF-κB transcriptional activities were also evident after Ref-1 overexpression. Furthermore, using three-dimensional molecular structure modeling and virtual screening, this group found that resveratrol docks into a druggable pocket of Ref-1 protein.	*In vitro* studies revealed that resveratrol inhibited, in a dose-dependent manner, Ref-1-activated activator protein-1 DNA-binding activities as well as Ref-1 endonuclease activities and rendered melanoma cells more sensitive to dacarbazine treatment.	380
Investigated time-dependent effect of resveratrol. on gene and protein expression in WR-21 cells containing a mutated human c-Ha-ras oncogene.	This study demonstrated cyclic resveratrol-mediated expression of p53, mdm2, p21(cip/waf), Rb, and cyclin G at both the RNA and the protein level at <8 h. However, ras was not differentially expressed at either the RNA or the protein level. p53 was upregulated followed by p21cip/waf, then mdm2, and cyclin G, all downstream p53-activated targets. RNA transcription increased at >8 h for all genes except p53, but protein levels did not suggest uncoupling of transcription and translation. At 24 h, both p53 and Rb expression returned to baseline, suggesting collapse of DNA structure and spindle assembly checkpoints characteristic of mitotic catastrophe.	In summary, resveratrol at <8 h induced p53-mediated effects, including apoptosis and cell-cycle arrest (G2/M). However, later, it induced cell-cycle checkpoint dysfunction, indicative of mitotic catastrophe. Thus, future studies should better elucidate the temporal mechanism of the dietary bioactive agent resveratrol on cancer cells.	381

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effect of different polyphenols on the proliferation and invasive capacity of MB-49 murine bladder tumor cell lines and to identify the mediators involved in this process.	MB-49 murine bladder cancer cells were cultured in media supplemented with resveratrol, rutin, morin, quercetin, gallic acid, and tannic acid for periods of 24, 48, and 72 h to quantify the expression of urokinase-type plasminogen activator (uPA) and its receptor (uPAR) in the culture medium, as well as of metalloproteinase-9 (MMP-9) and cell proliferation. All the polyphenols studied significantly inhibited proliferation of MB-49 cells, varying according to the time periods and doses used. The cells in the media supplemented with the nutrients to study did not show inhibition of mRNA expression of urokinase-type plasminogen activator (uPA) or its high affinity receptor (uPAR). It was even slightly increased in certain cases. However, mRNA expression of metalloproteinase-9 was strongly inhibited.	These polyphenols exerted an effect on the proliferation and mediators of bladder tumor invasiveness in MB-49 cells.	382
Investigated effect of extracellular environmental stresses on glial cell proliferation using the influence of high salt culture conditions on the growth of rat C6 glioma cells.	Exposure to the culture medium containing high concentrations of NaCl reduced the number of viable cells in a concentration-dependent manner without any significant change in their viability. In contrast, proliferation of these cells was not substantially altered by culturing them in hyperosmotic medium containing either sucrose or glycerol, both of which were osmotically almost equivalent to high salt culture medium. Expression of the egr-1 gene was enhanced by culturing glioma cells in high salt medium while the reduction of glial fibrillary acidic protein content was observed under the same culture conditions. Further studies on the relationship between egr-1 gene expression and the cell cycle showed that cell-cycle progression was arrested at S-phase by culturing glioma cells in high salt medium. Moreover, both resveratrol and CPT-11 elevated egr-1 mRNA levels in glioma cells.	These observations suggest that high salt culture conditions might suppress the proliferation of rat C6 glioma cells as a consequence of arresting cell-cycle progression at S-phase, resulting secondarily in the compensatory enhancement of egr-1 gene expression.	383
Investigated the effects of resveratrol on rat adrenal steroidogenesis and to study the underlying mechanism.	Adrenocortical cells were isolated from the adrenal glands of normal male rats (*in vitro*) and from male rats administered resveratrol in their diet for 12 weeks (*ex vivo*). Cells from resveratrol-treated and nontreated rats were tested *ex vivo* for responsiveness to ACTH, and cells from normal rats were tested *in vitro* for responsiveness to ACTH in the presence and absence of resveratrol. Corticosterone and progesterone production were measured by RIA and expression of steroidogenic enzymes analyzed by PAGE/Western blotting. Corticosterone production was inhibited 47% by 50 μM resveratrol *in vitro* and 20% *ex vivo*, while progesterone production was elevated to 400% of the control value in *in vitro* experiments. Resveratrol treatment decreased adrenal cytochrome P450 c21-hydroxylase expression *in vivo* and cell culture conditions. No changes in cell viability or morphology were caused by exposure to resveratrol in both *ex vivo* and *in vitro* experiments.	This study showed that resveratrol suppresses corticosterone production by primary rat adrenocortical cell cultures *in vitro* and *ex vivo* by inhibiting cytochrome P450 c21-hydroxylase.	384

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effects of resveratrol on myeloma and bone cells using myeloma cell lines (RPMI 8226 and OPM-2).	Resveratrol reduced, dose-dependently, the growth of RPMI 8226 and OPM-2 by cell apoptosis. In cultures of human primary monocytes, resveratrol inhibited, dose-dependently, receptor activator of nuclear factor-κB (NF-κB) ligand-induced formation of tartrate-resistant acid phosphatase (TRACP)-positive multinucleated cells, TRACP activity in the medium, upregulation of cathepsin K gene expression, and bone resorption. These inhibitions are associated with a downregulation of RANK expression at both mRNA and cell surface protein levels and a decrease of NFATc1 stimulation and NF-κB nuclear translocation, whereas the gene expression of c-fms, CD14, and CD11a is upregulated. Resveratrol promoted, dose-dependently, the expression of osteoblast markers like osteocalcin and osteopontin in human bone marrow mesenchymal stem cells (hMSC-TERT) and stimulated their response to 1,25$(OH)_2$ vitamin D_3 [1,25$(OH)_2D_3$]. Moreover, resveratrol upregulated, dose-dependently, the expression of 1,25$(OH)_2D_3$ nuclear receptor.	These results suggest that resveratrol or its derivatives could be potential drugs for treating multiple myeloma.	385
Investigated the proapoptotic activity of resveratrol in human cancer cells, by triggering the accumulation of ceramide, a bioactive sphingolipid.	The biological effects of seven methoxylated and/or naphthalene-based resveratrol analogues were studied and compared them with resveratrol with the objective to identify an analogue with higher ceramide-mediated proapoptotic activity relative to resveratrol.	The compound with three hydroxyls and a naphthalene ring were the most effective in triggering apoptosis coupled to the induction of endogenous ceramide in human cancer cells.	386
Investigated the effect of resveratrol on hypoxia-induced HIF-1α protein accumulation and vascular endothelial growth factor (VEGF) expression in human tongue squamous cell carcinomas and hepatoma cells.	The studies showed that resveratrol significantly inhibited both basal level and hypoxia-induced HIF-1α protein accumulation in cancer cells, but did not affect HIF-1α mRNA levels. Pretreatment of cells with resveratrol significantly reduced hypoxia-induced VEGF promoter activities and VEGF expression at both mRNA and protein levels. The mechanism of resveratrol inhibition of hypoxia-induced HIF-1α accumulation seemed to involve a gradually shortened half-life of HIF-1α protein caused by an enhanced protein degradation through the 26S proteasome system. In addition, resveratrol inhibited hypoxia-mediated activation of extracellular signal-regulated kinase 1/2 and Akt, leading to a marked decrease in hypoxia-induced HIF-1α protein accumulation and VEGF transcriptional activation. It was observed that resveratrol also significantly inhibited the hypoxia-stimulated invasiveness of cancer cells.	These data suggested that HIF-1α/VEGF could be a promising drug target for resveratrol in the development of an effective chemopreventive and anticancer therapy in human cancers.	387

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated lymphoblastic leukemia (ALL) using resveratrol and cyclosporin A (CsA) and PK11195 which are modulators of the mitochondrial permeability transition pore (MPTP). The following cell lines were used: SEM and RS4;11 lines with the t(4;11) translocation, the B-ALL line REH, and the T-ALL line Jurkat.	This study showed that pretreatment with CsA or PK11195 significantly enhanced resveratrol-mediated apoptosis and mitochondrial membrane depolarization in these cells, as measured by annexin V and JC-1 staining, respectively. No significant multidrug resistance efflux of the fluorescent substrate calcein was observed in these ALL lines, indicating that CsA and PK11195 were acting at the level of the mitochondria to enhance loss of mitochondrial membrane potential and induction of apoptosis.	These data suggest targeting the MPTP sensitizes B- and T-cell ALL to the anticancer activity of resveratrol, and may be particularly useful for the treatment of high-risk t(4;11) ALL.	388
Investigated the effect of resveratrol, quercetin, catechin and epicatechin in the hormone-sensitive human cancer cell line T47D, at concentrations compatible with their calculated plasma concentrations after ingestion of a moderate quantity of wine (nM or pM).	The results indicated that cell growth was decreased, with cells being arrested at the S phase of the cycle. In addition, The study showed a bimodal modulation of the NO/NOS system, affecting its activity and transcription. The research showed that modulation of this system is sufficient to explain polyphenol action on this cell line.	This result suggests a potential importance of wine ingestion and possibly the consumption of other polyphenol-rich dietary foods and drinks in the control of breast cancer cell growth.	389
Investigated genistein, daidzein, apigenin, coumestrol, equol, naringenin, kaempferol, daidzein, and resveratrol for their ability to transactivate ERα or ERβ at a range of doses using mammary adenocarcinoma (MCF-7) cells.	MCF-7 cells were co-transfected with either ERα or ERβ, and an estrogen-response element was linked to a luciferase reporter gene. Dose-dependent responses were compared with the endogenous ligand 17β-estradiol. Purified genistein, daidzein, apigenin, and coumestrol showed differential and robust transactivation of ERα- and ERβ-induced transcription, with an up to 100-fold stronger activation of ERβ. Equol, naringenin, and kaempferol were weaker agonists. When activity was evaluated against a background of 0.5 nM 17β-estradiol, the addition of genistein, daidzein, and resveratrol superstimulated the system, while kaempferol and quercetin were antagonists at the highest doses.	This study showed that the transfection assay is an excellent model to evaluate the activation of ERα and ERβ by different phytoestrogens in a breast cancer context and can be used as a screening bioassay tool to evaluate the estrogenic activity of extracts of herbs and foods.	390
Investigated the ability of ascorbic acid, epigallocatechin gallate, genistein, quercetin, naringenin, and resveratrol to modulate the activity of the transcription factor nuclear factor κB (NF-κB) using a cell-based reporter system. The cell lines used were HCT 116 (human colon carcinoma) and HepG2 (human liver carcinoma).	HCT 116 and HepG2 cell lines were stably transfected with a NF-κB luciferase reporter vector. The reporter cell lines were preincubated with different concentrations (0–50 μM) of ascorbic acid, epigallocatechin gallate, genistein, quercetin, naringenin, and resveratrol for varying periods of times (1–12 h), after which the NF-κB inducer tumor necrosis factor-α (TNF-α) was added (4–8 ng/mL) for 4 h. Compound alone, without TNF-α, did not alter luciferase activity. Levels of TNF-α–induced NF-κB activity varied depending on compound type and concentration, whereas preincubation time and cell type contributed less. Significant changes in NF-κB activity were detected for some of the compounds at more physiological concentrations (1–10 μM).	These data suggest that dietary modulation of NF-κB activity involves distinct mechanisms, depending on compound type and concentration. More generally, this approach can be utilized for analyzing dietary compounds for effects on specific cellular factors over a range of concentrations and incubation times, in combination, and in different cell types.	391

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the activity of resveratrol on proliferation and differentiation of the acute promyelocytic leukemia cell line NB4.	The growth inhibitory properties of resveratrol appeared to be due to its induction of apoptotic cell death, as determined by morphological changes, DNA fragmentation, increased proportion of the subdiploid cell population and decreased mitochondrial transmembrane potential ($\delta\psi^m$). Colorimetric assay for activity of caspase-3 showed an obvious increase in caspase-3 activity in cells after treatment with resveratrol. However, the expression levels of protein Bcl-2 and Bax show no significant change in response to resveratrol treatment. These results suggest that apoptosis of NB4 cells induced by resveratrol requires caspase-3 activation and is related to the mitochondrial transmembrane potential. The combination of resveratrol and all-*trans*-retinoic acid (ATRA) induced 100% of the NB4 cells to become NBT-positive, whereas only a small part of cells became positive for NBT after a similar exposure to either resveratrol or ATRA alone	This study showed that resveratrol may be useful in treating acute promyelocytic leukemia.	392
Investigated the effect of increasing benzo(*a*)pyrene concentrations on COX-II expression, prostaglandin (PGE^2) output, and invasion using MDA-MB-231 cells, an invasive estrogen unresponsive breast cancer cell line.	Benzo(*a*)pyrene significantly increased invasion in MDA-MB-231 cells at concentrations greater than 4×10^{-8} M. Treatment of MDA-*M*B-231 cells with Vomitoxin enhanced invasion whereas co-treatment with attenuated benzo(*a*)pyrene-induced invasion in MDA-MB-231 cells. Immunohistochemical staining and Western blots demonstrated a significant benzo(*a*)pyrene treatment-induced increase in both the number of COX-II immunopositive MDA-MB-231 cells and COX-II protein levels. Moreover, benzo(*a*)pyrene treatment induced a profound (46-fold) increase in PGE_2 production by MDA-MB-231 cells. The aryl hydrocarbon receptor (AhR) antagonists resveratrol and α-naphthaflavone (α-NF) had no effect on their own, whereas benzo(*a*)pyrene-induced invasion was significantly inhibited by cotreatment with resveratrol and α-NF.	These data demonstrate that benzo(*a*)pyrene-induced changes in invasion are mediated through augmented COX-II expression and PGE_2 production involving an AhR regulated pathway. Moreover, these results suggest a potential role for the AhR signaling pathway in breast cancer invasion.	393
Investigated the expression of inflammatory cytokine mRNAs during the transformation process induced by chronic As exposure in non-tumorigenic human osteogenic sarcoma (N-HOS) cells using gene arrays, and results were confirmed by RT-PCR and protein arrays.	Caffeic acid phenethyl ester (CAPE), a naturally occurring immunomodulating agent, was used to evaluate the role of inflammatory factors in the process of As-mediated N-HOS cell transformation and in As-transformed HOS (AsT-HOS) cells. It was found that an 8-week continuous exposure of N-HOS to 0.3 μM arsenite resulted in HOS cell transformation. That exposure also caused substantial decreases in inflammatory cytokine mRNAs, such as interleukin (IL) IL-1α, IL-2, IL-8, IL-18, MCP-1, TGF-β2, and TNF-α, while it increased c-jun mRNA in a time-dependent manner. Co-incubation of N-HOS with As and CAPE (0.5–2.5 μM) prevented As-mediated declines in cytokine mRNAs in the cotreated cells, as well as their transformation to anchorage independence, while it caused decreases in c-jun mRNA. CAPE (up to 10 μM) had no effect on growth of N-HOS cells. However, CAPE (1–10 μM) treatment of AsT-HOS cells inhibited cell growth, induced cell cycle G2/M arrest, and triggered apoptosis, accompanied by changes in cytokine gene expression, as well as decreases in cyclin B1 and cdc2 abundance. Resveratrol and (-) epigallocatechin gallate (EGCG) induced similar changes in AsT-HOS cell growth but required much higher doses than CAPE to cause 50% growth arrest (<2.5 μM CAPE versus 25 μM RV or 50 μM EGCG).	The study suggests that inflammatory cytokines play an important role in the suppressive effects of CAPE on As-induced cell transformation and in the selective cytotoxicity of CAPE to As-transformed HOS cells.	394

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effect of resveratrol on the expression of genes and proteins involved in the extracellular matrix remodeling associated with tumor invasion in human cultured glioblastoma cells using RT-PCR, Western blot and SDS-zymography.	Human cultured glioblastoma cells were treated for 24, 48, and 72 h. Then, analyzed the expression of matrix metalloproteinase-2 (MMP-2) and the Secreted Protein Acidic and Rich in Cysteine (SPARC), involved in the regulation of cell-matrix interactions. The results showed a dose-related decrease of MMP-2 mRNA and protein levels 72 h after resveratrol treatment, and lower SPARC gene and protein expression 72 h after resveratrol treatment.	Resveratrol may influence the two major factors in the ECM remodeling occurring with tumor invasion, suggesting it may have uses as a therapeutic agent for brain tumors.	395
Investigated the modulation of genes, Ras and p53, to test the effect of resveratrol on gene expression, using WR-21 cell line because it contains a mutated human c-Ha-ras gene.	Cells at $\geq$70% confluency were incubated with media alone or with increasing concentrations of *trans*-resveratrol (0.1–1000 μM) for 24 h. Resveratrol (30-100 μM) decreased cellular proliferation by 80% (bromodeoxyuridine incorporation) and increased apoptosis by 60% (TUNEL). Cells were then treated with media alone or with 50 μM resveratrol for 24 h. RNA was isolated for nylon-based macroarray analyses and protein for immunoblotting. Resveratrol increased (+) and decreased (-) gene expression associated with apoptosis (Birc5+, Cash+, Mcl-1+, Mdm2+, Rpa-like+), cellular proliferation (Ctsd+, Mdm2+, Egr1+, ODC+) and cell cycle (cyclin D+, cyclin g+, Gadd45a-, Mad2l-, Mdm2+). Resveratrol consistently increased by $\geq$6-fold Mdm2 expression and other downstream p53 effectors, but not p53 itself at 24 h. Subsequent cell cycle analysis indicated a significant accumulation of cells in G2/M, and a decrease in G_1/G_0 suggesting a G_2/M blockade. Further RT-PCR and Western blot analyses indicated no differential changes in Ras mRNA expression or $p21^{ras}$ protein levels, respectively.	These results suggest that resveratrol potently inhibits cellular proliferation, increases apoptosis, alters cell cycle dynamics and modulates associated gene expression. Furthermore, these effects appear mediated, in part, by p53 without direct modulation of mutant c-Ha-ras expression.	396
Investigated whether resveratrol modulates IGF-II (potent mitogen and inhibitor of apoptosis in breast cancer) in breast cancer cells (MCF-7 and T47D), regulation of IGF-II by resveratrol is dependent on the ER status; IGF-II mediates resveratrol effects on breast cancer cells.	Treatment of MCF-7 and T47D cells with resverarol (10^{-6} M) caused stimulation of precursor IGF-II mRNA and protein; this effect was blocked by coincubation with 17β-estradiol (10^{-9} M). Cell growth stimulated by resveratrol (10^{-6} M) was blocked by addition of a blocking IGF-I receptor antibody, or the antiestrogen tamoxifen (10^{-7} M). In contrast, resveratrol treatment (10^{-4} M) inhibited IGF-II secretion and cell growth in MCF-7 and T47D cells. No increase in IGF-II levels is seen in estrogen receptor (-) MCF-10 cells, even though cell growth was inhibited by resveratrol 10^{-4} M and precursor IGF-II blocked the inhibitory effect of resveratrol. No change in IGF-I was observed with resveratrol treatment (10^{-6} to 10^{-4} M).	The study demonstrates that resveratrol regulates IGF-II and that IGF-II mediates resveratrol effect on cell survival and growth in breast cancer cells.	397

