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Comprehensive Invited Review

Cancer Chemoprevention Through Dietary Antioxidants: Progress and Promise

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ABSTRACT

It is estimated that nearly one-third of all cancer deaths in the United States could be prevented through appropriate dietary modification. Various dietary antioxidants have shown considerable promise as effective agents for cancer prevention by reducing oxidative stress which has been implicated in the development of many diseases, including cancer. Therefore, for reducing the incidence of cancer, modifications in dietary habits, especially by increasing consumption of fruits and vegetables rich in antioxidants, are increasingly advocated. Accumulating research evidence suggests that many dietary factors may be used alone or in combination with traditional chemotherapeutic agents to prevent the occurrence of cancer, their metastatic spread, or even to treat cancer. ***The reduced cancer risk and lack of toxicity associated with high intake of fruits and vegetables suggest that specific concentrations of antioxidant agents from these dietary sources may produce cancer chemopreventive effects without causing significant levels of toxicity*****. This review presents an extensive analysis of the key findings from studies on the effects of dietary antioxidants such as tea polyphenols, curcumin, genistein, resveratrol, lycopene, pomegranate, and lupeol against cancers of the skin, prostate, breast, lung, and liver. This research is also leading to the identification of novel cancer drug targets.** *Antioxid. Redox Signal.* 10, 475–510.

I. INTRODUCTION

Cancer is a disease in which a series of cumulative genetic and epigenetic changes that are initiated in a normal cell occur. Chemoprevention is a strategy to completely halt or slow the process of cancer development by intervening in the process of carcinogenesis. Cells must develop several acquired capabilities in order to become a malignant cancer: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, tissue invasion, and metastasis. Each of these physiologic changes acquired during tumor development causes evading of an anticancer defense mechanism (102).

In recent years, for a variety of reasons, the most important of which is potential human acceptance, there has been increasing interest in the potential cancer chemopreventive properties of diet-derived and other botanical agents. One way to reduce cancer burden is to develop practical preventive approaches. Various epidemiological evidences suggest that intake of fruits, vegetables, and whole grains may reduce cancer risk in some individuals, and this has been attributed to these foods being rich sources of numerous bioactive compounds (216, 275). Dietary chemopreventive substances are regarded as being generally safe, and some of them may even have efficacy by preventing or reversing premalignant lesions and/or reducing second primary tumor incidence. An ideal chemopreventive agent should be nontoxic to normal cells, highly effective against multiple sites, has known mechanism of action, economical to use, capable of oral consumption, and should be accepted by the human population. Chemotherapeutic agents are costly and used when the disease has significantly progressed and then they are less effective. Therefore, the concept of chemoprevention is gaining increasing attention. It is becoming increasingly appreciated that chemoprevention is a practical approach for cancer control.

Natural dietary agents such as fruits, vegetables, and spices have drawn a great deal of attention from both the scientific community and the general public, owing to their *putative* ability to suppress cancers. Dietary agents consist of a wide variety of biologically active compounds that are ubiquitous in plants, and have been used in traditional medicines for thousands of years. Hippocrates recognized and professed the importance of various foods in the primary constitution of the person ~2,500 years ago. The discovery of new agents which are effective, safe, nontoxic, and the development of dose-schedules that will allow their beneficial use over chronic use is the principal need in the chemoprevention of cancer (268). The importance of adding citrus fruits, carotene-rich fruits and vegetables, and cruciferous vegetables to the diet for reducing the risk of cancer was highlighted in a report by the National Academy of Sciences of the United States as early as 1982 (223). In 1989, a report from the National Academy of Sciences on diet and health recommended consuming five or more servings of fruits and vegetables daily for reducing the risk of both cancer and heart disease (224). The health benefits of fruits and vegetable consumption and intake of vitamins was emphasized by The Five-a-Day program. Phytochemicals may provide desir-

able health benefits beyond basic nutrition to reduce the risk of chronic diseases (191). The most rational approach to chemoprevention is to design and test new agents that act on specific molecular and cellular targets. It is also required that these agents are safe and effective in experimental models before starting the clinical trials. Epidemiological studies with chemopreventive agents have to be confirmed with experimental data in cell culture and animal models before clinical trials are initiated (267).

