Cancer chemoprevention by resveratrol: *In vitro* and *in vivo* studies and the underlying mechanisms (Review)

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Abstract. Cancer, next only to heart diseases, is the second leading cause of deaths in the United States of America and many other nations in the world. The prognosis for a patient with metastatic carcinoma of the lung, colon, breast, or prostate (four of the most common and lethal forms of cancer, which together account for more than half of all deaths from cancer in the USA), remains dismal. Conventional therapeutic and surgical approaches have not been able to control the incidence of most of the cancer types. Therefore, there is an urgent need to develop mechanism-based approaches for the management of cancer. Chemoprevention via non-toxic agents could be one such approach. Many naturally occurring agents have shown cancer chemopreventive potential in a variety of bioassay systems and animal models, having relevance to human disease. It is appreciated that an effective and acceptable chemopreventive agent should have certain properties: (a), little or no toxic effects in normal and healthy cells; (b), high efficacy against multiple sites; (c), capability of oral consumption; (d), known mechanism of action; (e), low cost; and (f), acceptance by human population. Resveratrol is one such agent. A naturally occurring polyphenolic anti-oxidant compound present in grapes, berries, peanuts and red wine. In some bioassay systems resveratrol has been shown to afford protection against several cancer types. The mechanisms of resveratrol's broad cancer chemopreventive effects are not completely understood. In this review, we present the cancer chemopreventive effects of resveratrol in an organ-specific manner. The mechanisms of the anti-proliferative/cancer chemopreventive effects of resveratrol are also presented. We believe that continued efforts are needed, especially well-designed pre-clinical studies in the animal models that closely mimic/represent human disease, to establish the usefulness of resveratrol as cancer chemo-preventive agent. This should be followed by human clinical trials in appropriate cancer types in suitable populations.

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1. Introduction

Cancer, next only to heart diseases, is the second leading cause of deaths in the United States of America and many other nations in the world. Despite of immense efforts to improve treatment and find cures for this disease, overall mortality rates for most forms of cancer have not significantly declined in the past 25 years (1). The prognosis for a patient with metastatic carcinoma of the lung, colon, breast, or prostate (four of the most common and lethal forms of cancer, which together account for more than half of all deaths from cancer in the USA), remains dismal (2). Conventional medicine treats cancer along the lines of an infection, i.e. an invader to be eliminated (3 and refs. therein). This thinking has led to radical attempts to get rid of the tumor through the 'cut, burn and poison' technique of surgery, radiation and chemotherapy. This approach has not been successful in the management of cancer and has often been criticized (4 and refs. therein). Due to variety of reasons, the pre-cancerous cells are formed in the body but the immune system detects and destroys them before it becomes a problem. Clearly, if the immune system is weak and unable to perform its proper function, the cancer appears. The conventional medicine and therapy, rather than bolstering the immune system, destroys it even more with strong immune suppressants (5). In fairness to conventional medicine, it has been a standard idea that cancer cells do not trigger an immune response by the body. This idea may not be correct, however, cancer therapy inflicts considerable damage to the body, which

further weakens it and diverts energy and resources away from dealing with the cancer and toward repairing the damage from therapy. Thus, indeed, there is an urgent need to develop mechanism-based approaches for the management of cancer i.e. to develop strategies, which can eliminate only the damaged (pre-malignant) or malignant cells without harming the normal ones. The answer to combat cancer may, therefore, lie with the prevention rather than cure. Chemoprevention via non-toxic agents could be such an approach (6).

Chemoprevention is defined as the use of pharmacological or natural agents to prevent arrest or reverse the process of cancer development (i. e. carcinogenesis) before invasion and metastasis occur (6,7). It is believed that the dietary factors may contribute to as much as one-third of potentially preventable cancers; and the long-term preventive effect of plant-based agents for chemoprevention of cancer and several other chronic diseases is well documented (8 and refs. therein). Many naturally occurring agents have shown cancer chemo-preventive potential in a variety of bioassay systems and animal models, having relevance to human disease (9-16). It is appreciated that an effective and acceptable chemopreventive agent should have certain properties: (a), little or no toxic effects in normal and healthy cells; (b), high efficacy against multiple sites; (c), capability of oral consumption; (d), known mechanism of action; (e), low cost; and (f), acceptance by human population. For these properties, in the recent past, the phytochemicals present in the diet and beverages consumed by humans have received much attention (6-16). Resveratrol (Fig. 1) is one such agent (17-64,67-72,82,101-105 and refs. therein), which has been shown to possess many biological activities (shown in Fig. 2) relevant to human diseases (78).

Resveratrol, chemically known as *3,5,4'-trihydroxy-stilbene* (Fig. 1), is a naturally occurring polyphenolic anti-oxidant compound present in grapes, berries, peanuts and red wine. Some epidemiological studies have indicated that red wine protects against many diseases including cancer (25-34 and references therein). The traditional Japanese and Chinese folk medicines have used root extract of the weed *Polygonum cuspidatum*, which contains resveratrol, to fight liver, skin and circulatory-diseases (32-34 and refs. therein). The cancer chemopreventive properties of resveratrol were first appreciated when Jang *et al* demonstrated that resveratrol possesses cancer chemopreventive activity against all the three major stages of carcinogenesis i.e. initiation, promotion and progression (31 and refs. therein).