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effects and possible mechanism(s) of action of resveratrol on human embryonal rhabdomyosarcoma (RD) cells.	This study showed that resveratrol inhibited cell proliferation of RD cells in a dose-dependent manner with an IC_{50} of 48.1 μmol/l and induce an arrest in the S/G_2 phase of the cell cycle. As evident from immunocytochemical data, resveratrol treatment increased the size of the RD cells. Furthermore, resveratrol treatment resulted in a significant downregulation of cyclin B expression as demonstrated by Western blot analyses. This study shows that resveratrol exerts a strong inhibition of rhabdomyosarcoma cell proliferation in part by arresting cells in S/G_2 phase of the cell cycle.	These findings warrant further investigation to establish potential use of resveratrol as a relatively nontoxic chemotherapeutic agent for the treatment of rhabdomyosarcoma.	398
Investigated the effects of resveratrol on the growth of weakly metastatic Line IV clone 3 and on autologous, highly metastatic Line IV clone 1 cultured melanoma cells.	Comparable inhibition of growth and colony formation resulted from treatment by resveratrol in both cell lines. Flow cytometric analysis revealed that resveratrol-treated clone 1 cells had a dose-dependent increase in S phase and a concomitant reduction in the G_1 phase. No detectable change in cell cycle phase distribution was found in similarly treated clone 3 cells. Western blots demonstrated a significant increase in the expression of the tumor suppressor gene p53, without a commensurate change in p21 and several other cell cycle regulatory proteins in both cell types. Chromatography of Line IV clone 3 and clone 1 cell extracts on resveratrol affinity columns revealed that the basal expression of dihydronicotinamide riboside quinone reductase 2 (NQO2) was higher in Line IV clone 1 than clone 3 cells. Levels of NQO2 but not its structural analog NQO1 were dose-dependently increased by resveratrol in both cell lines.	These studies suggest induction of NQO2 may relate to the observed increased expression of p53 that, in turn, contributes to the observed suppression of cell growth in both melanoma cell lines.	399
Investigated the effects of apigenin, kaempferol and resveratrol on the synthesis of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) at transcriptional level in lipopolysaccharide (LPS)-stimulated J774.2 macrophages.	Apigenin (30 μM), kaempferol (30 μM) and resveratrol (50 μM) significantly decreased the number of TNF-α mRNA copies in LPS-activated J774.2 macrophages. Apigenin and kaempferol caused inhibition of IL-1β gene expression in J774.2 macrophages, but resveratrol was ineffective.	These results indicate that apigenin, kaempferol, and resveratrol exert inhibitory effects on the TNF-α and except for of resveratrol on IL-1 β gene expression in J774.2 macrophages at the transcriptional level. In addition, these compounds may be the mediators responsible for protective role of a diet high in fruits and vegetables in the cardiovascular and inflammatory diseases.	400
Investigated how resveratrol induces S phase arrest via Tyr15 phosphorylation of Cdc2 in human ovarian carcinoma Ovcar-3 cells.	Overexpression of Cdc2AF, a mutant resistant to Thr14 and Tyr15 phosphorylation, ablated resveratrol-induced S phase arrest. The research group observed that resveratrol causes phosphorylation of cell division cycle 25C (Cdc25C) tyrosine phosphatase via the activation of checkpoint kinases Chk1 and Chk2, which in turn were activated via ATM (ataxia telangiectasia mutated)/ATR (ataxia telangiectasia-Rad3-related) kinase in response to DNA damage, as resveratrol also increased phospho-H2A.X (Ser139), which is known to be phosphorylated by ATM/ATR in response to DNA damage. The involvement of these molecules in resveratrol-induced S phase was also supported by the studies showing that addition of ATM/ATR inhibitor caffeine reverses resveratrol-caused activation of ATM/ATR-Chk1/2 as well as phosphorylation of Cdc25C, Cdc2 and H2A.X, and S phase arrest. In additional studies assessing whether observed effects of resveratrol are specific to Ovcar-3 cells, the group observed that it also induces S phase arrest and H2A.X (Ser139) phosphorylation in other ovarian cancer cell lines PA-1 and SKOV-3, albeit at different levels; whereas, resveratrol showed only marginal S phase arrest in normal human foreskin fibroblasts with undetectable level of phospho-H2A.X (Ser139).	These findings demonstrate that resveratrol causes Cdc2-tyr15 phosphorylation via ATM/ATR-Chk1/2-Cdc25C pathway as a central mechanism for DNA damage and S phase arrest selectively in ovarian cancer cells, and provide a rationale for the potential efficacy of ATM/ATR agonists in the prevention and intervention of cancer.	401

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated resveratrol using a cellular system of lymphocytes isolated from human peripheral blood and Comet assay.	This study showed that resveratrol-Cu^2 system is capable of causing DNA degradation in cells such as lymphocytes. Also, *trans*-stilbene, which does not have any hydroxyl groups, is inactive in the lymphocyte system. Pre-incubation of lymphocytes with resveratrol indicates that it is capable of either traversing the cell membrane or binding to it.	The results support the hypothesis that anticancer properties of various plant derived polyphenols may involve mobilization of endogenous copper and the consequent prooxidant action.	402
Investigated the roles of CYP1A1 and 1B1 in tobacco smoke carcinogen, e.g. benzo[*a*]pyrene, induced DNA binding and their inhibition by 5,7-dimethoxyflavone (DMF), compared with 3′,4′-dimethoxyflavone (3′,4′-DMF) and resveratrol using human oral epithelial squamous cell carcinoma (SCC)-9 cells.	A low concentration of benzo[*a*]pyrene (1 μM) dramatically induced benzo[*a*]pyrene-DNA adduct formation (approximately 40-fold) in a time-dependent manner, while it only increased CYP1A1/1B1 activities, as measured by ethoxyresorufin *O*-deethylation, approximately 3-fold. Furthermore, benzo[*a*]pyrene induced both CYP1B1 and CYP1A1 mRNA and protein expression, as determined by the branched DNA assay and Western blot analysis, but with considerably higher levels of CYP1B1. Combined treatment of SCC-9 cells with 1 μM benzo[*a*]pyrene and 20 μM DMF inhibited benzo[*a*]pyrene-DNA adduct formation. The mechanism of this effect appeared to be direct inhibition of CYP1B1 enzyme with a K; value of 0.58 μM, a highly potent inhibition considering the high cellular uptake of DMF in the SCC-9 cells. DMF also inhibited CYP1A1, but not CYP1B1 protein, and mRNA expression in the cells. In an extension to other polyphenols, the structural analogue 3′,4′-DMF, in contrast to DMF, inhibited the expression of CYP1B1 both at the mRNA and protein levels. Resveratrol had no effect on CYP1B1 in the SCC-9 cells.	Based on this study, CYP1B1 mRNA may be an early biomarker of oral cancer, being a sensitive signal for tobacco-carcinogen exposure. Methoxylated dietary flavonoids, e.g., DMF and 3′,4′-DMF, may be potent chemoprotectants by direct inhibition of CYP1B1/1A1 function and/or their protein expression.	403
Investigated how activating transcription factor 3 (ATF3) mRNA and protein expression are up-regulated in HCT-116 human colorectal cancer cells following treatment with NSAIDs, troglitazone, diallyl disulfide, and resveratrol.	Overexpressed full-length ATF3 protein in the sense and antisense orientations. Overexpression of ATF3 in the sense orientation decreased focus formation *in vitro* and reduced the size of mouse tumor xenografts by 54% *in vivo*. Conversely, overexpression of antisense ATF3 was protumorigenic *in vitro*, however, not *in vivo*. ATF3 in the sense orientation did not modulate apoptosis, indicating another mechanism is involved. With microarray analysis, several genes relating to invasion and metastasis were identified by ATF3 overexpression and were confirmed by real-time reverse transcription-PCR, and several of these genes were modulated by sulindac sulfide, which inhibited invasion in these cells. Furthermore, overexpression of ATF3 inhibited invasion to a similar degree as sulindac sulfide treatment, whereas antisense ATF3 increased invasion.	In conclusion, ATF3 represents a novel mechanism in which NSAIDs exert their anti-invasive activity, thereby linking ATF3 and its gene regulatory activity to the biological activity of these compounds.	404

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effects of resveratrol and the potential correlation of CYP1A1 and CYP1B1 expression in human medulloblastoma cells (UW228-3).	UW228-3 were treated with CYP1A1 selective inhibitor (α-naphthoflavone, α-NF), selective CYP1A1/1A2 inducer (β-naphthoflavone, β-NF), and their combination with resveratrol, respectively. The influences of those treatments on the expressions of CYP1A1, 1A2 and 1B1 as well as the cell growth, differentiation and death were analyzed. It was found that neither α-NF nor β-NF had any effect on cell growth. α-NF inhibited resveratrol-induced CYP1A1 expression without interfering cell differentiation and apoptosis. β-NF could upregulate resveratrol-induced CYP1A1 expression but not enhance the anticancer effects of resveratrol. CYP1A2 was undetectable in the cells irrespective to the treatments. Aryl hydrocarbon receptor (AhR) was absent in UW228-3 cells under normal culture and treated with resveratrol but induced by both α- and β-NF. Immunohistochemical examination performed on 11 pairs of human medulloblastoma and noncancerous cerebellar tissues revealed that AhR was undetectable in either of them, whereas CYP1A1 was expressed in cerebellum but downregulated or diminished in their malignant counterparts.	These data suggest that CYP1A1 and 1B1 expression in human medulloblastoma cells are AhR-independent and have no direct links with resveratrol-induced differentiation and apoptosis. Appearance of CYP1A1 expression may reflect a more maturated status and a better prognosis of medulloblastomas.	405
Investigated the ability of various compounds to activate PXR-mediated transcription using HuH7 cells following transient transfection with human PXR (hPXR).	The pregnane X receptor (PXR) mediates the induction of enzymes involved in steroid metabolism and xenobiotic detoxification. The receptor is expressed in liver and intestinal tissues and is activated by a wide range of compounds. The ability of a diverse range of dietary compounds to activate PXR-mediated transcription was assayed in HuH7 cells following transient transfection with human PXR (hPXR). The compounds investigated included phytochemicals such as lignans and phytoestrogens, organochlorine dietary contaminants such as polychlorinated biphenyls (PCBs) and triclosan and selected steroid, drug and herbal compounds. The hPXR activation at the top concentrations tested (10 μM) relative to the positive control 10 μM rifampicin ranged from 1.3% (*trans*-resveratrol) to 152% (ICI 182780). Hydroxylated compounds were marginally more potent than the parent compounds (tamoxifen activation was 74.6% whereas 4 hydroxytamoxifen activation was 84.2%) or significantly greater (vitamin D_3 activation was 1.6%, while hydroxylated vitamin D_3 activation was 55.6%). Enterolactone, the metabolite of common dietary lignans, was a medium activator of PXR (35.6%), compared to the lower activation of a parent lignan, secoisolariciresinol (20%). Two non-hydroxylated PCB congeners (PCB 118 and 153), which present a larger fraction of the PCB contamination of fatty foods, activated hPXR by 26.6% and 17%, respectively. The pesticide *trans*-nonachlor activation was 53.8%, while the widely used bacteriocide triclosan was a medium activator of hPXR at 46.2%.	The responsiveness of PXR to activation by lignan metabolites suggests that dietary intake of these compounds may affect the metabolism of drugs that are CYP3A substrates. Additionally, the evidence that organochlorine chemicals, particularly triclosan, activate hPXR suggests that these environmental chemicals may, in part, exhibit their endocrine disruptor activities by altering PXR-regulated steroid hormone metabolism with potential adverse health effects in exposed individuals.	406

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the ability of pterostilbene and 3,5-hydroxypterostilbene (natural 3,5-dimethoxy analogs of *trans*-resveratrol and piceatannol) in inducing apoptosis in sensitive and resistant leukemia cells (HL60 and HUT78), Fas-ligand resistant lymphoma cell lines (HUT78B1 and HUT78B3), and the multi drug-resistant leukemia cell lines (HL60-R and K562-ADR, a Bcr-Abl-expressing cell line resistant to imatinib mesylate).	When tested in HL60 and HUT78, 3′-hydroxypterostilbene was 50–97 times more potent than *trans*-resveratrol in inducing apoptosis, while pterostilbene appeared barely active. However, both compounds, but not *trans*-resveratrol and piceatannol, were able to induce apoptosis in HUT78B1, HUT78B3, HL60-R and K562-ADR. Of note, pterostilbene-induced apoptosis was not inhibited by the pancaspase-inhibitor Z-VAD-fmk, suggesting that this compound acts through a caspase-independent pathway. On the contrary, 3′-hydroxypterostilbene seemed to trigger apoptosis through the intrinsic apoptotic pathway: indeed, it caused a marked disruption of the mitochondrial membrane potential $\delta\psi$ and its apoptotic effects were inhibited by Z-VAD-fmk and the caspase-9-inhibitor Z-LEHD-fmk. Moreover, pterostilbene and 3′-hydroxypterostilbene, when used at concentrations that elicit significant apoptotic effects in tumor cell lines, did not show any cytotoxicity in normal hemopoietic stem cells.	The data show that pterostilbene and particularly 3′-hydroxypterostilbene are interesting antitumor natural compounds that may be useful in the treatment of resistant hematological malignancies, including imatinib nonresponsive neoplasms.	407
Compared the estrogen agonist and antagonist activity of eight phytoestrogens (genistein, daidzein, equol, miroestrol, deoxymiroestrol, 8-prenylnaringenin, coumestrol and resveratrol) in a range of assays all based within the same receptor and cellular context of the MCF7 human breast cancer cell line.	The relative binding of each phytoestrogen to estrogen receptor (ER) of MCF7 cytosol was calculated from the molar excess needed for 50% inhibition of [^{3}H]estradiol binding (IC_{50}), and was in the order coumestrol (35×)/8-prenylnaringenin (45×)/deoxymiroestrol (50×)>miroestrol (260×)>genistein (1000×)>equol (4000×)>daidzein (not achieved: 40% inhibition at 10^4-fold molar excess)>resveratrol (not achieved: 10% inhibition at 10^5-fold molar excess). For cell-based assays, the rank order of potency [estimated in terms of the concentration needed to achieve a response equivalent to 50% of that found with 17β-estradiol (IC_{50})] remained very similar for all the assays whether measuring ligand ability to induce a stably transfected estrogen-responsive ERE-CAT reporter gene, cell growth in terms of proliferation rate after 7 days or cell growth in terms of saturation density after 14 days. The IC_{50} values for these three assays in order were for 17β-estradiol (1×10^{-11}M, 1×10^{-11}M, 2×10^{-11}M), and in rank order of potency for the phytoestrogens, deoxymiroestrol (1×10^{-10}M, 3×10^{-11}M, 2×10^{-11}M)> miroestrol (3×10^{-10}M, 2×10^{-10}M, 8×10^{-11}M)>8-prenylnaringenin (1×10^{-9}M, 3×10^{-10}M, 3×10^{-10}M)>coumestrol (3×10^{-8}M, 2×10^{-8}M, 3×10^{-8}M) >genistein (4×10^{-8}M, 2×10^{-8}M, 1×10^{-8}M)/equol (1×10^{-7}M, 3×10^{-8}M, 2×10^{-8}M)>daidzein (3×10^{-7}M, 2×10^{-7}M, 4×10^{-8}M)>resveratrol (4×10^{-6}M, not achieved, not achieved).	Despite using the same receptor context of the MCF7 cells, this rank order differed from that determined from receptor binding. The most marked difference was for coumestrol and 8-prenylnaringenin which both displayed a relatively potent ability to displace [^{3}H]estradiol from cytosolic ER compared with their much lower activity in the cell-based assays. Albeit at varying concentrations, seven of the eight phytoestrogens (all except resveratrol) gave similar maximal responses to that given by 17β-estradiol in cell-based assays, which makes them full estrogen agonists. No evidence was found for any estrogen antagonist action of any of these phytoestrogens at concentrations of up to 10^{-6}M on either reporter gene induction or on stimulation of cell growth.	408

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effects of resveratrol on the steady-state free radical (FR) concentration and mode of cell death induced by the histone deacetylase inhibitors butyrate and trichostatin A.	The study showed that there was no correlation between cell death induction by butyrate or trichostatin A (TSA) and FR levels. Treatment with resveratrol or *N*-acetyl-L-cysteine (NAC) of cells, in which the FR concentration was high, resulted in an almost complete reduction of FR levels. When, however, the cellular FR concentration was marginal, resveratrol caused a minor, and NAC a marked increase of FRs as well as of the extent of cell death. Thus, resveratrol and NAC acted as antioxidants only when the cellular FR levels were high, and acted as pro-oxidants when facing a low FR concentration. Because resveratrol and the antioxidant NAC exhibited analogous effects, it is concluded that the observed actions of resveratrol are due to polyphenolic redox reactions and not related to the stilbene moiety of the molecule.	The results indicate that the redox status of a given cell type plays an important role in determining whether resveratrol and other antioxidants promote cell death or protect cells from it.	409
Investigated the hypothesis that phytoestrogen exposure regulates PTEN protein expression in the breast cancer cell line, MCF-7.	When MCF-7 cells were stimulated with resveratrol, quercetin or genistein, there was an increase in PTEN protein levels. Concomitantly, phytoestrogen stimulation resulted in decreased Akt phosphorylation and an increase in p27 protein levels, indicating active PTEN lipid phosphatase activity. In contrast, it was found that MAPK phosphorylation and cyclin D1 levels, which are regulated by PTEN's protein phosphatase activity, were not altered. Using semiquantitative RT-PCR, the research group found that mRNA levels were slightly increased in cells stimulated by phytoestrogens, suggesting that the mechanism for increased PTEN protein expression is dependent upon transcription.	The data provide evidence that a mechanism for protective nature of phytoestrogens is partially through increased PTEN expression. More importantly, it provides a novel target for the regulation of PTEN expression and suggests that dietary changes may be adjunctive to traditional preventive and therapeutic strategies against breast cancer.	410
Investigated resveratrol using human glioma U251 cells to understand the molecular mechanisms by which resveratrol acts as an anticancer agent, as glioma is a particularly difficult cancer to treat and eradicate.	The data show that resveratrol induces dose- and time-dependent death of U251 cells, as measured by lactate dehydrogenase release and internucleosomal DNA fragmentation assays. Resveratrol induced activation of caspase-3 and increased the cleavage of the downstream caspase substrate, poly(ADP-ribose) polymerase. Resveratrol-induced DNA fragmentation can be completely blocked by either a general caspase inhibitor (Z-VAD-FMK) or a selective caspase-3 inhibitor (Z-DEVD-FMK), but not by a selective caspase-1 inhibitor. Resveratrol induced cytochrome c release from mitochondria to the cytoplasm and activation of caspase-9. Resveratrol also increased expression of proapoptotic Bax and its translocation to the mitochondria. Resveratrol inhibited U251 proliferation, as measured by MTS assay [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt], and induces G_0/G_1 growth arrest, as determined by flow cytometry. The cyclin-dependent kinase inhibitor, olomoucine, prevented cell cycle progression and resveratrol-induced apoptosis.	These results suggest that multiple signaling pathways may underlie the apoptotic death of U251 glioma induced by resveratrol, which warrants further exploration as an anticancer agent in human glioma.	411