Figure 1 illustrates the sources of a few dietary agents with chemical structures of the bioactive chemopreventive molecule present therein. The rationale behind the protective effects of fruit and vegetables *may be* the presence of antioxidant molecules which are able to scavenge oxidant species efficiently. Reactive oxygen species (ROS) include a variety of diverse chemical molecules ranging from extremely unstable moieties such as superoxide anions and hydroxyl radicals, to others, such as hydrogen peroxide that is freely diffusible, relatively long-lived and able to cause DNA damage (85).

II. ROLE OF OXIDATIVE STRESS IN CANCER

Cells are capable of counterbalancing the production of reactive oxygen species (ROS) with antioxidants under normal physiological conditions. Endogenous cellular antioxidant defenses include superoxide dismutase, glutathione peroxidase, and catalase. Superoxide dismutases are localized to the cytosol and mitochondria and function to reduce superoxide anion to hydrogen peroxide and water. Glutathione peroxidases, localized in the cytosol and mitochondria, remove the majority of hydrogen peroxide, whereas catalase, located in peroxisomes, is responsible for the removal of high levels of hydrogen peroxide (155). ROS produce single- or double-stranded DNA breaks, purine, pyrimidine, or deoxyribose modifications, and DNA cross-links. Persistant DNA damage can result in either arrest or induction of transcription, induction of signal transduction pathways, replication errors, and genomic instability.

Oxidative stress is caused by a cellular excess of reactive oxygen and nitrogen species, including superoxide (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$), and peroxynitrite ($ONOO^-$). These species have been involved in many processes linked to carcinogenesis such as cell transformation, proliferation, apoptosis resistance, metastasis, and angiogenesis. These reactive species have also been found to induce genetic alterations, including DNA damage, mutations, epigenetic changes, or genomic instability (193). It has been shown that the malignant phenotype of cancer cells can be reversed by reducing the cellular levels of O^{2-} and overexpression of the O^{2-} detoxifying enzymes superoxide dismutases can reduce tumor cell growth, metastasis, and other malignant features of cancer cells (327).

Several studies have also demonstrated that H_2O_2 can induce cell proliferation, apoptosis resistance, increased angiogenesis, invasion, and metastasis (192). It has been reported that an increase in the levels of H_2O_2-detoxifying enzymes could reduce