2. An overview of cancer chemopreventive effects of resveratrol

It is reported (31), that resveratrol: (i), acts as an antioxidant and antimutagen; (ii), induces phase II drug-metabolizing enzymes (anti-initiation activity); (iii), mediates anti-inflammatory effects; (iv), inhibits cyclooxygenase and hydro-peroxidase functions (anti-promotion activity); and (iv), induces human promyelocytic leukemia cell differentiation (anti-progression activity). In addition, resveratrol also inhibited the development of preneoplastic lesions in carcinogen-treated mouse mammary glands in culture and inhibited tumorigenesis in a mouse skin cancer model (31).
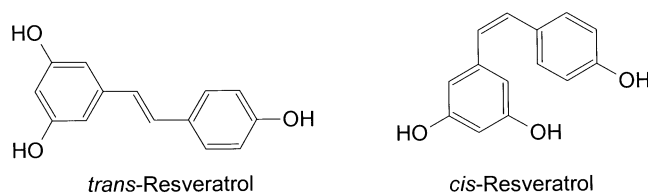

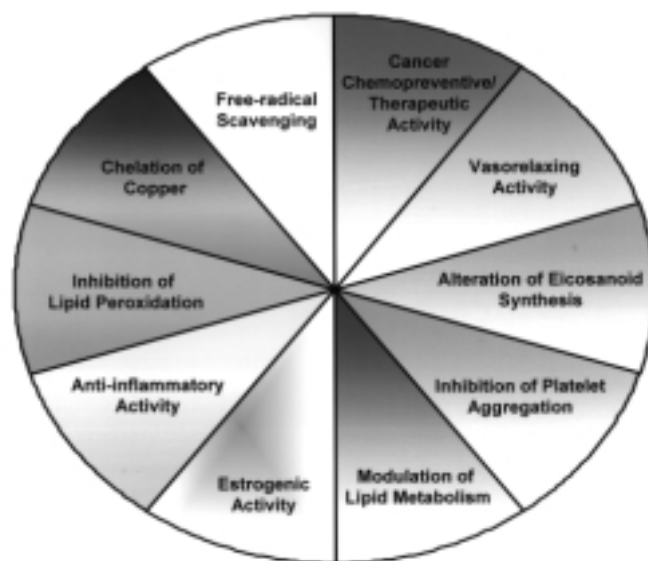Figure 1. Chemical structure of *cis*- and *trans*-resveratrol.

Figure 2. Major biological effects of resveratrol.

Following the observation by Jang *et al* (31), many studies have shown cancer chemopreventive and/or therapeutic potential of resveratrol (30-32,34-64,67-72,82-100,102-105 and refs. therein). Resveratrol has been shown to impart anti-proliferative effects on human breast epithelial cells (44,46,51-54 and refs. therein). Carbo *et al* (55) have demonstrated that resveratrol administration to male Wistar rats, inoculated with Yoshida AH-130 ascites hepatoma tumors, resulted in a significant decrease in tumor cell content and this response was found to be associated with a G2/M phase arrest and apoptosis (55). Elattar and Virji (56,57), have shown that resveratrol induced significant dose-dependent inhibition in human oral squamous carcinoma cell (SCC-25) growth and DNA synthesis. Resveratrol reduced viability and DNA synthesis capability of human promyelocytic leukemia (HL-60) cells, via an induction of apoptosis through BCl-2 pathway (58). Hsieh and Wu (41) investigated the effects of resveratrol on growth, induction of apoptosis, and modulation of prostate-specific gene expression using DU-145, PC-3, and JCA-1 human CaP cells. This study suggested that resveratrol negatively modulates CaP cell growth, by affecting mitogenesis as well as inducing apoptosis, in a prostate cell type-specific manner (41). Resveratrol has also been shown to regulate PSA gene expression by an AR-independent

mechanism (59). In another study, Mitchell *et al* demonstrated the inhibitory effects of resveratrol on androgen action in the LNCaP cells (60). This study found that resveratrol represses different classes of androgen-regulated genes at the protein or mRNA level including prostate-specific antigen, human glandular kallikrein-2, AR-specific coactivator ARA70, and the WAF1/p21 (60). In another study, Kampa *et al* have shown that many antioxidant polyphenols present in wine, including resveratrol inhibit the proliferation of human prostate cancer cell lines (61).

Recently, employing cDNA microarray technology, Narayanan *et al* demonstrated that resveratrol treatment to LNCaP cells causes alterations in the p53-responsive genes, p300, Apaf-1, NF-κB/p50 and p65 and PPAR families of genes (62). Based on the data the authors suggested that the modulation of multiple signaling pathways by resveratrol might be responsible for the growth inhibition of LNCaP cells (62).

Furthermore, resveratrol has shown strong anti-proliferative properties that has been attributed to its ability to efficiently scavenge the essential tyrosyl radical of the small protein of ribonucleotide reductase and, consequently, to inhibit deoxyribonucleotide synthesis (63,64). It was also observed that resveratrol non-competitively inhibited the cyclooxygenase (COX)-2 transcription and activity in human mammary epithelial cells and colon cancer cells (65,66). Resveratrol was found to act as a potential inhibitor of inducible NO synthase (iNOS) (67) and inducible COX-2 (53). Resveratrol also demonstrated anti-inflammatory effects and inhibited the activity of hydroperoxidase enzymes (suggestive of anti-promotion activity) in addition to cause the differentiation of human promyelocytic leukemia cells, indicating that this compound may also depress the progression phase of cancer (8).

Several studies have shown that the cancer preventive activity of resveratrol could be attributed to its ability to trigger apoptosis in carcinoma cells (68-70). Few researchers have shown that resveratrol is metabolized by the enzyme cytochrome P450 (CYP)-1B1, which is found in a variety of different tumors. When resveratrol is metabolized by the CYP1B1, an anti-leukemic agent piceatannol is formed (71,72 and refs. therein) that has been previously identified as an anti-leukemic agent. This observation provides a novel explanation for the cancer preventive properties of resveratrol.

Taken together, these studies suggested that resveratrol may be developed as a potential cancer chemopreventive agent.