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the chemotactic response of MDA-MB-231 metastatic human breast cancer cells to resveratrol, estradiol (E2), or epidermal growth factor (EGF) since cancer cell invasion is dependent on cell migration.	Resveratrol decreased while E2 and EGF increased directed cell migration. Resveratrol may inhibit cell migration by altering the cytoskeleton. Resveratrol induced a rapid global array of filopodia and decreased focal adhesions and focal adhesion kinase (FAK) activity. E2 or EGF treatment did not affect filopodia extension but increased lamellipodia and associated focal adhesions that are integral for cell migration. Combined resveratrol and E2 treatment resulted in a filopodia and focal adhesion response similar to resveratrol alone. Combined resveratrol and EGF resulted in a lamellipodia and focal adhesion response similar to EGF alone. E2 and to a lesser extent resveratrol increased EGFR activity. The cytoskeletal changes and EGFR activity in response to E2 were blocked by EGFR1 inhibitor indicating that E2 may increase cell migration via cross-talk with EGFR signaling.	These data suggest a promotional role for E2 in breast cancer cell migration but an antiestrogenic, preventative role for resveratrol.	412
Investigated agents that could have antimicrobial activity against *Helicobacter pylori*.	*H. pylori* American Type Culture Collection (ATCC) strain 49503 (a toxin-producing strain known to be associated with gastric cancer) was grown, a cell suspension prepared in 2 mL PBS and diluted 10-fold. One hundred μL of this cell suspension was added to vitamin C 0.5%, vitamin E 0.5%, garcinol 100 μg/mL, Protykin (containing 50% *trans*-resveratrol) 100 μg/mL and garcinol + Protykin 100 μg/mL in Lennox broth, and incubated for 16 h under microaerophilic conditions. Three replicates of 10 μL from each 10^7 dilution tube were plated, colonies were counted after 16 h, and growth of *H. pylori* was confirmed by the CLO test. These colony counts were compared to control cultures without the addition of any antioxidants. The experiments were then repeated with the addition of 15 μg/mL of clarithromycin to experimental and control samples. Enhanced killing of *H. pylori* by 37.6% was noted when vitamin C was added, which increased to 66% when clarithromycin was added, compared to controls ($p < 0.05$). With garcinol and Protykin alone there was 91.4 and 87% killing of *H. pylori*, respectively, while a combination of garcinol + Protykin resulted in 90.8% killing compared to controls ($p < 0.05$). When clarithromycin was added, there was 76.3% increased killing with garcinol alone, 55.3% with Protykin alone, and 73.7% with garcinol + Protykin compared to controls (containing clarithromycin) ($p < 0.05$). Vitamin E had no effect on *H. pylori* growth compared to controls.	This study shows that some antioxidants such as vitamin C, garcinol and Protykin, but not vitamin E, may have potential as antimicrobial agents against *H. pylori*.	413
Investigated cell proliferation stimulatory activity against the MCF-7 and T-47D human breast cancer cell lines using various isolates.	From the rhizomes of *Belamcanda chinensis*, three new compounds, belalloside A (**1**), belalloside B (**2**), and belamphenone (**3**), along with 13 known compounds, resveratrol (**4**), iriflophenone (**5**), irisflorentin (**6**), tectorigenin (**7**), irilin D (**8**), tectoridin (**9**), iristectorin A (**10**), iristectorin B (**11**), hispiduloside, androsin, irigenin, iridin, and jaceoside, have been isolated and characterized. Along with **4**, **5**, **7**, and **9**, **3** was shown to stimulate not only MCF-7 but also T-47D human breast cancer cell proliferation.	Various compounds were shown to stimulate MCF-7 but also T-47D human breast cancer cell proliferation.	414

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated a series of synthetic (nonylphenol, diethylstilbestrol, and bisphenol A) and natural (quercetin, resveratrol, and genistein) phenolic estrogens for their ability to affect the viability and proliferation of A549 lung cancer cells.	To assess and distinguish the cytotoxic effect of individual estrogens, used both the MTT tetrazolium spectrophotometric method and the fluorescence assay, while the induction of the cell specific apoptotic process was examined by fluorescence microscopy after treatment of cells with SYTO 24 green fluorescent dye. A systematic study of interferences for both fluorescence and MTT methods was shown.	The results showed that both natural and synthetic estrogens decreased the viability and proliferation of A549 lung cancer cells in a dose-dependent manner but at different sensitivities. Nonylphenol appeared very different as compared to the other estrogens, acting by inducing the higher inactivation rate of the cells within a very short time. The cytotoxic effect of the estrogens was directly related to their structural and conformational characteristics including chain length, number, and position of hydroxyl groups and degree of saturation.	415
Investigated the mechanisms of action of resveratrol in human prostate cancer using DNA microarray analysis of the temporal transcriptional program induced by treatment of the human prostate cancer cell line LNCaP with resveratrol.	Spotted DNA microarrays containing over 42,000 elements were used to obtain a global view of the effects of resveratrol on gene expression. Prostate-specific antigen (PSA) and androgen receptor (AR) expression were determined by Northern blot and immunoblot analyses. Cell proliferation was determined by the 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide assay and cell cycle analysis by flow cytometry. It was observed that time-dependent expression changes in >1600 transcripts as early as 6 h after treatment with resveratrol. Most striking was the modulation of a number of important genes in the androgen pathway including PSA and AR. Resveratrol also down-regulated expression of cell cycle and proliferation-specific genes involved in all phases of the cell cycle, induced negative regulators of proliferation, caused accumulation of cells at the sub-G_1 and S phases of the cell cycle, and inhibited cell proliferation in a time- and dose-dependent manner.	The study showed that resveratrol produces gene expression changes in the androgen axis and cell cycle regulators that may underlie its putative anticancer activities in prostate cancer.	416
Investigated the potential of resveratrol to overcome the resistance of tumor cells against TRAIL.	While resveratrol enhanced TRAIL-induced apoptosis through G_1 cell cycle arrest and survivin depletion, resveratrol failed to sensitise cells with high expression levels of Bcl-2 or FADD-DN. Interestingly, overexpression of Bcl-2 or FADD-DN did not interfere with resveratrol-mediated cell cycle arrest or survivin depletion, but blocked release of cytochrome c and Smac from mitochondria into the cytosol, enhanced caspase activation and apoptosis upon combined treatment with resveratrol and TRAIL indicating that overexpression of Bcl-2 or FADD-DN decoupled the effect of resveratrol on the cell cycle and apoptosis. Similarly, cell cycle arrest at G_1 using the cell cycle specific inhibitor mimosine or downregulation of survivin expression by antisense oligonucleotides failed to enhance TRAIL-induced apoptosis in Bcl-2- or FADD-DN-transfected cells. Likewise, inhibition of caspase activity using the broad range caspase inhibitor zVAD.fmk did not interfere with resveratrol-mediated cell cycle arrest and survivin depletion, while blocking apoptosis upon combined treatment with resveratrol and TRAIL.	The study shows that resveratrol is a potent sensitiser for TRAIL in certain tumors. However, it may be ineffective in others, e.g., in tumors with enhanced Bcl-2 expression or defective death receptor signalling.	417

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated to identify resveratrol target genes in the human erythroleukemic K562 cell line, to show that the tensin gene and protein levels are remarkably induced by resveratrol. Tensin, a cell-matrix adhesion protein binding the integrins and cytoskeletal actin filaments, also interacts with PI3-kinase and JNK signaling pathways.	Tensin induction by resveratrol is associated with increased K562 cell adhesion to fibronectin, cell spreading and actin polymerization. The same responses were observed in the tensin-deficient MCF7 human breast cancer cell line. In K562 and MCF7 cells treated by resveratrol, tensin was found in punctate and intracytoplasmic areas. In MCF7 epithelial cells, induction of tensin is not exclusively associated with plasma membrane-bound vinculin, suggesting a dual localization of tensin in both focal and fibrillar adhesions. Pharmacological blockade of PI3-kinase and Rho GTPases/Rho-kinase resulted in selective depletion of focal adhesions, disorganization of tensin localization and disruption of stress fibers. Resveratrol increased cell motility and attachment to fibronectin in MCF7 cells submitted to mechanical laminar flow stress, and abrogated estrogen-induced MCF7 cancer cell invasion.	These data suggest induction of tensin by resveratrol contributes to the chemopreventive and anti-invasive activity of this natural dietary compound in tensin-negative and -deficient leukemic cells or epithelioid cancers.	418
Investigated the biochemical effects of resveratrol on the concentration of deoxyribonucleoside triphosphates (dNTPs), the products of ribonucleotide reductase (RR), and on the incorporation of ^{14}C-labeled cytidine into the DNA of HL-60 human promyelocytic leukemia cells.	Incorporation of ^{14}C-labeled cytidine into the DNA of resveratrol-treated HL-60 cells was measured. Concentration of dNTPs was determined by a HPLC method. Cytotoxic effects of resveratrol, Ara-C, and tiazofurin were analyzed using growth inhibition and clonogenic assays. Induction of apoptosis was studied using a Hoechst/propidium iodide staining method. The study showed that resveratrol effectively inhibited incorporation of ^{14}C-labeled cytidine into DNA. Furthermore, incubation of HL-60 cells with resveratrol significantly decreased intracellular dCTP, dTTP, dATP, and dGTP concentrations. Based on these results, the research group investigated the combination effects of resveratrol with Ara-C or tiazofurin, both antimetabolites, which are known to exhibit synergistic effects in combination with other inhibitors of RR.	In growth inhibition, apoptosis, and clonogenic assays, resveratrol acted synergistically with both Ara-C and tiazofurin in HL-60 cells. The study showed that resveratrol could become a viable candidate as one compound in the combination chemotherapy of leukemia and therefore deserves further testing.	419
Analyzed signaling downstream of phosphoinositide 3-kinase (PI3K) pathway to understand the mechanisms of resveratrol-induced apoptosis in MCF-7 cells.	Apoptotic death by resveratrol in MCF-7 was mediated by Bcl-2 downregulation as overexpression of this protein abolished apoptosis. Decreased Bcl-2 levels were not related to cytochrome c release, activation of caspases 3/8 or poly(ADP-ribose) polymerase proteolysis. However, resveratrol decreased mitochondrial membrane potential and increased reactive oxygen species and nitric oxide production. NF-κB, a regulator of Bcl-2 expression, and calpain protease activity, a regulator of NF-κB, were both inhibited by resveratrol. The patterns for NF-κB and calpain activities followed that of PI3K and were inhibited by LY294002. NF-κB inhibition coincided with diminished MMP-9 activity and cell migration.	These data suggest that resveratrol-induced apoptosis in MCF-7 could involve an oxidative, caspase-independent mechanism, whereby inhibition of PI3K signaling converges to Bcl-2 through NF-κB and calpain protease activity. Therefore, Bcl-2 and NF-κB could be considered potential targets for the chemopreventive activity of resveratrol in estrogen-responsive tumor cells.	420
Investigated mechanisms by which resveratrol and its *in vivo* metabolite(s) suppress the invasion, estimated intracellular peroxide level and expression of hepatocyte growth factor (HGF), a known cell motility factor, in AH109A cells.	Exogenously added reactive oxygen species (ROS) promoted the intracellular peroxide level and the expression of HGF. Resveratrol and resveratrol-loaded rat sera canceled the rise in the peroxide level and HGF expression in ROS-stimulated tumor cells.	These results suggest an involvement of the antioxidative property of resveratrol and sera from rats orally given resveratrol in their suppressive effects on ROS-potentiated invasion of AH109A cells.	421

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the interactions of ellagic acid and quercetin with resveratrol, with the hypothesis that the selected polyphenols would interact synergistically in the induction of apoptosis and reduction of cell growth in human leukemia cells (MOLT-4).	Alterations in cell cycle kinetics, proliferation, and apoptosis (caspase-3 activity) were examined after incubation with ellagic acid, quercetin, and resveratrol as single compounds and in combination. Results showed a more than additive interaction for the combination of ellagic acid with resveratrol and furthermore, significant alterations in cell cycle kinetics induced by single compounds and combinations were observed. An isobolographic analysis was performed to assess the apparent synergistic interaction for the combinations of ellagic acid with resveratrol and quercetin with resveratrol in the induction of caspase 3 activity, confirming a synergistic interaction with a combination index of 0.64 for the combination of ellagic acid and resveratrol and 0.68 for quercetin and resveratrol.	Results indicate that the anticarcinogenic potential of foods containing polyphenols may not be based on the effects of individual compounds, but may involve a synergistic enhancement of the anticancer effects.	422
Investigated whether indole-3-carbinol (I3C) and 3,3′-diindolylmethane (DIM) influence nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1) expression and to provide the potential molecular mechanism of their effects on anti-tumorigenesis.	The I3C repressed cell proliferation and induced NAG-1 expression in a concentration-dependent manner. In addition, DIM increased the expression of NAG-1 as well as activating transcription factor 3 (ATF3), and the induction of ATF3 was earlier than that of NAG-1. The DIM treatment increased luciferase activity of NAG-1 in HCT-116 cells transfected with NAG-1 promoter construct.	The results suggest that I3C represses cell proliferation through upregulation of NAG-1 and that ATF3 may play a pivotal role in DIM-induced NAG-1 expression in human colorectal cancer cells. Furthermore, the mixture of I3C with resveratrol enhances NAG-1 expression, suggesting the synergistic effect of these two unrelated compounds on NAG-1 expression.	423
Evaluated the antiapoptotic effect of resveratrol, studying its activity on cell cycle progression using paclitaxel-treated human neuroblastoma (HN) SH-SY5Y cell line.	We determined the mitotic index of cultures exposed to resveratrol and paclitaxel alone or in combination, the cell cycle distribution by flow cytometric analysis (FACS), and the modulation of some relevant cell cycle regulatory proteins. Resveratrol is able to induce S-phase cell arrest and this interference with the cell cycle is associated with an increase of cyclin E and cyclin A, a downregulation of cyclin D1, and no alteration in cyclin B1 and cdk 1 activation.	The resveratrol-induced S-phase block prevents SH-SY5Y from entering into mitosis, the phase of the cell cycle in which paclitaxel exerts its activity, explaining the antiapoptotic effect of resveratrol.	424
Investigated a resveratrol derivative 3,4,5,4′-tetrahydroxystilbene (R-4) to show that it exhibits potent growth inhibitory effect against transformed human cells.	The study reported that 3,4,5,4′-tetramethoxystilbene (MR-4), converted from R-4, was more potent against cancer cell lines (WI38VA, IMR-90SV, HeLa, LNCaP, HT-29, and HepG2), but had almost no inhibitory effect on the growth of normal cells (WI38, IMR-90, BJ-T) at the concentrations tested. The IC_{50} value of MR-4 on the growth inhibition of transformed WI38VA human cells was 0.5 μM, as compared to the value of greater than 50 μM for the normal WI38 cells. Resveratrol, however, did not exhibit such clear differential effect and the IC_{50} value of R-3 for WI38VA cells was about 50 μM. The growth inhibitory effect of MR-4 correlated with the induction of apoptosis in the transformed cells. When normal WI38 cells and transformed WI38VA cells were compared, MR-4 induced increases of the Bax/Bcl-2 mRNA ratio, p53 and Bax protein level, activation of caspases, and DNA fragmentation in transformed, but not in normal cells. Further analysis revealed that MR-4 caused a rapid appearance of perinuclear aggregation of mitochondria in WI38VA but not in WI38 cells, suggesting that the mitochondria could serve as an early target of MR-4. R-3 also induced apoptosis and mitochondrial clustering but only at a much higher concentration, close to 500 μM.	The specific activation of the mitochondria-mediated apoptotic pathway could be a major reason for the striking differential growth inhibitory effect of MR-4.	425

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Subjected resveratrol (**1**) to regioselective acetylation catalysed by *Candida antarctica* lipase (CAL) to obtain 4′-acetylresveratrol (**2**).	CAL biocatalyzed regioselective alcoholysis of 3,5,4′-triacetylresveratrol (**3**), 3,5,4′-tributanoylresveratrol (**6**), and 3, 4, 5′-trioctanoylresveratrol (**9**) afforded derivatives **4**, **5**, **7**, **8**, **10**, and **11**. Further resveratrol analogues (**12–18**) were obtained through methylation and hydrogenation reactions, whereas the 3,4,4′-trimethoxystilbene (**19**) was obtained by complete synthesis. Resveratrol and its lipophylic analogues were subjected to cell-growth inhibition bioassays toward DU-145 human prostate cancer cells. Compounds **2–19** showed cell-growth inhibition activity comparable to or higher than resveratrol (GI_{50} =24.09 μM), displaying low or very low toxicity against non-tumorigenic human fibroblast cells. Comparison of the trimethoxy stilbenes 12 (GI_{50} =2.92 μM) and 19 (GI_{50} =25.39 μM) indicates that the position of the substituents is important for the activity.	The study showed the marked activity of methyl ethers **12**, **13**, and **18** in comparison with that of the corresponding esters suggests that the different chemical reactivity, rather than steric factors, strongly influences the activity.	426
Investigated molecular characterization of the promoter region upstream of exon 1c in the human vitamin D receptor (VDR) gene.	In transient transfection assays, luciferase reporter constructs containing -800 to +31 of the VDR gene exhibit basal promoter activity in T47D breast cancer cells, which is enhanced by 1,25-dihydroxyvitamin D_3, estrogen, and the phytoestrogen resveratrol. Deletion constructs and site-directed mutagenesis were used to map three distinct GC-rich Sp1 consensus sites that independently mediate the effects of estrogen, resveratrol, and 1,25-dihydroxyvitamin D_3 on VDR promoter activity. Upregulation of the VDR promoter by 1,25-dihydroxyvitamin D_3 was mapped to an Sp1 site 261bp upstream of exon 1c, estrogen responsiveness to a proximal Sp1 site beginning at 50, and resveratrol regulation to a distal Sp1 site beginning at 381. Studies with estrogen receptor (ER) subtype specific ligands suggest that the effect of estrogen on VDR promoter is dependent on both ERα and ERβ, whereas the effect of resveratrol is dependent only on ERα.	These studies demonstrate transcriptional regulation of the exon 1c VDR promoter in breast cancer cells, and identify three distinct GC-rich, Sp1 consensus sites that differentially confer responsiveness to estrogen, resveratrol and 1,25-dihydroxyvitamin D_3.	427
Investigated some possible mechanisms by which resveratrol and β-sitosterol inhibit the growth of human prostate cancer PC-3 cells. These mechanisms include the effect of the phytochemicals on apoptosis, cell cycle progression, prostaglandin synthesis, and the production of reactive oxygen species (ROS).	Prostaglandins have been known to play a role in regulating cell growth and apoptosis. PC-3 cells were supplemented with 50 μM resveratrol or 16 μM β-sitosterol alone or in combination for up to 5 days. Phytochemical supplementation resulted in inhibition in cell growth. β-Sitosterol was more potent than resveratrol, and the combination of the two resulted in greater inhibition than supplementation with either alone. Long-term supplementation with resveratrol or β-sitosterol elevated basal prostaglandin release but β-sitosterol was much more potent than resveratrol in this regard. β-Sitosterol was more effective than resveratrol in inducing apoptosis, and the combination had an intermediate effect after 1 day of supplementation. Cells supplemented with resveratrol were arrested at the G_1 phase and at the G_2/M phase in the case of β-sitosterol while the combination resulted in cell arrest at the two phases of the cell cycle. β-Sitosterol increased ROS production while resveratrol decreased ROS production. The combination of the two phytochemicals resulted in an intermediate level of ROS. The observed changes in prostaglandin levels and ROS production by these two phytochemicals may suggest their mediation in the growth inhibition. The reduction in ROS level and increase by resveratrol supplementation in PC-3 cells reflects the antioxidant properties of resveratrol.	The study shows phytochemicals may induce the inhibition of tumor growth by stimulating apoptosis and arresting cells at different locations in the cell cycle and the mechanism may involve alterations in ROS and prostaglandin production.	428

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effect of epigallocatechin-gallate (EGCG), resveratrol and curcuma on cell proliferation and radiation-induced apoptosis in the human leukaemic cell line, EOL-1, derived from a patient with eosinophilic leukemia.	Cells were X-irradiated with 0, 2, 4, 6, or 8 Gy and cultured in the presence of EGCG, resveratrol, or curcuma (concentrations ranging from 0 to 200 μM) for 1, 2, or 3 days of culture. Cell proliferation was measured using trypan blue exclusion. Apoptosis was evaluated using light microscopy (morphology study after May-Grunwald Giemsa staining) and flow cytometry (annexin-V staining). Irradiation alone induced a dose-related reduction in cell proliferation and the appearance of polyploid cells in EOL-1 cells. Additionally, EOL-1 cells underwent a dose-related increase of apoptosis which, from the second day on, was accompanied by a dose-related increase of necrosis. When cells were exposed to EGCG, resveratrol or curcuma alone, a decrease in cell proliferation was observed, beginning from 25 μM EGCG and 50 μM resveratrol and curcuma, while an increase in the percentage of apoptotic cells was noted from 50 μM EGCG, 100 μM resveratrol and curcuma in EOL-1 cells, after only one day of culture. Simultaneous exposure to X-irradiation and, EGCG, resveratrol or curcuma resulted in a synergistic decrease of cell proliferation as well as in a synergistic increase of apoptosis and necrosis.	These results suggest that, depending on the concentration, EGCG, resveratrol and curcuma enhance radiation-induced apoptosis in the leukaemic cell line, EOL-1 (EGCG >resveratrol >curcuma).	429
Investigated the effect of resveratrol on angiogenesis *in vitro* and *ex vivo*.	This research group found that resveratrol directly inhibited human umbilical vein endothelial cell growth and decreased the gelatinolytic activities of matrix metalloproteinase-2. Resveratrol directly inhibited human umbilical vein endothelial cell growth and decreased the gelatinolytic activities of matrix metalloproteinase-2. Tube formation was inhibited by treatment with resveratrol after plating endothelial cells on Matrigel. Resveratrol treatment also inhibited endothelial cell attachment to basement membrane components fibronectin and laminin, and displays similar behavior on cell chemotaxis. In addition, resveratrol has been found to be an angiogenesis inhibitor in the rat aorta matrix culture model.	The study shows inhibition of angiogenesis associated with cancer may be a novel mechanism for the anticancer activity of resveratrol.	430
Investigated the feasibility of using cultured rainbow trout CRL-2301 liver cells as a model for benzo[*a*]pyrene (B*a*P)-induced carcinogenesis and its prevention by dietary phytochemicals.	Treatment with 1 nM B*a*P resulted in extensive time-dependent covalent binding to cellular DNA and marked cytochrome P450 (CYP) 1A induction, for both about a 20-fold increase, which is similar to what has been observed in cultured human cells. A surprisingly high expression of epoxide hydrolase (EH) activity in these cells likely contributed substantially to the bioactivation of B*a*P. Two methoxylated flavones and the stilbene resveratrol were effective inhibitors of both the B*a*P-DNA binding and CYP 1A induction, in particular 5,7-dimethoxyflavone (5,7-DMF), supporting a role for these dietary compounds as cancer chemopreventive agents. Unlike in human liver or bronchial cells, the main mechanism of inhibition of B*a*P-induced CYP 1A activity in trout liver cells appears to be direct competition at the protein level. Different cellular responses in any particular model used can be expected and the effect of cell context on the biological responses to xenobiotics, including carcinogens as well as polyphenols, must be considered.	Trout CRL-2301 cell sensitivity to B*a*P treatment is a clear advantage when contemplating a model system for studies of PAH-induced carcinogenesis and cancer chemoprevention. However, extrapolation to human organs should be done cautiously.	431