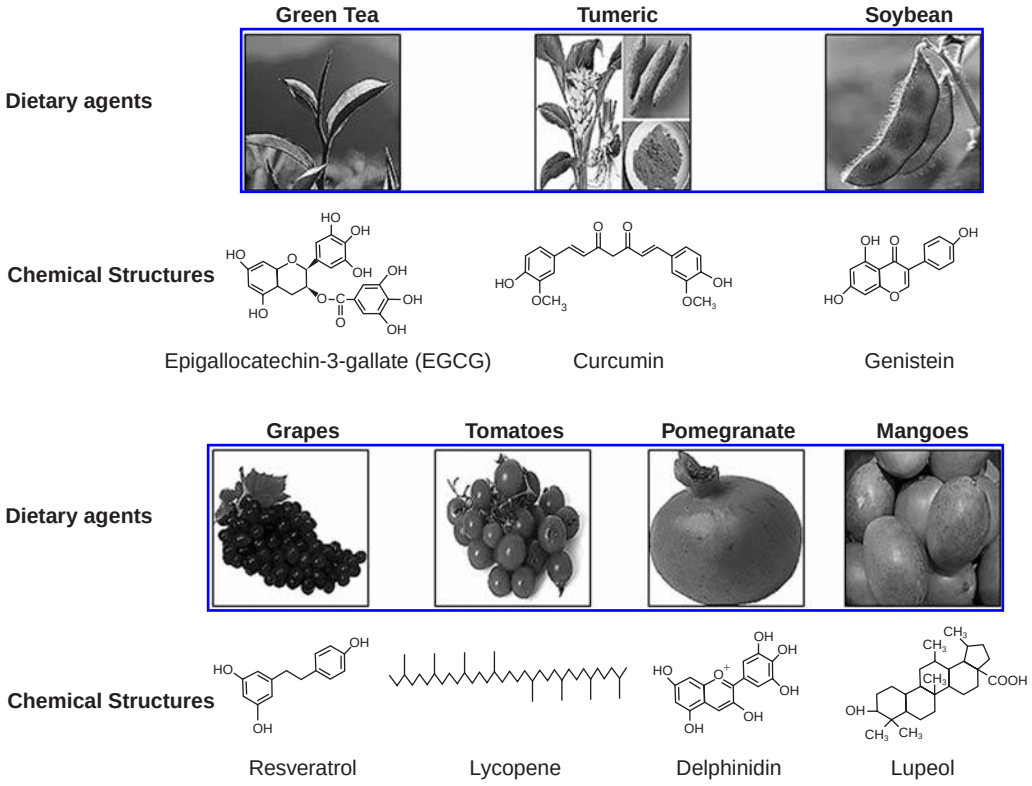

FIG. 1. Major dietary agents and their chemical structures.

cell proliferation, promote apoptosis, and inhibit invasion, metastasis, and angiogenesis. The key role of H_2O_2 in carcinogenesis is supported by experimental data that have shown that cancer cells commonly have increased levels of H_2O_2. It has also been shown that H_2O_2 can induce malignant transformation and that the expression of the H_2O_2-detoxifying enzymes catalase or glutathione peroxidase in cancer cells can reverse their malignant phenotype (19). The expression of the ROS generation system Nox1 in normal NIH3T3 fibroblasts resulted in cells with malignant characteristics that produced tumors in athymic mice, and a 10-fold increase in H_2O_2 levels was observed in these transformed cells. The concentration of H_2O_2 was decreased and the growth rate of cells was normalized when human catalase was expressed in these transformed cells (19).

Oxidative stress is generated by a large variety of mechanisms, including mitochondrial respiration, ischemia/reperfusion, inflammation, and metabolism of foreign compounds. Excessive generation of ROS that overwhelms the antioxidant defense system can oxidize cellular biomolecules. Free radicals generate a large number of oxidative modifications in DNA, including strand breaks and base oxidations. Epidemiological data provide evidence that it is possible to prevent cancer and other chronic diseases, some of which share common pathogenetic mechanisms, such as DNA damage, oxidative stress, and chronic inflammation. An obvious approach is avoidance of exposure to recognized risk factors. As complementary strategies, it is possible to render the organism more resistant to mutagens/carcinogens and/or to inhibit progression of the disease by administering chemopreventive agents. The multiple pathways leading to genotoxic damage and, later on, to cancer or other mutation-related diseases can be modulated exogenously. Blocking agents which prevent carcinogens from reaching or reacting with critical target sites, are inhibitors of tumor initiation and suppressing agents, which prevent the evolution of the neoplastic process are inhibitors of promotion and progression (Fig. 2).

When cells are exposed to chemical carcinogens, they are metabolized often and the metabolic products are either retained or excreted by the cell. Once inside the cells, carcinogens or their metabolic products affect the expression and regulation of genes which are involved in control of cell cycle, repair of DNA, and cell differentiation. Genotoxic mechanisms such as DNA adduct formation and induction of chromosome breakage may result by the action of some carcinogens. Other carcinogens may also act by nongenotoxic mechanisms like induction of inflammation, immunosuppression, and formation of ROS. These mechanisms alter signal transduction pathways that finally result in genomic instability, loss of proliferation control, and resistance to apoptosis, which are the characteristic features of cancerous cells (Fig. 3).

Many molecular and cellular targets of chemopreventive compounds have been identified. Some of the major signaling pathways that lie downstream of the erbB family of membrane-associated receptor tyrosine kinases are shown in Fig. 4. Cell-signaling kinases such as MAPK, phosphatidylinositol 3-kinase (PI3K)/Akt, and transcription factor NF-κB are also important targets of certain dietary antioxidants.