3. The French paradox

Despite the heavy consumption of cheese, butter, eggs, rich creamy sauces, and other fat-containing foods, the French population appears to be surprisingly healthy, with low incidence of coronary heart diseases and certain types of cancer. Although a typical French diet contains approximately 15% more saturated fat than an American diet, and even though they exercise less than Americans, the rate of heart diseases for the French people is 60% lower than that of Americans (73-76 and refs. therein). Similarly, the incidence of certain cancer types are much lower in French population than

in American (76 and refs. therein). This has been attributed to high consumption of red wine by French people that in fact ranks to the highest per capita consumption in the world. This phenomenon has been dubbed as the French Paradox (73-77 and refs. therein).

4. Chemical structure of resveratrol

The chemical structure of resveratrol is important because from its structure, the information regarding its biological activity may be obtained. In Fig. 1, the chemical structures of *cis*- and *trans*-resveratrol some of their derivatives is shown. Because of the presence of more than one phenol groups, this agent is classified as a polyphenol. Polyphenols are often antioxidants, as they can react with free radicals to form a stable molecule that is less toxic than the original radical (78-81 and refs. therein).

5. Resveratrol and cancer

As discussed earlier in this review, following a study by Jang *et al* (31) many studies in cell culture system as well as in animal models have shown the cancer chemopreventive as well as cancer therapeutic effects of resveratrol. In the following pages, we have summarized the organ specific cancer chemo-preventive effects of this polyphenol i.e. antioxidant that may be a constituent of diet and/or beverages consumed by human population.

Resveratrol and prostate cancer. Prostate cancer is the third most frequently diagnosed cancer in males in Western industrialized countries and according to an estimate in the year 2002, about 189,000 men will be diagnosed with CaP in the USA and about 30,200 prostate cancer-related deaths are predicted. Studies, conducted in cell culture system, have evaluated the anti-proliferative effects of resveratrol on prostate carcinoma cells. Hsieh and Wu (41) investigated the effects of resveratrol on growth, induction of apoptosis, and modulation of prostate-specific gene expression using DU-145, PC-3, and JCA-1 human prostate carcinoma cells (41). This study suggested that resveratrol negatively modulates CaP cell growth, by affecting mitogenesis as well as inducing apoptosis, in a prostate cell-type-specific manner. Resveratrol has also been shown to regulate PSA gene expression by an AR-independent mechanism (41,59). Mitchell *et al* demonstrated the inhibitory effects of resveratrol on androgen action in the androgen-dependent human prostate carcinoma LNCaP cells (60). This study found that 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 WAF1/p21 (60). This study further suggested that resveratrol might be a useful chemopreventive agent for prostate cancer. In another study, Kampa *et al* have shown that many antioxidant polyphenols present in wine, including resveratrol, inhibit the proliferation of human prostate cancer cell lines (61).

Recent studies showed the unique ability of resveratrol to exert opposing effects on two important processes in cell cycle progression, induction of S phase and inhibition of DNA

synthesis in prostate carcinoma cells (82). The mechanism of the anti-proliferative effects of resveratrol against prostate cancer has not been fully understood; but some studies have suggested that it might be related to its ability to inhibit ribonucleotide reductase (63) and cyclooxygenase 2 transcription (65). Expression of PSA, a prostate specific protein used as a marker to monitor responsiveness of prostate cancer patients to various treatment modalities, was found to be significantly down-regulated by resveratrol, via an AR-independent mechanism (41,59).

Kampa *et al* (61) showed that resveratrol (at low concentrations) imparts a direct inhibitory effect of on the proliferation of human prostate cancer cell lines via an inhibition of the production of NO (61). cDNA microarray studies have characterized the alterations in gene expression pattern in human prostate cancer cells in response to resveratrol. Over a 48-h exposure of androgen-sensitive LNCaP cells to resveratrol, a total of 555 genes, showed more than a two-fold difference in expression (62).

Resveratrol and breast cancer. Breast cancer is the most common non-skin cancer in women. It is estimated that 203,500 new cases of invasive breast cancer will be diagnosed in 2002, and that 39,600 women will die from the disease. Resveratrol has also been shown to have a direct anti-proliferative effect of breast cancer cells, irrespective of their estrogen receptor status (44,83). Resveratrol has also been reported to inhibit the development of preneoplastic lesions in cancinogen-treated mouse mammary organ cultures (50). Other *in vitro* studies have shown that resveratrol inhibited growth of 4T1 breast cancer cells in a dose- and time-dependent manner (86). However, in this study, resveratrol was found to have no effect on the growth of 4T1-implanted tumors or its metastasis when administered intraperitoneally daily (1, 3, or 5 mg/kg) for 23 days starting at the time of tumor inoculation (86). Ciolino *et al* (87) reported that resveratrol does not competitively bind the AhR complex; in contrast, Casper *et al* (88) showed that resveratrol bound the AhR receptor but did not block formation of a nuclear AhR complex in T47D cells co-treated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In this study the treatment of T47D or MCF-7 breast cancer cells with 10 µM resveratrol was found to inhibit the induction of CYP1A1 mRNA and CYP1A1-dependent activity after treatment with TCDD (88). In contrast, resveratrol was not found to inhibit 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 (88). Resveratrol was found to induce 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. Thus, 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 (88).

Actinomycin D chase experiments in T47D cells demonstrated that resveratrol and dehydroepiandrosterone increased the rate of CYP1A1 mRNA degradation, whereas resveratrol did not affect CYP1A1-dependent activity in cells pretreated with TCDD. These data suggested that resveratrol inhibits CYP1A1 via an AhR-independent post-transcriptional pathway (89,90). Resveratrol (52-74 µM) was shown to antagonize the effect of linoleic acid, a potent breast cancer cell stimulator, and suppressed the growth of both ER-positive and -negative cell lines (91,92). A close structure similarity was found to exist between synthetic estrogen (4,4'-dihydroxy-*trans*-α,ß-diethylstilbene) and resveratrol.