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Examined whether or not resveratrol can sensitize DU145, an androgen-independent human prostate cancer cell line, to ionizing radiation.	DU145 cells are resistant to ionizing radiation-induced cell death, but pretreatment with resveratrol significantly enhanced cell death. Resveratrol acted synergistically with ionizing radiation to inhibit cell survival *in vitro*. Resveratrol also potentiated ionizing radiation-induced ceramide accumulation, by promoting its *de novo* biosynthesis.	This study showed that ceramide as an effective mediator of the anticancer potential induced by resveratrol.	432
Investigated the molecular mechanism of resveratrol and its effect on cell growth, morphology and gene expression in estrogen receptor-negative MDA-MB-231 human breast cancer cell line.	The study showed that resveratrol-induced growth inhibition in the estrogen receptor negative MDA-MB-231 breast cancer cells is due to the induction of apoptosis as demonstrated by morphological, nuclear staining and PARP cleavage analysis. Resveratrol-induced growth inhibition was associated with transient activation of p44/42 mitogen-activated protein kinase (MAPK) (Thr202/Tyr204). Most importantly, resveratrol inhibited both the phosphorylation at Ser240/244 and the expression of the pS6 ribosomal protein. This protein is known to play an important role in the translation of mRNAs that have oligopyrimidine tracts in their 5′ untranslated regions. Interestingly, only MAPK inhibitor was able to block resveratrol-induced growth inhibition suggesting that effects of resveratrol on cell growth are dependent on MAPK signaling.	The data demonstrated that resveratrol-induced apoptosis is associated with MAPK signaling and with the inhibition of proteins that are involved in protein translation. This is the first data linking resveratrol with downregulation of protein translation via p44/42 MAPK and S6 ribosomal protein. The study group will use these proteins as predictive biomarkers to evaluate the treatment efficacy of resveratrol in estrogen receptor-negative human breast cancer.	433
Investigated the effects of rhapontin on proliferation and DNA of human stomach cancer KATO III cells.	Growth inhibition and induction of apoptosis by rhapontin were observed in the KATO III cells. Morphological change showing apoptotic bodies was observed in the KATO III cells treated with rhapontin. The fragmentation of DNA by rhapontin to oligonucleosomal-sized fragments that is a characteristic of apoptosis was observed to be concentration- and time-dependent in the KATO III cells. *N*-Acetyl-L-cysteine suppressed the DNA fragmentation caused by rhapontin. On the other hand, it was found that resveratrol having stilbene moiety as well as rhapontin induced apoptosis in the KATO III cells. It is considered that stilbene moiety in the molecule is essential for the induction of apoptosis.	The data showed that the suppression of KATO III cell-growth by rhapontin results from the induction of apoptosis by the compound, and that active oxygen is involved in the induction of apoptosis caused by rhapontin in the KATO III cells.	434
Investigated the anti-invasive mechanism of resveratrol in human breast cancer cells (MCF-7).	Human breast cancer MCF-7 cells were exposed to resveratrol (2, 5, and 10 μM). The expression activity of matrix metalloproteinase (MMP)-9 was measured by zymogram analysis. Phosphorylated levels of HER-2 and mitogen-activated protein kinase (MAPK)/ERK were measured by Western blot analysis. The growth factor heregulin-β1 (HRG-β1) induced the phosphorylation of HER-2/neu receptor and MMP-9 expression in MCF-7 cells. Resveratrol significantly inhibited HRG-β1–mediated MMP-9 expression in human breast cancer cells. MEK inhibitor induced a marked reduction in MMP-9 expression, and it suggested that ERK1/2 cascade could play an important role in HRG-β1–mediated MMP-9 expression. Furthermore, resveratrol significantly suppressed HRG-β1–mediated phosphorylation of ERK1/2 and invasion of breast cancer cells. However, resveratrol had negligible effects on either HRG-β1-mediated phosphorylation of HER-2 receptor or expression of the tissue inhibitor of MMP, tissue inhibitor metalloproteinase protein 1.	The results suggest that resveratrol inhibited MMP-9 expression in human breast cancer cells. The inhibitory effects of resveratrol on MMP-9 expression and invasion of breast cancer cells are, in part, associated with the down-regulation of the MAPK/ERK signaling pathway.	435

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the molecular mechanisms of resveratrol and its interactive effects with TRAIL on apoptosis in prostate cancer PC-3 and DU-145 cells.	Resveratrol inhibited cell viability and colony formation, and induced apoptosis in prostate cancer cells. Resveratrol downregulated the expression of Bcl-2, Bcl-X(L) and survivin and upregulated the expression of Bax, Bak, PUMA, Noxa, and Bim, and death receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5). Treatment of prostate cancer cells with resveratrol resulted in generation of reactive oxygen species (ROS), translocation of Bax to mitochondria and subsequent drop in mitochondrial membrane potential, release of mitochondrial proteins (cytochrome c, Smac/DIABLO, and AIF) to cytosol, activation of effector caspase-3 and caspase-9, and induction of apoptosis. Resveratrol-induced ROS production, caspase-3 activity and apoptosis were inhibited by *N*-acetylcysteine. Bax was a major proapoptotic gene mediating the effects of resveratrol as Bax siRNA inhibited resveratrol-induced apoptosis. Resveratrol enhanced the apoptosis-inducing potential of TRAIL, and these effects were inhibited by either dominant negative FADD or caspase-8 siRNA.	The combination of resveratrol and TRAIL enhanced mitochondrial dysfunctions during apoptosis. These properties of resveratrol strongly suggest that it could be used either alone or in combination with TRAIL for the prevention and/or treatment of prostate cancer.	436
Investigated several lines of evidence suggesting that the induction of ceramide synthesis is involved with resveratrol inhibiting cell growth of colon carcinoma cells at least in part by inhibition of protooncogene ornithine decarboxylase (ODC).	Cell growth was determined by BrdU incorporation and crystal violet staining. Ceramide concentrations were detected by HPLC-coupled mass-spectrometry. Protein levels were examined by Western blot analysis. ODC activity was assayed radiometrically measuring ($^{14}CO_2$)-liberation. A dominant-negative PPARγ mutant was transfected in Caco-2 cells to suppress PPARγ-mediated functions. Antiproliferative effects of resveratrol closely correlate with a dose-dependent increase of endogenous ceramides ($p < 0.001$). Compared to controls, the cell-permeable ceramide analogues C2- and C6-ceramide significantly inhibit ODC-activity ($p < 0.001$) in colorectal cancer cells. C6-ceramide further diminished protein levels of protooncogenes c-myc ($p < 0.05$) and ODC ($p < 0.01$), which is strictly related to the ability of ceramides to inhibit cell growth in a time- and dose-dependent manner. These results were further confirmed using inhibitors of sphingolipid metabolism, where only co-incubation with a serine palmitoyltransferase (SPT) inhibitor could significantly counteract resveratrol-mediated actions.	These data suggest that the induction of ceramide *de novo* biosynthesis but not hydrolysis of sphingomyelin is involved in resveratrol-mediated inhibition of ODC. In contrast to the regulation of catabolic spermidine/spermine acetyltransferase by resveratrol, inhibitory effects on ODC occur PPARγ-independently, indicating independent pathways of resveratrol-action. This study suggests that resveratrol could show chemopreventive and therapeutic potential in the treatment of colorectal cancers.	437
Investigated the ability of resveratrol to induce senescence in cancer cells and as a means to halt tumor progression.	The study showed that chronic treatment with resveratrol in a subapoptotic concentration induces senescence-like growth arrest in tumor cells. In contrast to the widely accepted antioxidant property of resveratrol, the study demonstrated that one causative stimulus for senescence induction by chronic resveratrol is an increased level of reactive oxygen species (ROS). The ROS formed upon resveratrol exposure include hydrogen peroxide and superoxide and originate largely from mitochondria. Consistently, co-incubation with the antioxidant *N*-acetyl cysteine (NAC) interfered with resveratrol-mediated reactivation of the senescence program. Molecular mediators on the way from increased ROS levels to the observed growth arrest include p38 MAPK, p53 and p21.	The study provided evidence that resveratrol-initiated replication stress, apparent by activation of the ATM kinase pathway, is associated with increased ROS levels and senescence induction. This is the first report linking cell cycle effects with a prooxidant and prosenescent effect of RV in cancer cells.	438

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
The environmental contaminant 3-nitrobenzanthrone (3-NBA) is highly mutagenic and a suspected human carcinogen. Evaluated whether 3-NBA is able to deregulate critical steps in cell cycle control and apoptosis in human lung epithelial A549 cells.	Increased intracellular Ca^{2+} and caspase activities were detected upon 3-NBA exposure. As shown by cell cycle analysis, an increased number of S-phase cells was observed after 24 h of treatment with 3-NBA. Furthermore, 3-NBA was shown to inhibit cell proliferation when added to subconfluent cell cultures. The main metabolite of 3-NBA, 3-ABA, induced statistically significant increases in tail moment as judged by alkaline comet assay. The potential of 3-NBA and 3-ABA to enhance the production of reactive oxygen species (ROS) was demonstrated by flow cytometry using 2′,7’-dichlorofluorescein-diacetate (DCFH-DA). The enzyme inhibitors allopurinol, dicumarol, resveratrol, and SKF525A were used to assess the impact of metabolic conversion on 3-NBA–mediated ROS production. Resveratrol decreased dichlorofluorescein (DCF) fluorescence by 50%, suggesting a role for CYP1A1 in 3-NBA-mediated ROS production. Mitochondrial ROS production was significantly attenuated (20% reduction) by addition of rotenone (complex I inhibition) and thenoyltrifluoroacetone (TTFA, complex II inhibition).	The results of the study provided evidence for a genotoxic potential of 3-ABA in human epithelial lung cells. Moreover, both compounds lead to increased intracellular ROS and create an environment favorable to DNA damage and the promotion of cancer.	439
The prognosis of cancer disease is worsened upon shedding of tumor cells from the primary tumor, which escape to the bloodstream and form metastases at distant sites within the body. Inhibition of cell shedding from the primary tumor could therefore be exploited to avoid metastasis and delay the progression of the cancer disease. Investigated the effects of resveratrol, baicalein, epicatechin, epigallocatechin, and polyphenon 60 on cell shedding from multicellular tumor spheroids of the murine mammacarcinoma cell line 4T1, cell invasion into embryonic stem cell-derived tissues, generation of reactive oxygen species (ROS), and expression of matrix metalloproteinase 9 (MMP-9).	With increasing tumor spheroid growth, MMP-9 expression was upregulated and cells detached from tumor spheroids and formed subspheroids that displayed pronounced ROS generation. Upon incubation with polyphenols, tumor growth was arrested and cell shedding was totally abolished. Polyphenol treatment decreased ROS generation and downregulated MMP-9 expression. Furthermore, polyphenols significantly inhibited invasion of tumor cells into embryonic stem cell–derived, vascularized tissues.	These data suggest that polyphenols inhibit cell shedding and invasion by their antioxidative capacity and downregulation of MMP-9 expression.	440
Resveratrol exerts a drastic growth inhibitory effect on human breast cancer MDA-MB-231 cells grown both *in vitro* and *in vivo*. Investigated to show that resveratrol affects the aggregation properties of MDA-MB-231 cells into multicellular tumor spheroids (MCTSs), in association with induction of *de novo* synthesis of ceramide.	After 9 days of 3D growth in the presence of resveratrol (64 μM), MDA-MB-231 cells formed significantly smaller MCTSs. Further, cells from these aggregates failed to form colonies. Addition of resveratrol (64 μM) to preformed MDA-MB-231 MCTSs caused no significant size change, consistent with lack of ceramide induction. Only some apoptotic blebs were found on the MCTSs surface.	The study indicated that resveratrol might be effective for prevention of breast cancer cell growth.	441

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigated the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on human colon cancer cell lines to clarify the mechanisms underlying the chemopreventive effect of NSAIDs. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, induced apoptosis and strongly reduced the expression of an antiapoptotic protein, survivin, in both protein and mRNA levels in HCT-116 cells.	Conducted luciferase reporter assay using a reporter gene driven by the human survivin promoter. A series of analyses using luciferase reporter constructs containing fragments of the survivin promoter and electrophoretic mobility shift assay indicated that the -75/-66 bp region relative to the initiating codon was involved in celecoxib action to suppress survivin promoter activity. Celecoxib also suppressed the activity of TOPflash, T-cell factor reporter plasmid, and the reporter gene driven by the human cyclin D1 promoter, suggesting that this compound inhibited the expression of Wnt/β-catenin signaling target genes. Further, the study showed that other NSAIDs including indomethacin, resveratrol, and SC-560 induced apoptosis and suppressed the expression of survivin and the Wnt/β-catenin signaling pathway in HCT-116 cells, indicating that these effects were likely to be common among NSAIDs. Moreover, NSAIDs (celecoxib, SC-560 and indomethacin) also suppressed the expression of cyclin D1 and survivin on other colon cancer cell lines (DLD-1 and SW-620).	The results suggested that NSAIDs could inhibit proliferation and induce apoptosis in colon cancer cells by inhibition of survivin expression and the Wnt/β-catenin signaling pathway.	442
Investigated how resveratrol activated the caspase-dependent intrinsic pathway of apoptosis in human colorectal cancer cells. This effect was not mediated via estrogen receptors.	Pepstatin A, an inhibitor of lysosomal cathepsin D (CD), not (2S,3S)-*trans*-epoxysuccinyl-l-leucylamido-3-methylbutane ethyl ester, an inhibitor of cathepsins B and L, prevented resveratrol cytotoxicity. Similar protection was attained by small interference RNA-mediated knockdown of CD protein expression. Resveratrol promoted the accumulation of mature CD, induced lysosome leakage and increased cytosolic immunoreactivity of CD. Inhibition of CD or its post-transcriptional downregulation precluded Bax oligomerization, permeabilization of mitochondrial membrane, cytosolic translocation of cytochrome c, caspase 3 activation, and terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling positivity occurring in resveratrol-treated cells.	The study identified the lysosome as a novel target of resveratrol activity and demonstrated a hierarchy of the proteolytic pathways involved in its cytotoxic mechanism in which the lysosomal CD acts upstream of the cytosolic caspase activation. The data indicated that metabolic, pharmacologic, or genetic conditions affecting CD expression and/or activity could reflect on the sensitivity of cancer cells to resveratrol.	443
Human papillomavirus (HPV)-16 oncoproteins, E6 and E7, are associated with enhanced tumor angiogenesis in human cervical cancers. Investigated whether expression of HPV-16 E6 and E7 oncoproteins induced hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor expression in cervical cancer cells. In addition, investigated to assess the effect of resveratrol on 16 E6- and E7-induced HIF-1α and VEGF gene expression.	Human cervical cancer cell lines C-33A and HeLa were transiently co-transfected with pSG5-HPV-16 E6 or 16 E7 constructs along with HIF-1α small interfering RNA (siRNA) or nonspecific siRNA. The expression of HIF-1 α/VEGF was measured using real-time PCR, Western blot analysis, or ELISA. The *in vitro* angiogenic activity induced by 16 E6- and E7-transfected cells was examined. The effect of resveratrol on oncoprotein-induced HIF-1α/VEGF expression and *in vitro* angiogenesis was investigated. HPV-16 E6- and E7-transfected cervical cancer cells express increased HIF-1 α protein and VEGF expression. These stimulatory effects were abrogated by co-transfection with either HIF-1α siRNA or treatment with resveratrol. Blocking extracellular signal-regulated kinase 1/2 (ERK 1/2) and phosphoinositide-3-kinase by PD98059 and LY294002, respectively, abolished 16 E6- and E7-induced HIF-1 α and VEGF expression. Functionally, it was shown that HPV-16 E6- and E7-transfected cervical cancer cells stimulated *in vitro* capillary or tubule formation, and these angiogenic effects could be abolished either by co-transfection with HIF-1α siRNA or by treatment with resveratrol.	HPV-16 oncoproteins contributed to enhance angiogenesis in cervical cancer cells via HIF-1α-dependent VEGF expression. Resveratrol suppressed 16 E6- and E7-induced HIF-1α–mediated angiogenic activity and, thus, is a promising chemotherapeutic agent for human cervical cancer	444

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Resveratrol is a phenolic that has been shown to have antitumorigenic and anti-inflammatory properties. Macrophage inhibitory cytokine (MIC-1) is a member of the transforming growth factor β (TGF-β) superfamily that has been shown to have antitumorigenic activity and is upregulated in resveratrol-treated cancer cells. Resveratrol inhibits proliferation of human pancreatic cancer cells; however, the exact mechanism of action is not known. Using human pancreatic cancer cell lines (CD18 and S2-013), the role of MIC-1 in resveratrol-induced growth inhibition of human pancreatic cancer cell lines was investigated.	Proliferation assays conducted with resveratrol-treated human pancreatic cancer cell lines (CD18 and S2-013) at 24, 48, and 72 h revealed inhibition of cell proliferation compared to controls. Using oligonucleotide microarray analysis, this study identified marked upregulation of MIC-1 gene expression in resveratrol-treated human pancreatic cancer S2-013 cells. Real-time RT-PCR performed in CD18 and S2-013 cells treated with resveratrol (0–100 mum) for 24 h confirmed concentration and time-dependent upregulation of expression of one particular gene, MIC-1. Both cell lines pretreated with actinomycin D (a transcriptional inhibitor) and then resveratrol had reduced up-regulation of MIC-1 gene expression compared to those treated with resveratrol alone. Finally, resveratrol-induced growth inhibition was abolished in CD18 cells transfected with MIC-1 short interfering RNA.	Resveratrol up-regulated MIC-1 gene expression in part at the transcriptional level in pancreatic cancer cells. Furthermore, MIC-1 appeared to play a key role in resveratrol-induced growth inhibition in these cells.	445
The detection of renal tumors has increased significantly over recent years resulting in a greater demand for novel, minimally invasive techniques. Cryoablation has emerged as a valuable treatment modality for the management of renal cancer. Using the human renal cancer (RCC) cell line, the effects of freezing in renal cancer was evaluated *in vitro*.	786-O Cells were exposed to a range of freezing temperatures from −5 to −40°C and compared to non-frozen controls. The data showed that freezing to −5 did not affect 786-O cell viability, while −10, −15, and −20 resulted in a significant loss of viability (23, 70, and 91%, respectively). A complete loss of cell viability was evident at temperatures of −25 and colder. Following this analysis, variables involved in the success of cryoablation were investigated. For each of the temperatures tested, extended freeze hold times and passive thawing rates resulted in more extensive cell damage. Additionally, a double freeze-thaw cycle significantly increased cell death compared to a single cycle (62% vs. 22% at −10; 89% vs. 63% at −15, respectively). While these variables play an important part in the effective application of cryoablation, a molecular understanding of the cell death involved is critical to improving efficacy. Apoptotic inhibition afforded 12% (−10), 25% (−15), and 11% (−20) protection following freezing. Using fluorescence microscopy analysis, the results demonstrated that apoptosis peaked at 6h post-thaw. Next, apoptotic initiating agents including 5-FU and resveratrol applied prior to freezing exposure resulted in a significant increase in cell death compared to either application alone. Importantly, the combination of resveratrol and freezing was noticeably less effective when applied to normal renal cells.	The results herein demonstrated the efficacy of freezing and described a novel therapeutic model for the treatment of renal cancer that may distinguish between cancer and normal cells.	446