Whereas the free radical scavenging and antioxidant properties of dietary agents are well established, emerging literature reports suggest that their chemopreventive effects may also be ascribed to their ability to modulate many signal transduction

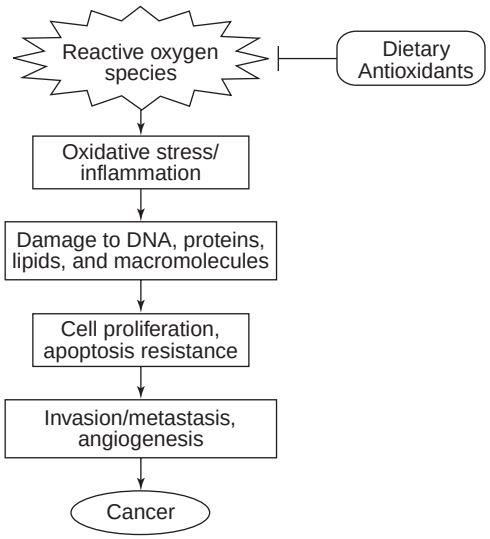

FIG. 2. Role of oxidative stress and inflammation in carcinogenesis.

pathways in a manner that favors inhibition of carcinogenesis (15, 141). Many of such agents interfere with signal transduction regulation at different levels, modulate hormone/growth factor activities, inhibit oncogenes, and activate tumor suppressor genes, induce terminal differentiation, activate apoptosis, restore immune response, inhibit angiogenesis, and decrease inflammation. Dietary antioxidants modulate many signal transduction pathways such as NF-κB, MAPKs, PI3K/Akt, β-catenin, and Nrf2 in a manner that favors inhibition of carcinogenesis. They also inhibit DNA modification or could also repair damaged DNA, decrease markers of cell proliferation, metastasis, and angiogenesis. They also cause induction of proapoptotic proteins and suppression of antiapoptotic proteins (Fig. 5). As the first line of defense to inhibit tumor initiation, many of the dietary agents have been shown to counteract the activity of exogenous and endogenous potential carcinogens by suppressing phase-I reactions which can lead either to activation or inactivation of the drug. They also act by activating phase-II reactions, usually known as conjugation reactions which are usually detoxicaton in nature and involve the interactions of the polar functional groups of phase I metabolites. The dynamic equilibrium between carcinogen-activating enzymes and detoxifying enzymes can determine the availability of the ultimate carcinogenic moiety to the cell after exposure to carcinogens.

To study cancer, research starts from the disease, followed by gene identification, and ending with specific cancer gene targeting and drug development. Various phytochemicals from natural products like fruits and vegetables are isolated, purified, and assayed *in vitro* to test their ability in killing precancerous and cancerous cells. Then, the preclinical studies on animal models and phase I-III clinical trials are conducted. This may lead to chemopreventive agents and/or anticancer drugs with pharmacological applications in chemotherapy (Fig. 6).

In this review, we provide the rationale and discuss the use of selected dietary antioxidants present in the fruits, vegetables, and beverages we consume as chemopreventive and/or chemotherapeutic agents for the prevention of carcinogenesis in ma-