It is still unclear whether resveratrol is an estrogen receptor agonist or antagonist. Presumably, resveratrol interacts with estrogen receptor to inhibit its activation (44,83,90,93). Resveratrol also inhibited the proliferation of the estrogen-receptor negative human breast carcinoma cell line MDA-MB-468. In addition, resveratrol significantly elevated the expression of the growth inhibitor TGF-ß2 mRNA without changes in TGF-ß1 and TGF-ß3 expression. These data suggested that resveratrol inhibits proliferation by altering autocrine growth modulator pathways in breast cancer cells (94,95).

Studies have shown that resveratrol down-modulates the p53 content in MCF-7 breast cancer cells (40,83,96,97). Several studies have shown that the anti-proliferative effects of resveratrol against breast cancer could be attributed to its ability to trigger apoptosis (34,40,95,98). In fact, resveratrol has been shown to inhibit the growth of both estrogen receptor (ER)-positive (MCF-7) and ER-negative (MCF-10, MDA-MB-231) breast cancer cells via an induction of apoptosis. Lu and Serrano (93) reported that resveratrol acts as an estrogen antagonist in the presence of estrogen, leading to inhibition of the growth of MCF-7 cells, while Clement *et al* (34) and Nakagawa *et al* (92) demonstrated that resveratrol inhibited the growth of T47D and MCF-7 cells by inducing apoptosis. Gehm *et al* (83) reported that resveratrol stimulated the proliferation of ER-positive T47D breast cancer cells by acting as an agonist for the ER. In contrast, Clement *et al* (34) reported that resveratrol inhibited the growth of T47D breast cancer cells by inducing Fas/Fas ligand-mediated apoptosis. Further studies by Bowers *et al* (99) revealed that resveratrol exhibits estrogen antagonist activity for ERα with selected estrogen response elements (EREs), while it has no antagonist activity for ERß. These data suggest that resveratrol differentially affects the transcriptional activities of ERα and ERß in an ERE sequence-dependent manner. Other studies also showed that low concentrations of polyphenols, and consecutively, consumption of wine, or other polyphenol-rich foods and beverages, may have a beneficial antiproliferative effect on breast cancer cell growth (83,91,92,97). In a recent study, it has been shown that resveratrol suppressed DMBA-induced mammary carcino-gensis, which was found to be correlated with down-regulation of NF-κB, COX-2 and matrix metalloprotease-9 expression (30). Thus it may be suggested that the NF-κB-pathway plays an important role in the chemopreventive effects of resveratrol against breast cancer (30). Resveratrol has been reported to inhibit COX-2 transcription and activity in phorbol ester-treated human mammary epithelial cells (54).

Resveratrol and skin cancer. In the USA, non-melanoma skin cancer that includes basal- and squamous-cell carcinoma, is the most frequently diagnosed form of cancer accounting for nearly half of all cancer types (85,100 and refs. therein). According to an estimate, more than a million new cases of skin cancers are diagnosed annually in the USA (85,100 and refs. therein). Depending on the cellular origin, human skin cancer is classified as melanocytic or epithelial; melanomas are less common but more lethal than epithelial skin cancers (31). Studies have shown that resveratrol prevents the development of skin cancer. In fact, the first study showing the cancer chemopreventive effect of resveratrol demonstrated that resveratrol acts as an effective agent for the prevention of chemically-induced skin carcinogenesis (31).

Jang and Pezzuto (8) showed that the application of TPA to mouse skin induces oxidative stress, as evidenced by numerous biochemical responses, including significant generation of H_2O_2 and enhanced levels of myeloperoxidase and oxidized glutathione reductase activities and decreases in glutathione levels and superoxide dismutase activity. TPA treatment was also found to elevate the expression of cyclooxygenase-1 (COX-1), COX-2, c-myc, c-fos, c-jun, transforming growth factor-ß1 (TGF-ß1) and tumor necrosis factor-α (TNF-α) (8 and refs. therein). The pre-treatment of mouse skin with resveratrol negated several of these TPA-induced effects in a dose-dependent manner. H_2O_2 and glutathione levels were restored to control levels, as were myeloperoxidase, oxidized glutathione reductase and superoxide dismutase activities (8). The reverse transcriptase-polymerase chain reaction (RT-PCR) analysis showed that TPA-induced increases in the expression of c-fos and TGF-ß1 were inhibited by resveratrol. In addition to the activities described above, resveratrol inhibited the *de novo* formation of inducible nitric oxide synthase (iNOS) in mouse macrophages stimulated with lipopolysaccharide (8).

She *et al* (103) showed that 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 inhibitor, 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 (103 and refs. therein). 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 (103). 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.

Further, She *et al* (104) determined that c-jun NH(2)-terminal kinases (JNKs) are involved in resveratrol-induced p53 activation and induction of apoptosis in JB6 mouse epidermal cells. Resveratrol activated JNKs dose-dependently

within a dose range of 10-40 µM. 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. The data suggested that JNKs act as mediators of resveratrol-induced activation of p53 and apoptosis, which may occur partially through p53 phosphorylation (104).

Chemopreventive potential of stilbenes (trans-resveratrol) is reported to be most effective among several red wine polyphenols viz. flavanols [(+)-catechin], flavonols (quercetin) and hydroxybenzoic acids (gallic acid), in 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 (102). The authors concluded that *trans*-resveratrol may be the most effective anticancer polyphenol present in red wine (102).