(Continued on next page)

Table 6. Evaluation of resveratrol with cell culture model systems. (*Continued*)

Model	What was measured	Effect	Ref.
This research group previously reported that breast cancer resistance protein (BCRP) is involved in the transport of phase II metabolites of the food carcinogen benzo[*a*]pyrene in the human intestinal cell line Caco-2. Furthermore, the expression of BCRP seemed most likely to be aryl hydrocarbon receptor (AhR) dependent. As numerous plant-derived anticarcinogens with AhR-agonistic activity have been identified to date, the study investigated the effects of naturally occurring dietary compounds and tert-butyl hydroquinone (TBHQ) for their effects on BCRP expression.	In Caco-2 cells, the most pronounced induction of BCRP expression could be observed after treatment with TBHQ (100 μM), dibenzoylmethane (DBM, 50 μM), and quercetin (25 μM), while green tea component (-)-epicatechin (50 μM) decreased BCRP expression. On mRNA level, quercetin, chrysin, flavone, and indole-3-carbinol showed a strong inducing effect, while genistein had no effect on BCRP mRNA expression. Curcumin and resveratrol showed a strong effect on BCRP induction in MCF-7 wild-type cells but no response in AhR-deficient MCF-7AHR(200) cells, supporting the hypothesis that BCRP is regulated via AhR-dependent signaling pathways. Inhibition of proteasome-mediated degradation of ligand-activated AhR caused a "superinduction" of BCRP mRNA. Antioxidant responsive element activators sulforaphane and diethylmaleate (DEM) had no inducing effect on BCRP mRNA expression. Caco-2 cells pretreated with quercetin or DBM showed an enhancement of apically transported benzo[*a*]pyrene-3-sulfate, indicating that induced BCRP was functionally active.	In conclusion, apart from the modulation of detoxifying enzymes in the intestine, induction of BCRP by dietary constituents may contribute to the detoxification of food-derived procarcinogens such as benzo[*a*]pyrene.	447
Investigated whether resveratrol could suppress the proliferation of multiple myeloma (MM) cells by interfering with NF-κB and STAT3 pathways.	Resveratrol inhibited the proliferation of human multiple myeloma cell lines regardless of whether they were sensitive or resistant to the conventional chemotherapy agents. Resveratrol also potentiated the apoptotic effects of bortezomib and thalidomide. It induced apoptosis as indicated by accumulation of sub-G_1 population, increase in Bax release, and activation of caspase-3. This correlated with downregulation of various proliferative and antiapoptotic gene products, including cyclin D1, cIAP-2, XIAP, survivin, Bcl-2, Bcl-xL, Bfl-1/A1, and TRAF2. In addition, resveratrol downregulated the constitutive activation of AKT. These effects of resveratrol are mediated through suppression of constitutively active NF-κB through inhibition of IκBα kinase and the phosphorylation of IκBα and of p65. Resveratrol inhibited both the constitutive and the interleukin 6–induced activation of STAT3. When $CD138^+$ plasma cells from patients with MM were examined, resveratrol inhibited constitutive activation of both NF-κB and STAT3, leading to downregulation of cell proliferation and potentiation of apoptosis induced by bortezomib and thalidomide.	These mechanistic findings suggest that resveratrol may have potential in the treatment of multiple myeloma.	448

In addition to data obtained with *in vivo* models, the following references describe results obtained with cell culture: 40, 450, 453, 456, 462, 464, 470, 471, 477, 479, 481, 483, 484, 498, 504.

Table 7. Evaluation of resveratrol with *in vivo* model systems.

Model	What was measured	Effect	Ref.
Sprague-Dawley female rats.	This study was carried out to determine whether grape seed extract (GSE), using genistein as the control, added to rodent diets protected against carcinogen-induced mammary tumorigenesis in rats and whether this was affected by the composition of the whole diet.	The results demonstrated that GSE is chemopreventive in an animal model of breast cancer and suggests that chemopreventive activity in GSE and genistein may depend on the diet.	458
Inhibitors of NF-κB activation. Mice.	Curcumin and resveratrol attenuated total protein degradation in murine myotubes at all concentrations of proteolysis-inducing factor (PIF), and attenuated the PIF-induced increase in expression of the ubiquitin-proteasome proteolytic pathway, as determined by the 'chymotrypsin-like' enzyme activity, proteasome subunits, and E2(14k).	Curcumin was ineffective in preventing weight loss and muscle protein degradation in mice bearing the MAC16 tumor, whereas resveratrol significantly attenuated weight loss and protein degradation in skeletal muscle, and produced a significant reduction in NF-κB DNA-binding activity. The inactivity of curcumin was probably due to a low bioavailability. These results suggest that agents which inhibit nuclear translocation of NF-κB may prove useful for the treatment of muscle wasting in cancer cachexia.	459
SKH-1 hairless mice.	Assess the involvement of IAP family protein survivin during resveratrol-mediated protection from multiple exposures of UVB radiations in the SKH-1 hairless mouse skin.	It was demonstrated that topical pretreatment of resveratrol resulted in significant inhibition of UVB exposure–mediated increases in (i) cellular proliferation (Ki-67 immunostaining); (ii) protein levels of epidermal cyclooxygenase (COX)-2 and ornithine decarboxylase (ODC), established markers of tumor promotion; (iii) protein and mRNA levels of surviving; and (iv) phosphorylation of survivin; in the skin of SKH-1 hairless mouse. Resveratrol pre-treatment also resulted in (i) reversal of UVB-mediated decrease of Smac/DIABLO, and (ii) enhancement of UVB-mediated induction of apoptosis, in mouse skin. The study suggested that resveratrol imparts chemopreventive effects against UVB exposure–mediated damage in SKH-1 hairless mouse skin by inhibiting survivin and the associated events.	454
Effect of resveratrol and in combination with 5-fluorouracil (5-FU) on murine hepatoma22 cell (liver cancer).	Transplantable murine hepatoma22 model was used to evaluate the antitumor activity of resveratrol alone or in combination with 5-FU *in vivo*. H22 cell cycles were analyzed with flow cytometry.	Resveratrol could induce the S phase arrest of H22 cells and enhance the antitumor effect of 5-FU on murine hepatoma22 and antagonize its toxicity markedly. These results suggest that resveratrol, as a biochemical modulator to enhance the therapeutic effects of 5-FU, may be potentially useful in cancer chemotherapy.	450
Male and female CD Virus Antibody Free (VAF) rats.	To evaluate the potential toxicity of resveratrol, rats were administered by gavage 0, 300, 1000, and 3000 mg resveratrol per kilogram body weight per day for 4 weeks.	Most of the adverse events occurred in the rats treated with 3000 mg per kilogram body weight per day. These included increased clinical signs of toxicity; reduced final body weights and food consumption; elevated BUN, creatinine, alkaline phosphatase, alanine aminotransferase, total bilirubin, and albumin; reduced hemoglobin, hematocrit, and red cell counts; and increased white cell counts. Increases in kidney weights and clinically significant renal lesions, including an increased incidence and severity of nephropathy, were observed. Diffuse epithelial hyperplasia in the bladder was considered equivocal and of limited biological significance. No histological effects on the liver were observed, despite the clinical chemistry changes and increased liver weights in the females. Effects seen in the group administered 1000 mg resveratrol per kilogram body weight per day included reduced body weight gain (females only) and elevated white blood cell count (males only).	

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
		Plasma resveratrol concentrations in blood collected 1 h after dose administration during week 4 were dose related but were relatively low given the high dosage levels; conjugates were not measured. Under the conditions of this study, no adverse effects were observed at a dose of 300 mg resveratrol per kilogram body weight per day.	460
Benzo(*a*)pyrene-induced lung tumorigenesis in A/J mice.	Inhibition of PAH bioactivation through reduced expression of the CYP1A1 and CYP1B1 genes in human bronchial epithelial cells.	Resveratrol added to the diet showed no effect on benzo*(a)*pyrene-induced lung tumorigenesis. Resveratrol did not change CYP1A1 and CYP1B1 gene expression or benzo, [*a*] pyrene protein adduct levels in the lung tissue.	461
Mice.	Ames assay and micronucleus formation assay were used to test the antimutagenic activities of resveratrol. Croton oil–induced enhancement of ODC activities of dorsal epidermis cells in mouse and mouse ear edema model were used to investigate the antipromotion effect of resveratrol. DMBA/croton oil–induced mouse skin tumor model was used to evaluate chemopreventive effect of resveratrol to cancer *in vivo*.	The Ames test showed resveratrol exhibited 42.2% inhibition on the reversion of *Salmonella typhimurium* TA100 induced by methylmethansulfonate, and resveratrol exhibited 91.8% inhibition on the reversion induced by benzo *(a)* pyrene. Pretreatment of resveratrol prevented cyclophosphamide (CTX)-induced micronucleus formation of polychromatic erythrocytes of mouse bone marrow in dose-dependent manner. Mice treated with 30 mg/kg of resveratrol for 6 days before croton oil-exposure have palliative ear edema. Treatment of 180 mg/kg resveratrol for 3 days caused a 69.3% decrease of ODC activities in croton oil–induced dorsal epidermis. It was shown that resveratrol could inhibit DMBA/croton oil–induced mouse skin papilloma, which includes prolonging the latent period of tumor occurrence, decreased incidence of papilloma, and reduced tumor number per mouse, in a dose-dependent manner.	462
Neuroblastoma (Neuro-2a) cells and determined effects on neuroblastoma tumors in syngeneic A/J mice.	Cytotoxic effects, cellular apoptosis, and alterations in the cell cycle were determined in Neuro-2a neuroblastoma cells exposed for varying lengths of time to a series of resveratrol concentrations. Expression of associated cell cycle regulatory proteins, cyclin E and p21, was detected by Western blot analysis, and the antitumor effects of resveratrol were investigated by treating subcutaneous neuroblastoma tumors with intraperitoneal injections of 40 mg/kg resveratrol daily for 28 days.	Resveratrol caused significant cytotoxicity and increased apoptosis and S-phase accumulation of neuroblastoma cells. S-phase accumulation was related to the downregulation of p21 and upregulation of cyclin E. In addition, resveratrol exerted antitumor effects on neuroblastomas in mice. Thus, resveratrol shows promise for the treatment of neuroblastoma.	463
Increased levels or overexpression of ornithine decarboxylase (ODC) is characteristic of tumor cells. Similarly, prostaglandins appear to be important in the pathogenesis of cancer because these affect mitogenesis, cellular adhesion, immune surveillance, and apoptosis. Cancers form much more prostaglandins than the original tissue from which they have arisen.	This study revealed that pretreatment of mice with resveratrol at a dose of 2.5 mg/kg body weight for two weeks blocked the *N*-nitrosodiethylamine (NDEA)-induced cytosolic ODC levels in the liver and lungs. The blockage was pronounced in hepatic tissue compared to pulmonary tissue. Resveratrol feeding caused a significant reduction in microsomal cyclooxygenase (COX) activities in the liver and lungs, while the dosage of NDEA (200 mg/kg body weight) induced COX activity 24 h after its administration.	Resveratrol pretreatment effectively blocks the induction of COX activity in the lungs by NDEA.	464

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
The pharmacokinetic properties of the resveratrol analogue, 3,4,5,4′-tetramethoxystilbene (DMU 212), were compared with those of resveratrol in the plasma, liver, kidney, lung, heart, brain, and small intestinal and colonic mucosa of mice.	DMU 212 or resveratrol were administered intragastrically, and drug concentrations were measured by HPLC. Metabolites were characterised by cochromatography with authentic reference compounds and were identified by mass spectrometry. The ratios of area of plasma or tissue concentration vs time curves of resveratrol over DMU 212 (AUC_{res}/AUC_{DMU212}) for the plasma, liver, small intestinal and colonic mucosa were 3.5, 5, 0.1, and 0.15, respectively. Thus, resveratrol afforded significantly higher levels than DMU 212 in the plasma and liver, while DMU 212 exhibited superior availability compared to resveratrol in the small intestine and colon. Resveratrol was metabolised to its sulfate or glucuronate conjugates, while DMU 212 underwent metabolic hydroxylation or single and double *O*-demethylation. DMU 212 and resveratrol inhibited the growth of human-derived colon cancer cells HCA-7 and HT-29 *in vitro* with IC_{50} values of between 6 and 26 μM.	Due to the superior levels achieved in the gastrointestinal tract after the administration of DMU 212, when compared to resveratrol, the results provide a good rationale to evaluate DMU 212 as a colorectal cancer chemopreventive agent.	465
Determine the effect of resveratrol on intestinal tumorigenesis and the protumorigenic COX pathway in $Apc^{Min/+}$ mice.	Resveratrol was administered as a powdered admixture in the diet at 0, 4, 20, or 90 mg/kg body weight for 7 wk. In two separate experiments, resveratrol did not affect intestinal tumor load. It was stable in the diet under experimental conditions, circulated in the plasma as the glucuronide-conjugated form and reached the tumors as evidenced by significant decreases in PGE_2 levels. However, immunohistochemical staining of intestinal tumors revealed no changes in COX-2 expression.	This study demonstrates that resveratrol consumed *ad libitum* in the diet does not modify tumorigenesis in $Apc^{Min/+}$ mice.	466
Antitumor effect of stilbenoids from *Vateria indica* against allografted sarcoma S-180 in DDY mice.	Examined the antitumor activity of the ethanol extract from the stem bark of *Vateria indica*, which contains various resveratrol oligomers. High-performance liquid chromatography analysis showed that the extract contains bergenin, hopeaphenol, vaticanol B, vaticanol C, and ε-viniferin. The *in vitro* assay displayed the anticancer activity of the extract against mouse sarcoma 180 cells ($IC_{50} = 29.5$ μM). In the animal study, the tumor growth of sarcoma S-180 cells subcutaneously allografted in DDY mice was significantly retarded by oral administration of the extract. The extract did not show significant toxicity to mice.	These results demonstrated that the ethanol extract containing various stilbenoids from the stem bark of *V. indica* has potent antitumor activity.	467
Effect of prepubertal resveratrol exposure on *N*-methyl-*N*-nitrosourea (MNU)-induced mammary carcinogenesis in female Sprague-Dawley rats.	Prepubertal rats were treated daily with either 10 or 100 mg/kg resveratrol for 5 days, and were compared with resveratrol-untreated animals. Six rats in each group were autopsied at 49 days of age, and their growth was evaluated. All remaining rats were given 50 mg/kg MNU, followed by monitoring for occurrence of mammary carcinoma. A dose of 100 mg/kg resveratrol significantly increased incidence of rat with mammary carcinomas and multiplicity (all histologically detected mammary carcinomas per rat), but did not affect latency, compared with untreated controls. Resveratrol did not affect body weight increase, but 100 mg/kg resveratrol caused slightly earlier vaginal opening.	Although all rats cycled, resveratrol-treated animals exhibited significantly increased irregularity of estrous cycle, spending more time in the estrus phase. Thus, short resveratrol treatment of prepubertal female rats affected endocrine function, and accelerated development of MNU-induced mammary carcinomas.	468

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Determine the antitumor activity of resveratrol and its effect on the expression of cell cycle proteins including cyclin D1, cyclin B1 and $p34^{cdc2}$ in transplanted liver cancer using the murine transplanted hepatoma H22 model.	Murine transplanted hepatoma H22 model was used to evaluate the *in vivo* antitumor activity of resveratrol. Following i.p. administration of resveratrol, the change in tumor size was recorded and the protein expression of cyclin D1, cyclin B1, and $p34^{cdc2}$ in the tumor and adjacent noncancerous liver tissues were measured by immunohistochemistry. Following treatment of H22 tumor bearing mice with resveratrol, the growth of murine transplantable liver cancer was inhibited by 36.3 or 49.3%, respectively. The inhibitory effect was significant compared to that in control group. The level of expression of cyclin B1 and $p34^{cdc2}$ protein was decreased in the transplantable murine hepatoma 22 treated with resveratrol whereas the expression of cyclin D1 protein did not change.	Resveratrol exhibits antitumor activities on murine hepatoma H22. The underlying anti-tumor mechanism of resveratrol might involve the inhibition of the cell cycle progression by decreasing the expression of cyclin B1 and $p34^{cdc2}$ protein.	469
Investigation in male F344 rats for the potential beneficial or adverse affect of prolonged dietary administration of moderate to high doses of lycopene, quercetin and resveratrol or a mixture of lycopene and quercetin.	Selected markers for toxicity and defense mechanisms were assayed in blood, liver and colon and the impact of the antioxidant administrations on putative preneoplastic changes in liver and colon was assessed. The dietary carcinogen, 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) served as a pro-oxidant, genotoxicity, and general toxicity control. IQ increased the levels of protein and DNA oxidation products in plasma, the area of glutathione *S*-transferase-placental form positive (GST-P) foci in the liver as well as the number of colonic aberrant crypt foci (ACF). All antioxidants and the antioxidant combination significantly increased the level of lymphocytic DNA damage, to an extent comparable with the effect induced by IQ. In contrast to the control group where no GST-P foci were detected, GST-P foci were detected in animals exposed to quercetin, lycopene, and the combination of the two. However, the increase in the volume of GST-P foci did not reach statistical significance.	These results indicate that moderate to high doses of common dietary antioxidants can damage lymphocyte DNA and induce low levels of preneoplastic liver lesions in experimental animals. Therefore, long-term exposure to moderate to high doses of antioxidants may modulate carcinogenesis via pro-oxidative mechanisms and nonoxidative mechanisms.	470
Prevention of the effects of benzo(*a*)pyrene (B*a*P) on the lung of Balb-C mice.	Balb-C mice were injected for 5 weeks with corn oil, B*a*P, resveratrol or B*a*P + resveratrol. Immunohistochemistry was performed on lung sections for the determination of CYP1A1 protein, BPDE-DNA adducts and apoptosis. A semiquantitative immunohistochemistry score (H score) was used for data analysis. Mice exposed to B*a*P had a significant induction of lung BPDE-DNA adducts when compared with controls. The BPDE-DNA adduct induction by B*a*P was abrogated significantly by resveratrol. A similar pattern was found by immunohistochemistry for apoptosis and CYP1A1. Western blotting confirmed that resveratrol prevented B*a*P-induced CYP1A1	All B*a*P-induced effects could be prevented by resveratrol, suggesting a possible chemopreventive role against the development of lung cancer.	471