In another study, chemopreventive capability of reseveratrol was found to be most effective compared to sesamol, sesame oil and sunflower oil in the *in vivo* 7,12 dimethyl-benz(a)anthracene initiated and TPA-promoted mouse skin carcinogenesis protocols (42).

Recent study from our laboratory has shown resveratrol treatment of A431 cells leads to induction of cyclin kinase inhibitor WAF1/CIP1/p21, which through the inhibition of cyclin D1 and cyclin E, and their regulatory subunits cdk2 and cdk6, results in an imposition of artificial checkpoint at G1 S transition thereby resulting in the arrest of cells in G0-G1 phase of the cell cycle (105).

The clinical observations and epidemiological data strongly suggest that non-melanoma skin cancer is related to cumulative exposure to solar ultraviolet radiation (9,99,100,105-107 and refs. therein). In a recent study from this laboratory (106), we examined whether resveratrol possesses a potential to ameliorate the damages caused by short-term UVB exposure to the mouse skin. Single topical application of resveratrol (25 µmole/0.2 ml acetone/mouse) to SKH-1 hairless mice was found to result in significant inhibition of UVB (180 mJ/cm^2)-mediated increase in bifold-skin thickness and skin edema. The resveratrol treatment to mouse skin was also found to result in significant inhibition of UVB-mediated induction of COX and ornithine decarboxylase (ODC) enzyme activities and protein expression of ODC, which are well-established markers for tumor promotion (106). In this study, resveratrol was found to inhibit UVB-mediated increased level of lipid peroxidation, suggesting that protective effects of resveratrol against the damages caused by UVB exposure, might be mediated via its antioxidant properties (106).

In another recent study from this laboratory (108), we demonstrated the involvement of nuclear transcription factor κB (NF-κB) pathway, which is known to play a critical role in skin biology and the development of skin cancer, in chemoprevention of UV damage by resveratrol. In the normal human epidermal keratinocytes, resveratrol was found to block UVB (40 mJ/cm^2)-mediated activation of NF-κB in a dose (5, 10 and 25 µM resveratrol for 24 h)- as well as time- (5 µM resveratrol for 12, 24 and 48 h) dependent fashion.

Resveratrol treatment of keratinocytes was also found to inhibit UVB-mediated: (i), phosphorylation and degradation of IκBα; and (ii), activation of IKKα (108). Based on these data, we suggested that NF-κB pathway plays a critical role in the chemopreventive effects of resveratrol against the adverse effects of UV radiation including photocarcinogenesis (108).

Resveratrol and liver cancer. Few studies have evaluated the chemopreventive effects of resveratrol against liver cancer. Carbo *et al* (55) demonstrated that resveratrol administration to rats inoculated with a fast growing tumour (the Yoshida AH-130 ascites hepatoma) caused a very significant decrease (25%) in the tumor cell content. This effect was found to be associated with an increase in the number of cells in the G2/M phase of the cell cycle. Interestingly, flow cytometric analysis of the tumor cell population revealed the existence of an aneuploid peak (representing 28% of total), which suggested that resveratrol causes apoptosis in the tumor cell population resulting in a decreased cell number. Sun *et al* demonstrated that resveratrol inhibited the growth of hepatoma cells line H22 in a dose- and time-dependent manner via the induction of apoptosis (109). Some studied have shown that *trans*-resveratrol decreased hepatocyte growth factor-induced cell scattering and invasion (110). However, *trans*-resveratrol did not: (i), decrease the level of the hepatocyte growth factor receptor c-met; (ii), impede the hepatocyte growth factor-induced increase in c-met precursor synthesis; (iii), decrease hepatocyte growth factor-induced c-met autophosphorylation, or Akt-1 or extracellular-regulated kinases-1 and -2 activation; (iv), decrease urokinase expression; and (v), block the catalytic activity of urokinase. It was also demonstrated that *trans*-resveratrol decreases hepatocyte growth factor-induced HepG2 cell invasion by an as yet unidentified post-receptor mechanism (110).

Resveratrol suppressed the invasion of the hepatoma cells even at low concentrations. Sera from rats orally given resveratrol restrained only the invasion of AH109A cells. Resveratrol and resveratrol-loaded rat serum suppressed reactive oxygen species-mediated invasive capacity. The anti-invasive activity of resveratrol was found to be independent of the anti-proliferative activity (111). Further, resveratrol was found to strongly inhibit cell proliferation at the micromolar range in a time- and dose-dependent manner in rat hepatoma Fao and human hepatoblastoma HepG2 cell lines. It was suggested that resveratrol prevents or to delays the entry to mitosis (112).

Ciolino and Yeh (113) examined the effect of resveratrol on the function of the aryl hydrocarbon receptor (AHR) and the transcription of cytochrome P450 (CYP)1A1 in human HepG2 hepatoma cells. Resveratrol was found to inhibit the increase in CYP1A1 mRNA caused by the AHR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in a concentration-dependent fashion. The induction of transcription of an aryl hydrocarbon-responsive reporter vector containing the CYP1A1 promoter by TCDD was also inhibited by resveratrol (113). Resveratrol was also found to inhibit the constitutive level of CYP1A1 mRNA and reporter vector transcription in HepG2 cells. The increase in CYP1A1 enzyme activity induced by TCDD was inhibited by resveratrol.

Further, resveratrol was found to prevent TCDD-induced transformation of the cytosolic AHR to its nuclear DNA-binding form (113). These data demonstrated that resveratrol inhibits CYP1A1 expression *in vitro*, by preventing the binding of the AHR to promoter sequences that regulate CYP1A1 transcription (113). This activity was suggested to be important for the chemopreventive activity of resveratrol.

Ciolino *et al* (87) also investigated the effect of resveratrol, on the carcinogen activation pathway regulated by the aryl hydrocarbon receptor. Resveratrol inhibited the metabolism of the environmental aryl hydrocarbon benzo[a]pyrene (B[a]P) catalyzed by microsomes isolated from B[a]P-treated human hepatoma HepG2 cells. Resveratrol was found to inhibit, in a concentration-dependent manner, the activity of CYP1A1/CYP1A2 in microsomes and intact HepG2 cells (72). Resveratrol inhibited the B[a]P-induced expression of the CYP1A1 gene, as measured at the mRNA and transcriptional levels. Resveratrol also abolished the binding of B[a]P-activated nuclear aryl hydrocarbon receptor to the xenobiotic-responsive element of the CYP1A1 promoter but did not bind to the receptor (72). These data demonstrated that resveratrol inhibits aryl hydrocarbon-induced CYP1A activity *in vitro* by directly inhibiting CYP1A1/CYP1A2 enzyme activity and by inhibiting the signal transduction pathway that up-regulates the expression of carcinogen activating enzymes (72).

Resveratrol and colorectal and intestinal cancers. Several studies conducted in cell culture system have shown that resveratrol possesses anti-proliferative/cancer chemopreventive effects against colorectal cancers (18,114). Schneider *et al* (64) 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 was found to cause a 70% growth inhibition. The cells accumulated at the S/G2 phase transition of the cell cycle. Further, resveratrol caused a significant decrease of ornithine decarboxylase (ODC) activity, a key enzyme of polyamine biosynthesis (which is enhanced in cancer growth), indicating that polyamines might represent one of several targets involved in the anti-proliferative effects of resveratrol (64). In another study, vaticanol C, a resveratrol tetramer isolated from the stem bark of Vatica rassak, was found to markedly suppress growth of cancer cells by an induction of apoptosis, which was characterized by nuclear changes and DNA ladder formation, in three different human colon cancer cell lines (115).

Wolter *et al* (116) investigated the effect of resveratrol on the human colonic adenocarcinoma Caco-2 cells. It was found to inhibit growth and proliferation of Caco-2 cells in a dose-dependent manner (12.5-200 μM). Further, resveratrol (200 μM) also increased caspase-3 activity at 24 and 48 h post-treatment. Resveratrol also perturbed cell cycle progression from the S to G2 phase at 50 μM, whereas higher concentrations led to reversal of the S phase arrest. Levels of cyclin D1 and cyclin-dependent kinase (cdk) 4 proteins were found to decrease by resveratrol-treatment (116). In this study, similar results were obtained for the colon carcinoma cell line HCT-116, indicating that cell cycle inhibition by resveratrol is independent of cyclooxygenase inhibition. In

the presence of 200 µM resveratrol, the phosphorylation state of the retinoblastoma protein in Caco-2 cells was shifted from hyperphosphorylated to hypophosphorylated state at 200 µM (116). This study suggested that resveratrol exerts chemopreventive effects on colonic cancer cells by inhibition of the cell cycle (116). In a subsequent study Wolter *et al* studied the effects of a natural resveratrol analogue piceatannol on growth, proliferation, differentiation and cell cycle distribution profile of the human colon carcinoma Caco-2 cells and HCT-116 cells (114). Treatment of Caco-2 cells with piceatannol was found to inhibit: (i), cellular proliferation; (ii), accumulation of cells in the S phase; (iii), down-regulation of cyclin D1, cyclin B1 and cdk 4.

Some studies have linked the effects of resveratrol with the activation of the p53 tumor suppressor (43,70,97,104). Employing human wild-type p53-expressing HCT116 colon carcinoma cell line and HCT116 cells with both p53 alleles inactivated by homologous recombination, Mahyar-Roemer *et al* (70) showed that resveratrol, at concentrations comparable to those found in some foods, could induce apoptosis independently of p53. The cell death was found to be mitochondria-mediated and not receptor-mediated. Resveratrol upregulated Bax regardless of p53 status. Remarkably, apoptosis was preceded by mitochondrial proliferation and signs of epithelial differentiation suggesting that resveratrol triggers a p53-independent apoptotic pathway in HCT116 cells that may be linked to differentiation (70). Another study showed that in HCT116 colon carcinoma cells and its 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. In the absence of Bax, membrane potential collapse was delayed, and the extent of apoptosis was reduced. Resveratrol also inhibited the formation of colonies by both HCT116 and HCT116 bax -/- cells (69). It was suggested that resveratrol at physiological doses can induce a Bax-mediated and a Bax-independent mitochondrial apoptosis.

Tessitore *et al* (117) investigated whether resveratrol affects azoxymethane (AOM)-induced colon carcinogenesis in 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 (200 µg/kg/day in drinking water) was found to significantly reduce the number of ACF/colon [25.7±3.6 (mean ± SEM) versus 39.4±3.3 in controls] and their multiplicity (2.7±0.3 versus 4.9±0.6 in controls), and also abolished large ACF (117). 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 (117). The cyclin kinase inhibitor WAF1/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 (117). This study suggested a protective role of resveratrol in colon carcinogenesis via a mechanism involving changes in bax and p21 expression (117).