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
	expression. This increase in CYP1A1 expression in response to B*a*P administration most likely causes B*a*P metabolism, BPDE-DNA adduct formation, and subsequent apoptosis.		
The antitumor and immunomodulatory activity of resveratrol on experimentally implanted tumor of H22 in Balb/c mice.	The cytotoxicity of peritoneal macrophages (Mφ) against H22 cells was measured by treating mice with H22 tumors with different concentrations of resveratrol, and the inhibitory rates were calculated and IgG contents were determined by a single immunodiffusion method. The plaque forming cell (PFC) was measured by an improved Cunningham method, and the levels of serum tumor necrosis factor-α (TNF-α) were measured by a cytotoxic assay against L929 cells. Resveratrol promoted the cytotoxicity of Mφ against H22 cells. Resveratrol (500 mg kg, 1000 mg kg, and 1500 mg kg) could curb the growth of the implanted tumor of H22 in mice. The inhibitory rates were 31.5, 45.6, and 48.7%, respectively, which could raise the level of serum IgG and PFC response to sheep red blood cells. Resveratrol (1000 mg kg and 1500 mg kg) and BCG (200 mg kg) could increase the production of serum TNF-α in mice H22 tumor. However, the effect of resveratrol was insignificant.	Resveratrol could inhibit the growth of H22 tumor in Balb/c mice. The antitumor effect of resveratrol might be related to directly inhibiting the growth of H22 cells and indirectly inhibiting its potential effect on nonspecific host immunomodulatory activity.	472
This study investigates whether dietary resveratrol could inhibit the proliferation and metastasis of tumors and hyperlipidemia in Donryu rats subcutaneously implanted with an ascites hepatoma cell line AH109A.	Hepatoma-bearing rats were fed resveratrol in the diet for 20 days, solid tumor growth and metastasis tended to be suppressed dose-dependently. Resveratrol significantly suppressed the serum lipid peroxide level, indicating its antioxidative properties or those of its metabolite(s) *in vivo*. Resveratrol dose-dependently suppressed both the serum triglyceride and very-low-density lipoprotein + low-density lipoprotein (VLDL + LDL)-cholesterol levels.	The hypocholesterolemic action of resveratrol is attributed, at least in part, to an increased excretion of neutral sterols and bile acids into feces. These results suggest that dietary resveratrol is hypolipidemic with a tendency for anti-tumor-growth and antimetastasis effects in hepatoma-bearing rats.	473
Suppression of ultraviolet B exposure–mediated activation of NF-κB in normal human keratinocytes by resveratrol, by investigating the effects of cutaneous damage in SKH-1 hairless mice.	These studies demonstrated that resveratrol imparts protection from UVB-mediated cutaneous damage in SKH-1 hairless mice. The mechanism of action of resveratrol is not clearly understood. The involvement of NF-κB was investigated as the mechanism of chemoprevention of UV damage by resveratrol. In the normal human epidermal keratinocytes, resveratrol blocked UVB-mediated activation of NF-κB in a dose-dependent as well as time-dependent fashion. Resveratrol treatment of keratinocytes also inhibited UVB-mediated phosphorylation and degradation of IκBα and activation of IKKα.	These studies suggest that the NF-κB pathway plays a critical role in the chemopreventive effects of resveratrol against the adverse effects of UV radiation including photocarcinogenesis.	455

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Investigation of the absorption and tissue distribution of ^{14}C-*trans*-resveratrol following oral administration to male Balb/c mice.	Male Balb/c mice were given a single oral dose of ^{14}C-*trans*-resveratrol and were sacrificed at 1.5, 3, or 6 h postdose. The distribution of radioactivity in tissues was evaluated using whole-body autoradiography, quantitative organ-level determination, and microautoradiography. In addition, identification of radioactive compounds in kidney and liver was done with high-performance liquid chromatography.	Autoradiographic survey of mouse sections as well as radioactivity quantification in various organs revealed a preferential fixation of ^{14}C-*trans*-resveratrol in the organs and biological liquids of absorption and elimination (stomach, liver, kidney, intestine, bile, urine). Moreover, the studies show that ^{14}C-*trans*-resveratrol derived radioactivity is able to penetrate the tissues of liver and kidney, a finding supported by microautoradiography. The presence of intact ^{14}C-*trans*-resveratrol together with glucurono- and/or sulfoconjugates in these tissues was also shown. This study demonstrates that *trans*-resveratrol is bioavailable following oral administration and remains mostly in intact form. The results also suggest a wide range of target organs for cancer chemoprevention by wine polyphenols in humans.	474
Investigation of the inhibitory effects of vitamin C (VC), vitamin E (VE), tea polyphenols (TP), garlic squeeze, curcumin, and grapeseed extract on NB-DNA and NB-hemoglobin (Hb) adductions in mice using an ultrasensitive method of accelerator mass spectrometry (AMS) with ^{14}C-labeled nitrobenzene.	These dietary constituents showed inhibitory effects on DNA or Hb adduction. VC, VE, TP, and grapestone extract could efficaciously inhibit the adductions by 33–50%, and all of these six agents could inhibit Hb adduction by 30–64%. Resveratrol, curcumin, VC and VE were also investigated as inhibitors of NB-DNA adduction *in vitro* using a liquid scintillation counting technique.	These agents in the presence of NADPH and S9 components also pronouncedly blocked DNA adduction in a dose-dependent fashion. The study suggests that these seven constituents may interrupt the process of NB-induced chemical carcinogenesis.	475
Prevention of short-term ultraviolet B radiation–mediated damage by resveratrol in SKH-1 hairless mice.	This study was designed to examine whether resveratrol possesses the potential to ameliorate the damage caused by short-term UVB exposure to mouse skin. Single topical application of resveratrol to SKH-1 hairless mice was found to result in significant inhibition of UVB-mediated increase in bifold skin thickness and skin edema. Treatment of mouse skin with resveratrol was also found to result in significant inhibition of UVB-mediated induction of cyclooxygenase and ornithine decarboxylase (ODC) enzyme activities and protein expression of ODC, which are well-established markers for tumor promotion. Resveratrol inhibits UVB-mediated increased level of lipid peroxidation, a marker of oxidative stress.	The results suggest that resveratrol may afford substantial protection against the damage caused by UVB exposure, and these protective effects may be mediated via its antioxidant properties.	456
Mammary carcinogenesis induction by 7,12-dimethylbenz(*a*)anthracene (DMBA) in female Sprague-Dawley rats. Analyzed effect on MCF-7 human breast cancer cell lines.	Investigated the chemopreventive potential of resveratrol by testing it against mammary carcinogenesis induced by DMBA in female Sprague-Dawley rats. Dietary administration of resveratrol had no effect on body weight gain and tumor volume but produced striking reductions in the incidence, multiplicity, and extended latency period of tumor development relative to DMBA-treated animals.	The results suggest that resveratrol suppresses DMBA-induced mammary carcinogenesis, which correlates with downregulation of NF-κB, cyclooxygenase-2, and matrix metalloprotease-9 expression.	476

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
	Histopathological analysis of the tumors revealed that DMBA induced ductal carcinomas and focal microinvasion *in situ*, whereas treatment with resveratrol suppressed DMBA-induced ductal carcinoma. Immunohistochemistry and Western blot analysis revealed that resveratrol suppressed the DMBA-induced cyclooxygenase-2 and matrix metalloprotease-9 expression in the breast tumor. Gel shift analysis showed suppression of DMBA-induced NF-κB activation by resveratrol. Treatment of human breast cancer MCF-7 cells with resveratrol also suppressed the NF-κB activation and inhibited proliferation at S-G_2-M phase.		
Suppression of *N*-nitrosomethylbenzylamine (NMBA)-induced rat esophageal tumorigenesis in F344 male rats.	Resveratrol was administered orally or intraperitoneally (i.p.) to F344 male rats. In the groups in which resveratrol was administered orally, the number of NMBA-induced esophageal tumors per rat was significantly reduced, and the size of maximum tumors in each group with resveratrol treatment was also significantly smaller than that in NMBA alone group. Although the pathological examination did not indicate significantly decreased incidence of carcinomas by administering resveratrol, the tendency of carcinogensis suppression was observed. Semiquantitative RT-PCR and ELISA analysis demonstrated that following NMBA treatment, the expression of COX-1 mRNA was strongly present in tumor tissues, while weakly present in nontumor tissues; the expression of COX-2 mRNA was induced in both tumor and nontumor tissues. The production of prostaglandin E_2 (PGE_2) increased approximately 6-fold, compared with the normal esophageal mucosa.	The higher expression of COX-1, the upregulated COX-2 expression, and the increased levels of PGE_2 synthesis were all significantly decreased by administering resveratrol. This study suggests that resveratrol suppressed NMBA-induced rat esophageal tumorigenesis by targeting COXs and PGE_2, and therefore may be a promising natural anticarcinogenesis agent for the prevention and treatment of human esophageal cancer.	477
Assessment of the anticancer potential of resveratrol, sesamol, sesame oil, and sunflower oil in the promotion stage of cancer development employing the *in vitro* Epstein-Barr virus early antigen activation assay induced by the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate (TPA).	The group studied the activities of these compounds in the brine shrimp cytotoxicity assay as well as on the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging bioassay to compare some mechanisms of anticancer activity. The group compared the observed chemoprotective capabilities of the four products with the *in vivo* 7,12-dimethylbenz(*a*)anthracene initiated and TPA-promoted mouse skin two-stage carcinogenesis protocols.	All the products tested showed a profound inhibitory effect on the Epstein-Barr virus early antigen induction using Raji cells. Comparatively, sesame oil was the most potent followed by sesamol and then resveratrol. Only sesamol and resveratrol showed a remarkable cytotoxic activity in the brine shrimp lethality assays as well as profound free radical scavenging activity in the DPPH bioassay. In both test systems, sesamol exhibited a more remarkable activity than resveratrol while sesame oil and sunflower oil did not exhibit any appreciable activity even at the highest concentrations tested. In the *in vivo* assay at a 50-fold molar ratio to TPA, sesamol offered 50% reduction in mouse skin papillomas at 20 weeks after promotion with TPA. Under an identical molar ratio to TPA, resveratrol offered a 60% reduction in the papillomas in mouse at 20 weeks. Sesamol seems to be an almost equally potent chemopreventive agent. Sesame oil and sunflower oil offered 20 and 40% protection, respectively, in the mouse skin tumor model. The antioxidant capabilities of these compounds could not solely explain the observed anticancer characteristics.	452

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Bioavalability of resveratrol and its effect on tumor growth were investigated using rabbits, rats, and mice.	Tissue levels of resveratrol were studied after i.v. and oral administration of resveratrol to rabbits, rats, and mice. Half-life of resveratrol in plasma, after i.v. administration of 20 mg resveratrol/kg b.wt., was very short. The highest concentration of resveratrol in plasma, either after i.v. or oral administration, was reached within the first 5 min in all animals studied. Extravascular levels (brain, lung, liver, and kidney) of resveratrol, which paralleled those in plasma, were always < 1 nmol/g fresh tissue. Resveratrol measured in plasma or tissues was in the *trans* form (at least 99%). Hepatocytes metabolized resveratrol in a dose-dependent fashion, which means that the liver can remove circulating resveratrol very rapidly. *In vitro* B16 melanoma (B16M) cell proliferation and generation of reactive oxygen species (ROS) was inhibited by resveratrol in a concentration-dependent fashion (100% inhibition of tumor growth was found in the presence of 5 μM resveratrol). Addition of 10 μM H_2O_2 to B16M cells, cultured in the presence of 5 μM resveratrol, reactivated cell growth. Oral administration of resveratrol did not inhibit growth of B16M inoculated into the footpad of mice (solid growth).	Oral administration of resveratrol decreased hepatic metastatic invasion of B16M cells inoculated intrasplenically. The antimetastatic mechanism involves a resveratrol (1 μM)-induced inhibition of vascular adhesion molecule 1 (VCAM-1) expression in the hepatic sinusoidal endothelium (HSE), which consequently decreased *in vitro* B16M cell adhesion to the endothelium via very late activation antigen 4 (VLA-4).	478
Investigated whether resveratrol and its three analogues (pterostilbene, piceatannol, and resveratrol trimethyl ether) would activate the peroxisome proliferator-activated receptor α (PPARα) isoform. This nuclear receptor is proposed to mediate the activity of lipid-lowering drugs such as the fibrates.	Pterostilbene, piceatannol, and resveratrol trimethyl ether were evaluated at 1, 10, 100, and 300 μM along with ciprofibrate (positive control), for the activation of endogenous PPARα in H4IIEC3 cells. Cells were transfected with a peroxisome proliferator response element-AB (rat fatty acyl CoA β-oxidase response element)-luciferase gene reporter construct. Pterostilbene demonstrated the highest induction of PPARα showing 8- and 14-fold increases in luciferase activity at 100 and 300 μM, respectively, relative to the control. The maximal luciferase activity responses to pterostilbene were higher than those obtained with the hypolipidemic drug, ciprofibrate (33910 and 19460 relative luciferase units, respectively), at 100 μM. Hypercholesterolemic hamsters fed with pterostilbene at 25 ppm of the diet showed 29% lower plasma low density lipoprotein (LDL) cholesterol, 7% higher plasma high density lipoprotein (HDL) cholesterol, and 14% lower plasma glucose as compared to the control group. The LDL/HDL ratio was also statistically significantly lower for pterostilbene, as compared to results for the control animals, at this diet concentration.	Results from *in vitro* studies showed that pterostilbene acts as a PPARα agonist and may be a more effective PPARα agonist and hypolipidemic agent than resveratrol. *In vivo* studies demonstrated that pterostilbene possesses lipid and glucose lowering effects.	479

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Effect and mechanism of action of quercetin, rutin, resveratrol and genistein on human pancreatic carcinoma cell line (Mia PACA-2) and rat pancreatic carcinoma (BSp73AS) using a nude mouse model to indicate effect.	The group measured effects of quercetin on pancreatic cancer in a nude mouse model. They investigated the effects of quercetin, rutin, resveratrol, and genistein on apoptosis and underlying signaling in pancreatic carcinoma cells *in vitro*. Quercetin decreased primary tumor growth, increased apoptosis and prevented metastasis in a model of pancreatic cancer. *In vitro* quercetin and resveratrol, but not rutin, markedly enhanced apoptosis, causing mitochondrial depolarization and cytochrome c release followed by caspase-3 activation. In addition, the effect of a combination of quercetin and resveratrol on mitochondrial cytochrome c release and caspase-3 activity was greater than the expected additive response. The inhibition of mitochondrial permeability transition prevented cytochrome c release, caspase-3 activation, and apoptosis caused by polyphenols. Nuclear factor-κB activity was inhibited by quercetin and resveratrol, but not genistein, indicating that this transcription factor is not the only mediator of the effects of polyphenols on apoptosis.	The results suggest that food-derived polyphenols inhibit pancreatic cancer growth and prevent metastasis by inducing mitochondrial dysfunction, resulting in cytochrome c release, caspase activation and apoptosis.	480
Antileukemic activity of resveratrol *in vitro* and *in vivo* was examined using a mouse myeloid leukemia cell line (32Dp210) and tested in C3H (H-2^k) mice.	Treatment of 32Dp210 leukemia cells with resveratrol at micromolar concentrations significantly and irreversibly inhibited their clonal growth *in vitro*. The clonal growth inhibition by resveratrol was associated with extensive cell death and an increase in hypodiploid (sub-G_1) cells. Resveratol caused internucleosomal DNA fragmentation, suggesting apoptosis as the mode of cell death in 32Dp210 cells. DNA fragmentation was associated with activation of caspase-3, because cleavage of procaspase-3 was detected in resveratrol-treated cells. Although 32Dp210 cells treated with resveratrol *in vitro* did not produce leukemia *in vivo*, only a weak antileukemic effect of resveratrol was observed when administered orally. At doses of 8 mg or 40 mg/kg body daily, five times/wk, resveratrol did not affect the survival of mice injected with leukemia cells. Weak potential antileukemic activity of resveratrol was suggested only at a dose of 80 mg/kg body (2 survivors of 14 mice treated).	Despite strong antiproliferative and proapoptotic activities of resveratrol against 32Dp210 cells *in vitro*, a potential antileukemia effect *in vivo*, if present, occurs only in a small fraction of mice.	481
Effect of resveratrol on growth of 4T1 mammary carcinoma cells *in vitro* and *in vivo* (female BALB/c mice).	*In vitro*, resveratrol inhibited growth of 4T1 breast cancer cells in a dose- and time-dependent manner. *In vivo*, however, resveratrol had no effect on time to tumor take, tumor growth, or metastasis when administered intraperitoneally daily (1, 3, or 5 mg/kg) for 23 days starting at the time of tumor inoculation. Resveratrol had no effect on body weight, organ histology, or estrous cycling of the tumor-bearing mice.	These studies indicate that resveratrol is a potent inhibitor of 4T1 breast cancer cells *in vitro*, it is nontoxic to mice at 1–5 mg/kg, and has no growth-inhibitory effect on 4T1 breast cancer *in vivo*.	482

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
Characterization of the estrogen-modulatory effects of resveratrol in a variety of *in vitro* and *in vivo* mammary models using effect of resveratrol and in combination with 17β-estradiol (E2) in MCF-7, T47D, LY2, and S30 mammary cancer cell lines.	With cells transfected with reporter gene systems, the activation of estrogen response element-luciferase was studied, and using Western blot analysis, the expression of E2-responsive progesterone receptor (PR) and presnelin 2 protein was monitored. Furthermore, the effect of resveratrol on formation of preneoplastic lesions (induced by 7,12-dimethylbenz(a)anthracene) and PR expression (with or without E2) was evaluated with mammary glands of BALB/c mice placed in organ culture. Finally, the effect of p.o. administered resveratrol on *N*-methyl-*N*-nitrosourea-induced mammary tumors was studied in female Sprague-Dawley rats. As a result, in transient transfection studies with MCF-7 cells, resveratrol showed a weak estrogenic response, but when resveratrol was combined with E2 (1 nM), a clear dose-dependent antagonism was observed. Similar mixed estrogenic/antiestrogenic effects were noted with S30 cells, whereas resveratrol functioned as a pure estrogen antagonist with T47D and LY2 cells. Furthermore, in MCF-7 cells, resveratrol induced PR protein expression, but when resveratrol was combined with E2, expression of PR was suppressed. With T47D cells, resveratrol significantly down-regulated steady-state and E2-induced protein levels of PR. With LY2 and S30 cells, resveratrol downregulated presnelin 2 protein expression. Using the mouse mammary organ culture model, resveratrol induced PR when administered alone, but expression was suppressed in the presence of E2 (1 nM). Furthermore, resveratrol inhibited the formation of estrogen-dependent preneoplastic ductal lesions induced by 7,12-dimethylbenz(a)anthracene in these mammary glands ($IC_{50} = 3.2\ \mu M$) and reduced *N*-methyl-*N*-nitrosourea-induced mammary tumorigenesis when administered to female Sprague-Dawley rats by gavage.	In the absence of E2, resveratrol exerts mixed estrogen agonist/antagonist activities in some mammary cancer cell lines, but in the presence of E2, resveratrol functions as an antiestrogen. In rodent models, carcinogen-induced preneoplastic lesions and mammary tumors are inhibited. These data suggest that resveratrol may have beneficial effects if used as a chemopreventive agent for breast cancer.	483
Inhibition of intestinal tumorigenesis and modulation of host-defense–related gene expression in Min mice using human familial adenomatous polyposis.	Resveratrol was administered for seven weeks to Min mice starting at five weeks of age. The control group was fed the same diet and received water containing 0.4% ethanol. Resveratrol prevented the formation of colon tumors and reduced the formation of small intestinal tumors by 70%. Comparison of the expression of 588 genes in the small intestinal mucosa showed that resveratrol downregulated genes that are directly involved in cell cycle progression or cell proliferation (cyclins D1 and D2, DP-1 transcription factor, and Y-box binding protein). Resveratrol upregulated several genes that are involved in the	The data show the complexity of the events associated with intestinal tumorigenesis and the multiplicity of the molecular targets of resveratrol. The high potency and efficacy of resveratrol support its use as a chemopreventive agent in the management of intestinal carcinogenesis.	484

Table 7. Evaluation of resveratrol with *in vivo* model systems. (*Continued*)