Schneider *et al* (118) studied the effect of oral administration of resveratrol, a natural constituent of grapes, on tumorigenesis in Min mice. Min mice are congenic mice genetically predisposed to develop intestinal tumors as a result of a mutation of the Apc gene. Resveratrol (0.01% in the drinking water containing 0.4% ethanol) was administered for seven weeks to Min mice starting at five weeks of age. The control group animals were fed the same diet and received water containing 0.4% ethanol. In this study, resveratrol was found to prevent the formation of colon tumors and reduce the formation of small intestinal tumors by 70% (118). Comparison of the expression of 588 genes in the small intestinal mucosa showed that resveratrol downregulated genes which are directly involved in cell cycle progression or cell proliferation (cyclins D1 and D2, DP-1 transcription factor, and Y-box binding protein) (118). In addition, resveratrol was found to upregulate several genes involved in the 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-ß, inhibin-ß A subunit, and desmocollin 2) (118).

Resveratrol and lung cancer. Hecht *et al* (119) evaluated the chemopreventive activities of butylated hydroxyanisole (BHA), myo-inositol, curcumin, esculetin, resveratrol and lycopene-enriched tomato oleoresin (LTO) against lung tumor induction in A/J mice by the tobacco smoke carcinogens benzo[a]pyrene (BaP) 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 BaP and NNK (3 µmol each) for 8 weeks, then sacrificed 26 weeks after the first carcinogen treatment. In this study, the mice treated with BHA (20 or 40 µmol) by gavage 2 h before each dose of BaP 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 (119). Treatment with dietary myo-inositol (30,000 ppm) or esculetin (2000 ppm) from 1 week after carcinogen treatment until termination significantly reduced lung tumor multiplicity, with the effect of myo-inositol being significantly greater than that of esculetin (119). Treatment with dietary LTO (167, 1667 or 8333 ppm) from 1 week before carcinogen treatment until termination had no effect on lung tumor multiplicity. The results of this study demonstrate that BHA is an effective inhibitor of BaP 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. Resveratrol was found to be ineffective in this study (119).

Kimura and Okuda (120,121), studied the effects of stilbene glucosides isolated from medicinal plants and grapes on tumor growth and lung metastasis in mice bearing highly metastatic Lewis lung carcinoma (LLC) tumors. Stilbene glucosides are naturally occurring phytoalexins, found in a variety of medicinal plants. Among the stilbene derivatives, resveratrol 3-O-D-glucoside is found in grapes and wine. Tumor growth in the right hind paw and lung metastasis were inhibited by oral administration of resveratrol 3-O-D-glucoside

and 2,3,5,4'-tetrahydroxystilbene-2-O-D-glucoside for 33 consecutive days, in LLC-bearing mice (120). The number of CD8^{+} and NK1.1^{+} T cells in the spleen was not affected by the treatment; therefore, the inhibitory effects of these stilbene glucosides on tumor growth and lung metastasis could not be explained by natural killer or cytotoxic T lymphocyte activation. Resveratrol 3-O-D-glucoside inhibited DNA synthesis in LLC cells at a concentration of 1000 μM, but not at lower concentrations (10-100 μM). 2,3,5,4'-Tetra-hydroxystilbene-2-O-D-glucoside also inhibited DNA synthesis in LLC cells (IC_{50} = 81 μM). In addition, both stilbene glucosides were found to inhibit the formation of capillary-like tube networks (angiogenesis) of HUVECs at concentrations of 100-1000 μM (120). The authors of this study suggested that the antitumour and antimetastatic activity of resveratrol 3-O-D-glucoside and 2,3,5,4'-tetrahydroxystilbene-2-O-D-glucoside, might be due to the inhibition of DNA synthesis in LLC cells and angiogenesis of HUVECs (120,121).

Resveratrol and blood cancer. Several studies have evaluated the anti-proliferative/chemopreventive effects of resveratrol against leukemia (37,38,58,98,122-124). Resveratrol reduced the viability and DNA synthesis capability of cultured human promyelocytic leukemia (HL-60) cells (58). In this study, the growth inhibitory and antiproliferative properties of resveratrol were suggested 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 sub-diploid cell population. Further, resveratrol treatment resulted in a gradual decrease in the expression of anti-apoptotic Bcl-2 (58). Another study has shown that the involvement of caspases and CD95-CD95 ligand pathway in resveratrol-mediated induction of apoptosis in the myeloid leukemia HL60 cells (34). Resveratrol-treated tumor cells exhibited 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 (34). Resveratrol-induced cell death was found to be 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 (34). However, resveratrol treatment of normal human peripheral blood lymphocytes (PBLs) did not affect cell survival for up to 72 h, which correlated with the absence of a significant change in either CD95 or CD95L expression on treated PBLs (34). These data showed specific involvement of the CD95-CD95L system in the anti-cancer activity of resveratrol and highlight the chemotherapeutic potential of this natural product, in addition to its recently reported chemopreventive activity (34).

Another study has shown that resveratrol induces Fas signaling-independent apoptosis in THP-1 human monocytic leukaemia cells (125). Bernhard *et al* (125) demonstrated that resveratrol, in the concentration range of 20 μM and above, 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 (125). Expression of transgenic p16/INK4A, which causes arrest in G0/G1, was found to reduce 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 (125). Furthermore, a caspase-8-negative, Fas-resistant Jurkat cell line was shown to be 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 (125). The almost complete inhibition by z-IETD-fmk and the lack of inhibition by crmA suggested caspase-6 to be the essential initiator caspase (125).

Using leukemia lines derived from patients with pro-B t(4;11), pre-B, and T-cell ALL, Dorrie *et al* (122) demonstrated that resveratrol induced extensive apoptotic cell death not only in CD95-sensitive leukemia lines, but also in B-lineage leukemic cells that are resistant to CD95-signaling. Multiple dose treatments of the leukemic cells resulted in >80% cell death with no statistically significant cytotoxicity against normal peripheral blood mononuclear cells under identical conditions. Inhibition of CD95-signaling with a CD95-specific antagonistic antibody indicated that CD95-CD95 ligand interactions were not involved in initiating resveratrol-induced apoptosis (122). 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 (122). The broad-spectrum caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone was ineffective in blocking the depolarization of mitochondrial membranes induced by resveratrol, indicating that resveratrol action was independent of upstream caspase-8 activation via receptor ligation (122). However, increases in caspase-9 activity ranged from 4- to 9-fold in several cell lines after treatment with resveratrol. 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 (122).