Model	What was measured	Effect	Ref.
	recruitment and activation of immune cells (cytotoxic T lymphocyte Ag-4, leukemia inhibitory factor receptor, and monocyte chemotactic protein 3) and in the inhibition of the carcinogenic process and tumor expansion (tumor susceptibility protein TSG101, transforming growth factor-β, inhibin-β A subunit, and desmocollin 2).		
Prevention of tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma–bearing mice (LLC).	Resveratrol significantly reduced the tumor volume, tumor weight and metastasis to the lung in mice bearing highly metastatic LLC tumors. Resveratrol did not affect the number of $CD4^+$, $CD8^+$ and natural killer (NK)1.1.(+) T cells in the spleen. Therefore, the inhibitory effects of resveratrol on tumor growth and lung metastasis could not be explained by natural killer or cytotoxic T-lymphocyte activation. In addition, resveratrol inhibited DNA synthesis most strongly in LLC cells. Resveratrol increased apoptosis in LLC cells, and decreased the S phase population. Resveratrol inhibited tumor-induced neovascularization in an *in vivo* model. Moreover, resveratrol significantly inhibited the formation of capillary-like tube formation from human umbilical vein endothelial cells (HUVEC). Resveratrol inhibited the binding of vascular endothelial growth factor (VEGF) to HUVEC.	The study suggests that the antitumor and antimetastatic activities of resveratrol might be due to the inhibition of DNA synthesis in LLC cells and the inhibition of LLC-induced neovascularization and tube formation (angiogensis) of HUVEC by resveratrol.	485
Investigation whether resveratrol affects azoxymethane (AOM)-induced colon carcinogenesis using male F344 rats.	Resveratrol was administered to male F344 rats. Aberrant crypt foci (ACF) were isolated and proliferation, apoptosis and expression of the cell cycle genes Bax and p21 were determined.	Resveratrol significantly reduced the number of ACF/colon and their multiplicity, and also abolished large ACF. In resveratrol-treated rats, Bax expression was enhanced in ACF but not in the surrounding mucosa. In both controls and resveratrol-treated rats, proliferation was higher in ACF than in normal mucosa. p21 was expressed in ACF of controls and of resveratrol-treated rats and in normal mucosa of controls, but was lost in normal mucosa of resveratrol-treated animals. The results suggest a protective role of resveratrol in colon carcinogenesis with a mechanism involving changes in Bax and p21 expression.	486
Potential activities of six compounds—butylated hydroxyanisole (BHA), *myo*-inositol, curcumin, esculetin, resveratrol and lycopene—as chemopreventive agents against lung tumor induction in A/J mice by benzo(*a*)pyrene (B*a*P) and 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK).	Groups of 20 A/J mice were treated weekly by gavage with a mixture of B*a*P and NNK (3 μmol each) for 8 weeks, then sacrificed 26 weeks after the first carcinogen treatment. Mice treated with BHA (20 or 40 μmol) by gavage 2 h before each dose of B*a*P and NNK had significantly reduced lung tumor multiplicity. Treatment with BHA (20 or 40 μmol) by gavage weekly or with dietary BHA (2000 ppm), curcumin (2000 ppm) or resveratrol (500 ppm) from 1 week after carcinogen treatment until termination had no effect on lung tumor multiplicity. Treatment with dietary *myo*-inositol (30,000 ppm) or esculetin (2000 ppm) from 1 week after carcinogen treatment until termination significantly reduced lung	The results of this study demonstrate that BHA is an effective inhibitor of B*a*P plus NNK-induced lung tumorigenesis in A/J mice when administered during the period of carcinogen treatment and that, among the compounds tested, *myo*-inositol is most effective after carcinogen treatment.	487

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
	tumor multiplicity, with the effect of *myo*-inositol being significantly greater than that of esculetin. Treatment with dietary LTO (167, 1667 or 8333 ppm) from 1 week before carcinogen treatment until termination had no effect on lung tumor multiplicity.		
Inhibition of tumor growth in a rat tumor model.	Resveratrol was administered to rats that were inoculated with a fast growing tumor (the Yoshida AH-130 ascites hepatoma). Tumor cell content was measured. Flow cytometric analysis of the tumor cell population was employed.	Resveratrol administration to the rats caused a very significant decrease (25%) in the tumor cell content. The effects of this diphenol were associated with an increase in the number of cells in the G_2/M cell cycle phase. Flow cytometric analysis of the tumor cell population revealed the existence of an aneuploid peak (representing 28% of total), which suggests that resveratrol causes apoptosis in the tumor cell population resulting in a decreased cell number.	488
Investigation of cancer chemopreventive activity three major stages of carcinogenesis.	Resveratrol was tested for anti-initiation activity, antipromotion activity, and antiprogression activity. It was tested in carcinogen-treated mouse mammary glands in culture, a mouse skin cancer model, and a rat anti-inflammation model.	Resveratrol was found to act as an antioxidant and antimutagen and to induce phase II drug-metabolizing enzymes; it mediated anti-inflammatory effects in a rat model and inhibited cyclooxygenase and hydroperoxidase functions; and it induced human promyelocytic leukemia cell differentiation. It inhibited the development of preneoplastic lesions in carcinogen-treated mouse mammary glands in culture and inhibited tumorigenesis in the two-stage mouse skin cancer model.	40
Investigation of antitumorigenic activities of two flavonols, a stilbene and a hydroxybenzoic acid employing a two-stage CD-1 mouse skin cancer model using 9,10-dimethyl-1,2-benzanthracene (DMBA) as initiator and phorbol 12-myristate 13-acetate (TPA) as promoter.	Animals were treated with (+)-catechin, *trans*-resveratrol, quercetin and gallic acid at doses ranging from 0 to 25 μmol (dissolved in 200 μL acetone), twice a week for eighteen weeks. The solution was applied topically to the shaved dorsal region of each animal. The relative potencies of the polyphenols were compared by evaluating the percentage inhibition of tumor formation in individual mice and the number of mice developing one or more tumors with the different dose schedules. Analyses revealed that quercetin was the most ($ED_{50} < 1$ μmol) and gallic acid the least effective (ED_{50} 5–10 μmol). (+)-Catechin and *trans*-resveratrol were intermediate, with ED_{50} values of 5 and 6 μmol, respectively.	This group showed recently that *trans*-resveratrol is absorbed much more efficiently than (+)-catechin and quercetin in humans after oral consumption. Taking this and the relative concentrations in red wine into account, together with the present results, they conclude that *trans*-resveratrol may be the most effective anticancer polyphenol present in red wine as consumed by healthy human subjects.	453
Investigation of resveratrol and epigallocatechin-3-gallate (EGCG) effectiveness to protect against chemically induced mammary cancer by modulating mammary gland architecture, cell proliferation, and apoptosis using female Sprague-Dawley CD rats.	Animals were exposed to either resveratrol (1 g/kg AIN-76A diet), EGCG (0.065% in the drinking water), or control diet (AIN-76A) for the entirety of their life starting at birth. At 50 days postpartum, rats were treated with 60 mg dimethylbenz[*a*]anthracene (DMBA)/kg body weight to induce mammary cancer. Resveratrol, but not EGCG, suppressed mammary carcinogenesis (fewer tumors per rat and longer tumor latency). Analysis of mammary whole mounts from 50-day-old rats revealed that resveratrol, but not EGCG, treatment resulted in more differentiated lobular structures. Bromodeoxyuridine (BrdU) incorporation studies showed that resveratrol treatment caused a significant reduction in proliferative cells in	The research group concluded that resveratrol in the diet can reduce susceptibility to mammary cancer, while EGCG in the drinking water at the dose used was not effective.	489

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
	mammary terminal ductal structures at 50 days postpartum, making them less susceptible to carcinogen insult. The epithelial cells of terminal end buds in the mammary glands of resveratrol-treated rats also showed an increase in apoptotic cells compared to the control or EGCG-treated rats as measured by a DNA fragmentation assay. At the given doses, resveratrol treatment resulted in a serum resveratrol concentration of 2.0 μM, while treatment with EGCG resulted in a serum EGCG concentration of 31.06 nM. 17β-Estradiol, progesterone, and prolactin concentrations in the serum were not significantly affected by resveratrol or EGCG. Neither polyphenol treatment resulted in toxicity as tested by alterations in body weights, diet and drink consumptions, and day to vaginal opening.		
Investigated the effects of resveratrol on vertebrate aging.	Used the annual fish, *Nothobranchius furzeri*, resveratrol treatment prolonged lifespan and delayed the onset of age-related dysfunctions in this fish. This result identified resveratrol as the first molecule which consistently retards aging in organisms as diverse as yeast, worm, fly and fish, but it also revealed the potential of this short-lived fish as an animal model for pharmacological research.	Because *Nothobranchius furzeri* is related to stickleback (*Gasterosteus aculeatus*), the "pufferfishes" Takifugu and Tetraodon, and even more closely related to medaka (*Oryzias latipes*), it became a useful model system for the aging research community.	490
Employed the mouse Lewis lung carcinoma (LLC) model (C57BL/6 mice) to determine the anti-tumor activity of heyneanol A (HA).	HA, which is a tetramer of resveratrol, was isolated from the the root of *Vitis amurensis* Rupr. (Vitaceae). Administered HA and resveratrol by daily i.p. injection to the animals that were subcutaneously inoculated with LLC cells. HA dose-dependently decreased tumor growth without any adverse effect on body weight and seemed more potent than resveratrol. The tumor inhibitory effects were accompanied by a marked increase in tumor cell apoptosis detected by cleaved caspase-3 and TUNEL assays and decreased tumor cell proliferation index and tumor microvessel density, supporting the involvement of apoptotic and antiangiogenic activities in the anticancer effects. Next, investigated the cellular and molecular processes that mediate the apoptosis and antiangiogenesis effects using cell culture models. Mechanistically, treatment of LLC cells *in vitro* with HA or resveratrol significantly increased apoptotic cells. Both HA and resveratrol activated caspase-9 and caspase-3, caused PARP cleavage, which were completely blocked by a pan caspase inhibitor, Z-VAD-FMK. In addition, HA and resveratrol suppressed the bFGF-induced proliferation and capillary differentiation of human umbilical vein endothelial cells, inhibited the binding of bFGF to its receptor in a test tube assay and the bFGF-induced vascularization of Matrigel plugs *in vivo*. Remarkably, HA was fairly stable in cell culture medium and did not undergo intracellular conversion to resveratrol.	This study showed that heyneanol A is an active anticancer compound that induces caspase-mediated cancer cell apoptosis and inhibits angiogenesis rivaling the potency of resveratrol and merits further evaluation for cancer chemoprevention.	491

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
Investigated resveratrol to determine if it adds to the growth inhibitory effects of cisplatin and doxorubicin on human ovarian (OVCAR-3) and uterine (Ishikawa) cancer cells in culture and to evaluate whether it diminishes the cardiac toxicity of doxorubicin in rodent heart.	OVCAR-3 and Ishikawa cancer cells in culture were treated with cisplatin and doxorubicin, respectively, with and without resveratrol; and cell growth and viability were evaluated. Neonatal rat ventricular myocytes received doxorubicin in the presence and absence of resveratrol, and cell viability was evaluated. Mice received doxorubicin +/ resveratrol, and electrocardiograms were evaluated. Data were analyzed with analysis of variance and Scheffe's test. Resveratrol combined with cisplatin or with doxorubicin demonstrated an additive growth-inhibitory anticancer effect with a left shift of the cisplatin and doxorubicin dose/response curves. Resveratrol increased the viability of neonatal rat ventricular myocytes that were treated with doxorubicin and reduced doxorubicin-induced bradycardia and QTc interval prolongation in mice.	Resveratrol adds to the growth inhibitory/anticancer activity of cisplatin and doxorubicin *in vitro* and protects against doxorubicin-induced cardiac toxicity both *in vitro* and in mice.	492
Used Fischer rats to investigate the effects of resveratrol on angiogenesis in rat gliomas by color Doppler ultrasound (CDUS).	The correlation among the tumor growth rate, macroscopic angiogenesis measured by CDUS, and microscopic angiogenesis was assessed by immunohistochemical staining. Fischer rats were subcutaneously inoculated with rat RT-2 glioma cells and treated with resveratrol for 4 weeks. The tumor size was measured and the animal survival followed. CDUS examination was used to measure tumor blood flow shown as the color Doppler vascularity index (CDVI). Immunohistochemical staining of CD31 was carried out to assess the microvessel density (MVD) of the tumors. The CDVI, MVD, and tumor size were correlated. Rats treated with resveratrol (40 mg/kg/day) had slower tumor growth rates than those of the control groups ($p < 0.05$). The CDVI, MVD and tumor size were significantly correlated (linear regression, $p < 0.0001$).	Resveratrol-suppressed glioma growth was significantly correlated with the inhibition of macroscopic and microscopic angiogenesis.	493
Investigation of the effect of resveratrol on lung carcinoma.	The Lewis lung carcinoma results do not agree with previous reports where a clear effect of resveratrol was shown on tumor burden in both mice and rats. However, administration of the diphenol had a clear antimetastatic effect, decreasing both the number and the weight of the lung metastases. Similar effects were observed both at 5 and 25 mg/kg body weight per day, resulting in an approximately 40% reduction in the number of metastases.	These results suggest that resveratrol could be tentatively given as a preventive agent in cancer patients undergoing radiotherapy or chemotherapy.	494
Examination of antimutagenic effects and effect on the immune response of representative series of substances which commonly occur in human diet. Utilized the Ames bacterial mutagenicity tests and	Using the Ames test and *in vivo* micronucleus, the chemiluminescence test, the blastic transformation test and the comet assay, the research group examined antimutagenic effects of chemically identified chemoprotective substances in the pure form (resveratrol, diallylsulfide, phenethyl isothiocyanate, ellagic acid, epigallocatechin gallate, genistein, and curcumin) on mutagenicity induced by three	All complete vegetable homogenates and substances of plant origin tested showed a clear antimutagenic and immunomodulatory activities on mutagenicity and immunosuppression induced by reference mutagens. Only in the Ames test the effect of some phytochemicals against direct mutagen MNU was lower compared to indirect mutagens AFB1 and IQ. Similarly, resveratrol and epigallocatechin gallate had no inhibitory effect on mutagenicity MNU in the Ames test.	495

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
in vivo chemiluminescence test to investigate antigenotoxic and immunomodulatory effects of juices and vegetable homogenates (carrot + cauliflower, cauliflower, red cabbage, broccoli, onion, garlic) on the genotoxicity of AFB1 and pyrolysates of aminoacids.	reference mutagens: aflatoxin B1 (AFB1), 2-amino-3-metylimidazo[4,5,-*f*] chinolin (IQ) and *N*-nitroso-*N*-metylurea (MNU) and effect of phytochemicals on the immunosuppression caused by these mutagens.		
Investigation of human oral epithelial cell monolayers to determine the carcinogen (benzo[*a*]pyrene) transport, bioactivation, and DNA binding in a bioengineered human gingival epithelial tissue construct and the chemopreventive effects of dietary polyphenols.	Short-term experiments showed that polyphenols can traverse human gingival epithelial tissue as well as be effectively taken up by the tissue. The model cigarette smoke carcinogen B*a*P very slowly, but to a great extent, accumulated in the tissue with maximal uptake at 24 h. Such exposure clearly resulted in DNA binding of B*a*P by the tissue. This DNA binding was associated with B*a*P-induced CYP1B1 as well as CYP1A1 expression, as evidenced by mRNA measurements. Cotreatment of the oral tissue with dietary polyphenols, including resveratrol and quercetin, and B*a*P, resulted in significant inhibition of the B*a*P-DNA binding. Using fluorescence microscopy as well as simultaneous autoradiography, it was demonstrated that quercetin penetrates the entire stratified tissue layer, but that quercetin was also oxidized within the cells.	The bioengineered oral tissue construct opens up improved ways of understanding and preventing/treating smoking-induced oral cancer.	496
Investigation of resveratrol using nude mice to determine chemotherapeutic activity in breast cancer.	Resveratrol has been shown to induce transcription via both ERα and ERβ. The research group observed significantly lower tumor growth, decreased angiogenesis, and increased apoptotic index in ERα - ERβ+ MDA-MB-231 tumors in resveratrol-treated nude mice compared with controls. *In vitro*, a significant increase in apoptosis was found in resveratrol-treated MDA-MB-231 cells in addition to significantly reduced extracellular levels of VEGF.	This study supports the potential use of resveratrol as a chemotherapeutic agent in breast cancers.	497
Evaluation of resveratrol as an inhibitor of colon carcinogenesis using Wistar male rats.	Wistar male rats were divided into six groups, group 1 were control rats, group 2 were control rats that received resveratrol (8 mg/kg body weight p.o. every day), rats in groups 3–6 were treated weekly with 1,2-dimethylhydrazine (DMH, 20 mg/kg body weight, s.c. $\times$ 15 times). In addition, groups 4, 5, and 6 received resveratrol as in group 2. Modifying effects were assessed using aberrant crypt foci (ACF) and the extent of histopathological lesions as end point markers. At the end of 30 weeks, resveratrol markedly reduced tumor incidence, the degree of histological lesions and also the size of tumors significantly ($P < 0.05$) as compared to the unsupplemented DMH-treated rats. The number of ACF consisting of more	The results suggest resveratrol is as an effective chemopreventive agent, which suppresses DMH-induced colon carcinogenesis at various stages.	498

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
	than six aberrant crypts per rat was observed in group 6 (6.2 +/ 1.4), group 5 (7.7 +/− 1.0) and group 4 (8.2 +/− 1.4) which were significantly lower than that of group 3 (22.3 +/− 2.4) ($P < 0.05$). The most pronounced inhibition of ACF development was noted in rats fed resveratrol for the entire period and also during the post-initiation period. Also, resveratrol administration lowered the number of argyrophilic nucleolar organizing region-associated proteins per nucleus in non-lesional colonic crypts, which reflects the cell proliferation activity. Oxidative imbalance in DMH-treatment was significantly ($P < 0.01$) modulated on resveratrol supplementation as indicated by optimal concentration of thiobarbituric acid reactive substances, superoxide dismutase, catalase, and reduced glutathione.		
Exploration of the immunological mechanism of the antitumor function of resveratrol through *in vitro* or *in vivo* experiments.	The tumor cell growth repression rate was measured by MTT colorimetry. Flow cytometry was used to analyze the cell cycle of Hep2 cells (laryngeal squamous cancer cell line). The immune function and cytokine levels in the serum of the tumor-bearing mice were determined by MTT colorimetry, hemolysis spectrophotography, improved Mayer's method and ELISA. Resveratrol inhibited the tumor cell growth and enhanced the apoptosis of tumor cells in time- and concentration-dependent manners showing the phenomenon of obvious G_0/G_1 blocking and apoptotic peak. The maximal tumor inhibition rate came up to 42.76%. Furthermore, resveratrol improved function of T, B lymphocytes, killing activity of NK cells, release of antibodies, and the total complement activity in serum. It also increased contents of IL-2 and TGF-β1 but reduced that of IL-8 and VEGF.	Resveratrol not only affects tumor cells directly but also exert antitumor efficiency through reinforcing cell-mediated, humoral immune response and accommodating lymphocytes to secrete cytokines.	499
Investigation to examine the effects on angiogenesis-mediated processes and to define anti-angiogenesis mechanisms for flavonoids by examining the effects and mechanisms of resveratrol on angiogenesis and tumor growth using the chick chorioallantoic membrane (CAM) model of angiogenesis, the CAM tumor growth model, and the effect on p53 in fibroblast growth factor-2 (FGF2) stimulated human endothelial cells using immunoassay.	Resveratrol demonstrated potent inhibition (effective dose $50 = 0.7+/0.1$ μM) of FGF2-induced angiogenesis and tumor growth. Furthermore, resveratrol significantly ($P < 0.01$) inhibited platelet/fibrin clot-promoted human colon and fibrosarcoma tumor growth in the CAM tumor model. Resveratrol in a concentration-dependent (1–3 μM) manner significantly promoted apoptosis in FGF2-stimulated endothelial cells by increasing p53 protein production. These data indicated potent anti-angiogenesis efficacy, inhibition of tumor growth, and clot-mediated enhanced tumor growth.	These data suggest that resveratrol has the potential to exhibit anticancer benefits as a chemopreventive and chemotherapeutic agent.	500