Some studies revealed the proapoptotic potential of resveratrol and its hydroxylated analog piceatannol (71). Wieder *et al* (126) showed that both these agents are potent inducers of apoptotic cell death in BJAB Burkitt-like lymphoma cells with an ED50. The treatment of BJAB cells with both substances led to a concentration-dependent activation of caspase-3 and mitochondrial permeability transition. This study demonstrated that resveratrol- and piceatannol-induced cell death in these cells is independent of the CD95/Fas signaling pathway (126). Interestingly, it was found that piceatannol, but not resveratrol acted as an efficient inducer of apoptosis in an *ex vivo* assay with leukemic lymphoblasts of 21 patients suffering from childhood lymphoblastic leukemia (ALL) (126). Another study also showed a similar dose-dependent inhibition of leukemia cells by inducing apoptosis (123). This study also demonstrated that resveratrol imparts anti-leukemic activity against mouse (32Dp210, L1210) and human (U937, HL-60) leukemic cell lines by inhibiting cell proliferation (123). Long-term exposure to resveratrol also inhibited the clonal growth of normal hematopoietic progenitor cells but at a higher IC_{50} of resveratrol than that for most of the leukemia cell lines tested. The inhibitory effect of resveratrol on hematopoietic progenitors was partially reversible, whereas the effect on

leukemia cells was largely irreversible (123). The inhibition of leukemic cells by resveratrol was mediated via an induction of apoptosis. On the other hand, resveratrol did not induce or enhance spontaneously occurring apoptotic death in normal hematopoietic progenitor cells (123).

Resveratrol was found to induce a cell cycle arrest in the S phase in human histiocytic lymphoma U937 cells. Resveratrol induced arrest in the S phase at low concentrations (30-60 μM), but not at higher concentrations. Removal of resveratrol from the culture medium stimulated U937 cells to re-enter the cell cycle synchronously, as judged by the expression patterns of cyclins E and A and by fluorescent activated cell sorting analysis (127). Resveratrol inhibited the growth of THP-1 human monocytic leukemic 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 these cells, which were induced to differentiate into monocytes/macrophages by phorbol myristate acetate (127). A significant fraction of resveratrol-treated cells underwent apoptosis. Resveratrol treatment had neither an 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 shown to be 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 (123).

It was also shown that the treatment with 60 or 100 μM resveratrol for 24 h produced morphological features of apoptosis and DNA fragmentation in U937 cells (127). This was associated with caspase-3 activation and PLC-γ1 degradation. In contrast, resveratrol-induced caspase-3 activation and PLC-γ1 degradation and apoptosis were significantly inhibited in U937/Bcl-2 cells. Bcl-2 over-expressing cells exhibited less cytochrome *c* release and sustained expression levels of the IAP proteins during resveratrol-induced apoptosis. This study indicates 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 (127).

In an interesting study (128), resveratrol was shown to prevent apoptosis induced in human erythroleukemia K562 cells by H_2O_2 and other unrelated stimuli. In this study, resveratrol reversed the elevation of leukotriene B_4 and prostaglandin E_2, induced by H_2O_2 challenge in K562 cells (128). The reduction of leukotriene B_4 and prostaglandin E_2 correlated with the inhibition of the 5-lipoxygenase activity, and the cyclooxygenase and peroxidase activity of prostaglandin H synthase, respectively. Resveratrol also blocked lipoperoxidation induced by hydrogen peroxide in K562 cell membranes (128).

Resveratrol and thyroid cancer. A recent study showed that resveratrol imparts anti-proliferative effects in thyroid carcinoma cell lines (129). Two papillary thyroid carcinoma (PTC) and two follicular thyroid carcinoma (FTC) cell lines treated with resveratrol, showed activation and nuclear translocation of mitogen activated protein kinase (MAPK) *viz.* extracellular signal-regulated kinase (ERK)-1 and -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 inhibitor resulted in blockade of 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 demonstrated that resveratrol induces apoptosis in both papillary and follicular thyroid cancer cell lines. These effects were inhibited by pifithrin-α and by p53 antisense oligonucleotide transfection (129).

6. Conclusion

A structured path for the development of diet-derived agent as cancer chemopreventive agents is emerging fast. Several putative agents are identified on the basis of epidemiological and preclinical mechanistic studies. Resveratrol, a polyphenolic antioxidant, amply present in grapes, red wine and several kinds of nuts and berries, has shown promise against some cancer types. It is true that the investigation of chemopreventive agents should follow an orchestrated effort encompassing parallel pre-clinical studies (both *in vitro* in cell culture and *in vivo* in animal models) of the food source and the isolated agent in terms of efficacy, toxicity, biological mechanisms, and pharmacokinetics. The molecular mechanisms should be preferably investigated using pure constituents (isolated from food source). This should be preceded by pilot clinical trials on the pharmacokinetics and mechanism-based markers of efficacy of the selected intervention. Finally, the chemo-preventive agents should be developed following phase I-III in suitable populations. Although resveratrol has shown remarkable promise as a potent chemopreventive agent in several bioassay systems, there is a long way to go when it could be developed as an agent for chemoprevention/treatment of cancer. Continued efforts are needed, especially well-designed pre-clinical studies in the animal models that closely mimic/represent human disease, to establish the usefulness of resveratrol as cancer chemopreventive agent.

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