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
Evaluated the chemopreventive effects of resveratrol against UVB radiation-mediated skin tumorigenesis in the SKH-1 hairless mouse model.	The research group used a UVB initiation-promotion protocol in which the control mice were subjected to chronic UVB exposure (180 mJ/cm^2, twice weekly, for 28 weeks). The experimental animals received either a pretreatment (30 min before each UVB) or post-treatment (5 min after UVB) of resveratrol (25 or 50 μmole/0.2 mL acetone/mouse). The mice were followed for skin tumorigenesis and were killed at 24 h after the last UVB exposure, for further studies. The topical application of skin with resveratrol (both pre- and post- treatment) resulted in a highly significant inhibition in tumor incidence and delay in the onset of tumorigenesis. The post-treatment of resveratrol was found to impart equal protection as the pretreatment; suggesting that resveratrol-mediated responses may not be sunscreen effects. Because survivin is a critical regulator of survival/death of cells, and its overexpression has been implicated in several cancers, the research group evaluated its involvement in chemoprevention of UVB-mediated skin carcinogenesis by resveratrol. The data demonstrated a significant upregulation of survivin (both at protein and mRNA levels), upregulation of phospho-survivin protein, and downregulation of proapoptotic Smac/DIABLO protein in skin tumors; whereas treatment with resveratrol resulted in the attenuation of these responses. This study also suggests that resveratrol enhanced apoptosis in UVB exposure–mediated skin tumors.	The group demonstrated that resveratrol imparts strong chemopreventive effects against UVB exposure–mediated skin carcinogenesis (relevant to human skin cancers) and the chemopreventive effects of resveratrol may, at least in part, be mediated via modulations in survivin and other associated events. On the basis of this work, it is conceivable to design resveratrol-containing emollient or patch, as well as sunscreen and skin-care products for prevention of skin cancer and other conditions, which are believed to be caused by UV radiation.	457
Investigated the dose response of resveratrol using cDNA stress arrays coupled with drug metabolizing enzymatic (DME) assays to investigate the expression of stress-responsive genes and phase I and II detoxifying enzymes in rat livers using male and female CD rats	Male and female CD rats were treated with high doses of resveratrol (0.3, 1.0, and 3.0 g/kg/day) for a period of 28 days. Total RNA from rat liver was reverse-transcribed using gene-specific primers and hybridized to stress-related cDNA arrays. Among female rats, Phase I DME genes were repressed at 0.3 and 1.0 g/kg/day doses, while genes such as manganese superoxide dismutase, cytochrome P450 reductase, quinone oxidoreductase, and thiosulfate sulfurtransferase demonstrated a dose-dependent increase in gene expression. The modulation of these liver genes suggest the potential toxicity as observed among the rats at the highest dose level of resveratrol. Real-time PCR was conducted on some of the phase II DME genes and antioxidant genes to validate the cDNA array data. The gene expression from real-time PCR demonstrated good correlation with the cDNA array data. UGT1A genes were among the most robustly induced especially at the high doses of resveratrol. The research group performed phase I and phase II	This study reports that at lower doses of resveratrol, there are few significant changes in gene expression whereas the modulation of liver genes at the high dose of resveratrol may relate to the potential toxicity observed..	501

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
	enzymatic assays on cytochrome P450 2E1 (CYP2E1), cytochrome P450 1A1 (CYP1A1), NAD(P)H:quinone oxidoreductase (NQO1), glutathione *S*-transferase (GST), and UDP-glucuronosyl transferase (UGT). Induction of phase II detoxifying enzymes was most pronounced at the highest dose of resveratrol. CYP1A1 activity demonstrated a decreasing trend among the 3 dose groups and CYP2E1 activity increased marginally among female rats over controls.		
Investigated the effects of resveratrol on the development of mammary tumors appearing spontaneously in HER-2/neu transgenic mice at an early age.	The mechanisms involved in the resveratrol antitumor effect were evaluated by studying the immune effectiveness, tumor apoptosis, and expression of mRNA and protein for HER-2/neu in tumoral mammary glands from resveratrol-treated mice and in tumor cell lines. Resveratrol supplementation delayed the development of spontaneous mammary tumors ($p < 0.001$), reduced the mean number and size of mammary tumors ($p < 0.0001$) and diminished the number of lung metastases in HER-2/neu transgenic mice. The effects of resveratrol were associated with downregulation of HER-2/neu gene expression and increased apoptosis both in tumoral mammary glands and in murine (N202) and human (SKBr3) tumor cell lines. Neither the basal, the IL-2–induced NK activity nor the lymphocyte number and proliferation was modified in resveratrol-supplemented compared to control mice.	The results demonstrate that resveratrol supplementation delays the development and reduces the metastasizing capacity of spontaneous mammary tumors in HER-2/neu transgenic mice. The antitumor effect of resveratrol might be related to the downregulation of HER-2/neu expression and the induction of apoptosis in tumor cells.	502
Tested the synthetic resveratrol analog 3,4,5,4′-tetramethoxystilbene (DMU-212) to show its potent inhibitory effects of adenoma development in the Apc(Min+) mouse, a model of human intestinal carcinogenesis using Apc(Min+) mice.	Apc(Min+) mice received either stilbene derivative with the diet (0.2%), and adenomas were counted after experiments were terminated. Resveratrol and DMU-212 decreased adenoma load by 27% and 24%, respectively, compared to untreated controls. Cyclooxygenase (COX) enzymes are important mechanistic targets of resveratrol, and the research group investigated whether DMU-212 interferes with the expression and activity of COX in human colon cells. Incubation of HCA-7 cancer cells for 24-96 h with either stilbene derivative (1–50 μM) decreased prostaglandin E-2 (PGE-2) production, but only resveratrol decreased COX-2 protein expression. In mice, which received either stilbene derivative (0.2%) for 3 weeks with their diet, PGE-2 levels in the intestinal mucosa were reduced by between 45% and 62% compared to mice on control diet. While resveratrol inhibited enzyme activity in purified COX preparations, DMU-212 failed to do so. The PGE-2 decrease seen with DMU-212 in cells and *in vivo* is probably mediated via its metabolites.	The results suggest that alteration of the resveratrol molecule to generate DMU-212 does not abrogate its ability to decrease adenoma number in Apc^{Min+} mice or to interfere with PGE-2 generation in cells.	503

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
Investigated the apoptosis of implanted primary gastric cancer cells in nude mice induced by resveratrol and the relation between this apoptosis and expression of bcl-2 and bax.	A transplanted tumor model was established by injecting human primary gastric cancer cells into subcutaneous tissue of nude mice. Resveratrol (500, 1000, and 1500 mg/kg) was directly injected beside tumor body 6 times at an interval of 2 d. Then changes of tumor volume were measured continuously, and tumor inhibition rate of each group was calculated. The research group observed the morphologic alterations by electron microscope, measured the apoptotic rate by TUNEL staining method, detected the expression of apoptosis-regulated genes bcl-2 and bax by immunohistochemical staining and PT-PCR. Resveratrol could significantly inhibit carcinoma growth when it was injected near the carcinoma. An inhibitory effect was observed in all therapeutic groups, and the inhibition rate of resveratrol at the dose of 500, 1000, and 1500 mg/kg was 10.58%, 29.68%, and 39.14%, respectively. Resveratrol induced implanted tumor cells to undergo apoptosis with apoptotic characteristics, including morphological changes of chromatin condensation, chromatin crescent formation, nucleus fragmentation. The inhibition rate of 0.2 mL of normal saline solution, 1500 mg/kg DMSO, 500 mg/kg resveratrol, 1000 mg/kg resveratrol, and 1500 mg/kg resveratrol was 13.68 $\pm$ 0.37%, 13.8 $\pm$ 0.43%, 48.7 $\pm$ 1.07%, 56.44 $\pm$ 1.39%, and 67 $\pm$ 0.96%, respectively. The positive rate of bcl-2 protein of each group was 29.48 $\pm$ 0.51%, 27.56 $\pm$ 1.40%, 11.86 $\pm$ 0.97%, 5.7 $\pm$ 0.84% and 3.92 $\pm$ 0.85%, respectively, by immunohistochemical staining. The positive rate of bax protein of each group was 19.34 $\pm$ 0.35%, 20.88 $\pm$ 0.91%, 40.02 $\pm$ 1.20%, 45.72 $\pm$ 0.88%, and 52.3 $\pm$ 1.54%, respectively, by immunohistochemical staining. The density of bcl-2 mRNA in 0.2 mL normal saline solution, 1500 mg/kg DMSO, 500 mg/kg resveratrol, 1000 mg/kg resveratrol, and 1500 mg/kg resveratrol decreased progressively and the density of bax mRNA in 0.2 mL normal saline solution, 1500 mg/kg DMSO, 500 mg/kg resveratrol, 1,000 mg/kg resveratrol, and 1,500 mg/kg increased progressively with elongation of time by RT-PCR.	Resveratrol was able to induce apoptosis of transplanted tumor cells. This apoptosis may be mediated by downregulating apoptosis-regulated gene bcl-2 and upregulating the expression of apoptosis-regulated gene bax.	504
Evaluate the inhibitory effect of some antioxidants, including ascorbic acid and grape seed extract (GSE), on endogenous N'-nitrosonornicotine (NNN) formation in F344 rats treated with nornicotine and sodium nitrite.	The F344 rats were treated with nornicotine and sodium nitrite by gavage twice daily for 3 days. The study included four groups of rats: (1) negative control group A, to which no chemical was administered; (2) negative control group B, treated with nornicotine alone (2.5 μmol per gavage); (3) positive control group, to which both nornicotine (2.5 μmol per gavage) and sodium nitrite (7.5 μmol per gavage) were administered; and (4) rats treated with nornicotine (2.5 μmol per gavage), inhibitor (7.5	The study demonstrated endogenous NNN formation in rats treated with nornicotine and sodium nitrite, and the inhibitory effect of this process by ascorbic acid, dixydroxyfumaric acid, and catechin.	505

(Continued on next page)

Table 7. Evaluation of resveratrol with *in vivo* model systems. *(Continued)*

Model	What was measured	Effect	Ref.
	or 37.5 μmol per gavage), and sodium nitrite (7.5 μmol per gavage). The mean (+SD) total amount of NNN in the 3-day urine of rats treated with both nornicotine and sodium nitrite was 4.78 +/ 2.88 nmol. The order of inhibition of endogenous NNN formation in rats at the molar ratio [nitrite]:[inhibitor] 1:5 was as follows: ascorbic acid (91%) > dihydroxyfumaric acid (86%) approximately catechin (85%) > resveratrol (no inhibition). Treatment of rats with grape seed extract did not produce statistically significant inhibition of endogenous nornicotine nitrosation.		
Resveratrol has been reported to have antitumor effects, and recently it has been demonstrated that resveratrol partially blocks skeletal muscle wasting by interfering with NF-κB activation. This study investigated the potential antiwasting properties of resveratrol on different models of cancer cachexia in experimental animals.	Incubations of isolated extensor digitorum longus muscles in the presence of 30 μM of resveratrol caused a significant decrease in the rate of protein degradation. However, administration of resveratrol *in vivo* to both rats bearing the Yoshida AH-130 ascites hepatoma (at the dose of 1 mg/kg body weight) and mice bearing the Lewis lung carcinoma (at two different doses, 5 and 25 mg/kg body weight) had no effect on skeletal muscle mass or body weight in tumor-bearing rodents. In addition, a combination of resveratrol (3 mg/kg body weight) and fish oil was also unable to induce any changes in skeletal muscle weights.	It is concluded from this study that resveratrol is unable to influence muscle mass *in vivo* and has no potential role as anticachectic agent.	506

Table 8. Clinical and human trials.

Aim	Experimental approach	Conclusion	Ref.
Nutritional biomarkers may be better measures of dietary exposure than self-reported dietary data. Evaluated resveratrol metabolites, potential biomarkers of wine consumption, in humans after moderate consumption of sparkling, white, or red wines.	Performed 2 randomized, crossover trials and a cohort study. In the first study, 10 healthy men consumed 30 g of ethanol/day as sparkling wine or gin for 28 days. In the second trial, 10 healthy women consumed 20 g of ethanol/day as white or red wine for 28 days. Evaluated 52 participants in a study on the effects of a Mediterranean diet on primary prevention of cardiovascular disease (the PREDIMED Study). Used liquid chromatography–tandem mass spectrometry to analyze urinary total resveratrol metabolites (TRMs) and predictive values and ROC curve analyses to assess the diagnostic accuracy. Observed significant increases in TRMs [72.4 (95% confidence interval, 48.5–96.2; $P = 0.005$), 211.5 (166.6–256.3; $P = 0.005$), and 560.5 nmol/g creatinine (244.9–876.1; $P = 0.005$)] after consumption of sparkling, white, or red wine, respectively, but no changes after the washout or gin periods. In the cohort study, the reported daily dose of wine consumption correlated directly with TRMs ($r = 0.654$; $P < 0.001$). Using a cutoff of 90 nmol/g, used TRMs to differentiate wine consumers from abstainers with a sensitivity of 72% (60%–84%); and a specificity of 94% (87%–100%).	Resveratrol metabolites in urine may be useful biomarkers of wine intake in epidemiologic and intervention studies.	510
Examined the absorption, bioavailability, and metabolism of ^{14}C-resveratrol after oral and i.v. doses in six human volunteers.	Plasma and urine were collected and tested for absorption. Liquid chromatography/mass spectrometry analysis identified three metabolic pathways, i.e., sulfate and glucuronic acid conjugation of the phenolic groups and, interestingly, hydrogenation of the aliphatic double bond, the latter likely produced by intestinal microflora. Extremely rapid sulfate conjugation by the intestine/liver appears to be the rate-limiting step in the bioavailability of resveratrol.	Accumulation of resveratrol (the systemic bioavailability is very low) in epithelial cells along the aerodigestive tract and potentially active resveratrol metabolites may still produce cancer-preventive and other effects.	507
Examined whether acute intake of a red grape polyphenol extract has a positive effect on brachial artery flow-mediated dilatation. It has been shown that acute intake of red wine improves endothelial-dependent vasodilatation. It is not clear, however, which constituents of red wine are responsible for this effect.	Thirty (30) male patients were recruited with coronary heart disease. They were randomly assigned either to a red grape polyphenol extract (600 mg) dissolved in 20 ml of water ($n = 15$) or 20 mL of water (placebo) ($n = 15$). The extract of grapes contained 4.32 mg epicatechin, 2.72 mg catechin, 2.07 mg gallic acid, 0.9 mg *trans*-resveratrol, 0.47 mg rutin, 0.42 mg epsilon-viniferin, 0.28 mg, *p*-coumaric acid 0.14 mg ferulic acid and 0.04 mg quercetin per gram. Flow-mediated dilatation of the brachial artery was evaluated after reactive hyperemia induced by cuff obstruction of the forearm, using high-resolution ultasonography. Particularly, flow-mediated dilatation was measured after fasting and 30, 60, and 120 min after the intake of the grape extract or placebo. Intake of the red grape polyphenol extract caused an increase in flow-mediated dilatation, peaking at 60 min, which was significantly higher than the baseline values (4.52 ± 1.34 versus $2.6 \pm 1.5\%$; $P < 0.001$) and the corresponding values at 60 min after the intake of placebo (4.52 ± 1.34 versus $2.64 \pm 1.8\%$, $P < 0.001$). There was no change in FMD values after the intake of placebo throughout the whole duration of the study.	Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. These results could probably, at least partly, explain the favorable effects of red wine on the cardiovascular system.	511

(Continued on next page)

Table 8. Clinical and human trials. *(Continued)*

Aim	Experimental approach	Conclusion	Ref.
A phase I study of oral resveratrol (single doses of 0.5, 1, 2.5, or 5 g) was conducted in 10 healthy volunteers per dose level.	Resveratrol and its metabolites were identified in plasma and urine by high-performance liquid chromatography–tandem mass spectrometry and quantitated by high-performance liquid chromatography–UV. Consumption of resveratrol did not cause serious adverse events. Resveratrol and six metabolites were recovered from plasma and urine. Peak plasma levels of resveratrol at the highest dose were 539 $\pm$ 384 ng/mL (2.4 μmol/L, mean $\pm$ SD; n = 10), which occurred 1.5 h post-dose. Peak levels of two monoglucuronides and resveratrol-3-sulfate were 3- to 8-fold higher. The area under the plasma concentration curve (AUC) 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. Cancer chemopreventive effects of resveratrol in cells *in vitro* require levels of at least 5 μmol/L.	The results suggested that consumption of high-dose resveratrol might be insufficient to elicit systemic levels commensurate with cancer chemopreventive efficacy. However, the high systemic levels of resveratrol conjugate metabolites suggest that their cancer chemopreventive properties warrant investigation.	512
Recruiting: Resveratrol for Patients with Colon Cancer Sponsor: University of California, Irvine Identifier: NCT00256334 Enrollment: 6	Ages Eligible for Study: 18 years and above Genders Eligible for Study: Both Patients diagnosed with colon cancer by colonoscopic biopsy and tissue obtained under UCI04-05. Patients with a plan for surgical resection at UCIMC within 2–4 weeks of enrollment.	A prior report and data from this study group suggest that resveratrol modulates Wnt signaling, a signaling pathway that is activated in over 85% of colon cancers. In this proposal, studies will be performed to define the actions of resveratrol on the Wnt signaling pathway in a clinical trial in which patients with colon cancer will receive treatment with resveratrol and correlative laboratory studies will examine its effects directly on colon cancer and normal colonic mucosa. These studies will provide data on the mechanisms of resveratrol action and provide a foundation for future prevention trials, correlative studies, and therapeutic clinical research with this agent.	21
Recruiting: Resveratrol in Preventing Cancer in Healthy Participants University of Michigan Cancer Center Identifier: NCT00098969 Enrollment: 10–40	Ages Eligible for Study: 18–80 Years Genders Eligible for Study: Both Determine the concentration of resveratrol and its metabolites in the plasma, urine, and feces of healthy participants. Correlate dose with systemic concentration of this drug and its metabolites in these participants. Determine the safety of this drug in these participants.	Chemoprevention is the use of certain drugs to keep cancer from forming, growing, or coming back. The use of resveratrol may prevent cancer. This phase I trial is studying the side effects and best dose of resveratrol in preventing cancer in healthy participants.	21

Table 8. Clinical and human trials. *(Continued)*

Aim	Experimental approach	Conclusion	Ref.
Recruiting: Resveratrol in Treating Patients With Colorectal Cancer That Can Be Removed By Surgery	Ages Eligible for Study: 18 years and above	Resveratrol may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. This phase I trial is studying the side effects and best dose of resveratrol in treating patients with colorectal cancer that can be removed by surgery.	21
University of Michigan Cancer Center	Genders Eligible for Study: Both		
Identifier: NCT00433576	Determine the relationship between oral dose of resveratrol and the colon mucosal levels of resveratrol and its metabolites in patients with resectable colorectal cancer.		
Enrollment: 20	Determine the relationship between colon mucosal levels of resveratrol and its metabolites and plasma concentrations of resveratrol and its metabolites in these patients. Determine cyclooxygenase-2 (COX-2) expression in colorectal cancer tissue before and after treatment in these patients. Determine M_1G concentration in colonic cancer tissue and in circulating white blood cells (WBC) before and after treatment. Correlate M_1G concentration in colorectal cancer tissue with M_1G concentration in circulating WBC. Assess the Ki67 labeling index in normal and malignant tissues in at least 10 fields per section. Correlate COX-2 expression in colorectal cancer tissue with COX-2 expression in circulating WBCs. Assess the toxicity profile of this drug.		
Recruiting: Dietary Intervention in Follicular Lymphoma (KLYMF)	Ages Eligible for Study: 18 years and above	A dietary intervention study in patients with follicular lymphoma (FL) stage III/IV to assess the ability of several dietary factors to induce apoptosis, inhibit cell proliferation, and modulate tumor cell infiltrate *in vivo*.	21
Rikshospitalet-Radiumhospitalet HF, University of Oslo	Genders Eligible for Study: Both		
Identifier: NCT00455416	Permanent address in Norway, located in health region south or east. People living outside these areas in other health regions in Norway may be able to participate but after individual evaluation.		
Enrollment: 45	Histologically verified follicular lymphoma grade I or II without clinical signs of transformation to aggressive lymphoma. Stage III/IV. Previously untreated or at least 1 year since rituximab treatment or 6 months since cytotoxic chemotherapy. Not scheduled for disease-specific treatment for the next 3 months. At least one pathological superficial lymph node available for ultrasound guided biopsy. Cytologically and/or immunocytologically compatible with follicular lymphoma. Women with childbearing potential, only with use of safe contraceptives		