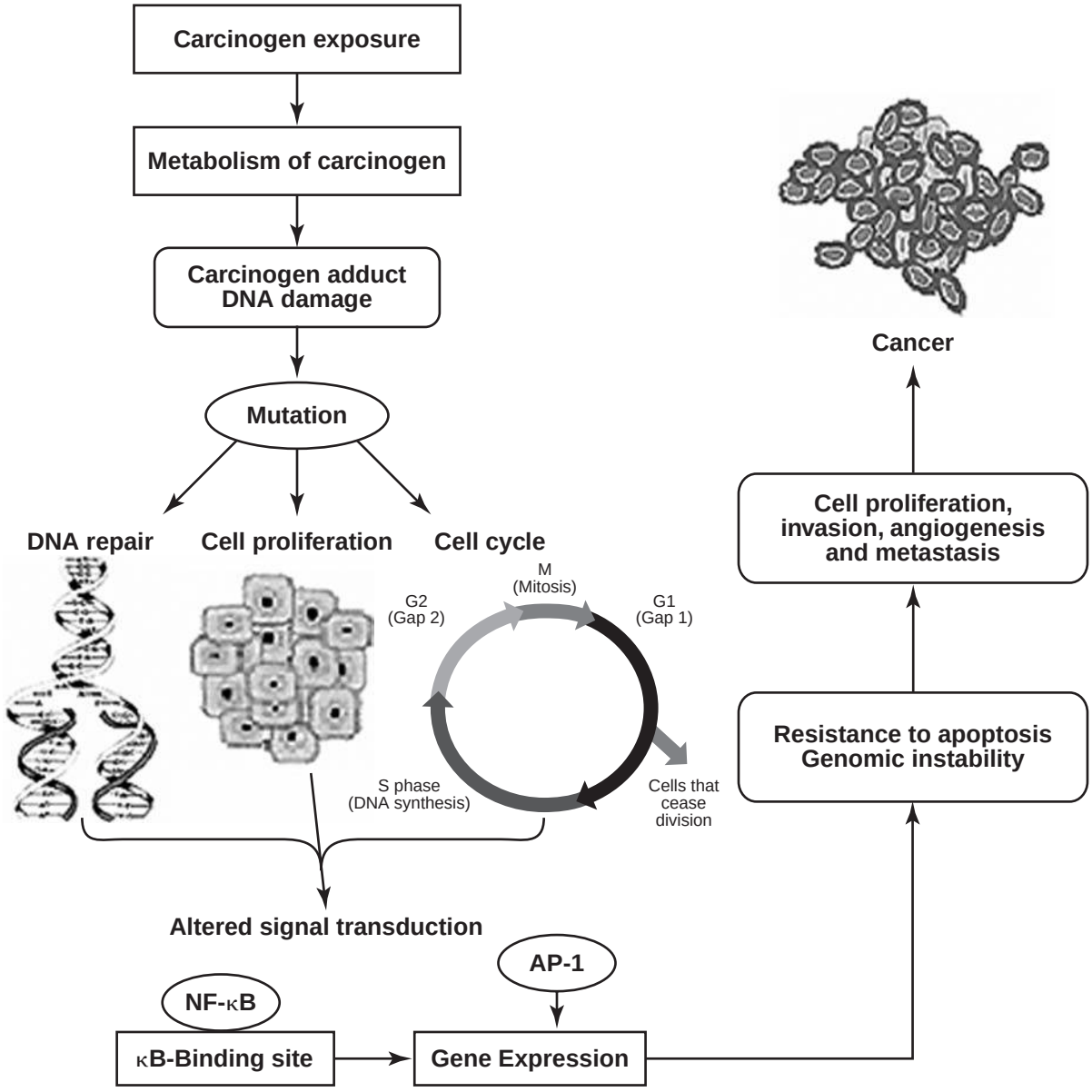

FIG. 3. Effect of carcinogen exposure on cell survival pathways.

jor organ-sites. We provide evidence for the effects of dietary agents such as tea polyphenols, curcumin, genistein, resveratrol, lycopene, pomegranate, and lupeol against cancers of the skin, prostate, breast, lung, and liver. Here, we selected these antioxidants which are present in abundance in the dietary substances and have shown potent chemopreventive effects against most commonly diagnosed cancer sites. We also present evidence for the efficacy and safety of these agents based on *in vitro*, animal, epidemiological studies, and clinical trials.

III. TEA POLYPHENOLS

Tea, derived from the plant *Camellia sinensis*, is the most popular beverage, consumed by over two-thirds of the world's population. It is processed in different ways in different parts of the world to give green, black, or Oolong tea. Worldwide, about three billion kilograms of tea are produced and consumed yearly. Both green and black teas have been studied for their health benefits, particularly for prevention and treatment of cancer. Tea is grown in over 30 countries, exclusively in the subtropical and tropical zones. The per capita worldwide consumption is 120 ml brewed tea per day. It is rich in substances with antioxidant properties and contains traces of proteins, carbohydrates, amino acids, and lipids, as well as more significant quantities of some vitamins and minerals.

Green, black, and Oolong tea are the three major commercial types of tea and differ in how they are produced and processed according to the different processes of drying and fermentation and in their chemical composition (Fig. 7). "Black tea" is fully fermented, "Oolong tea" is partially fermented, and

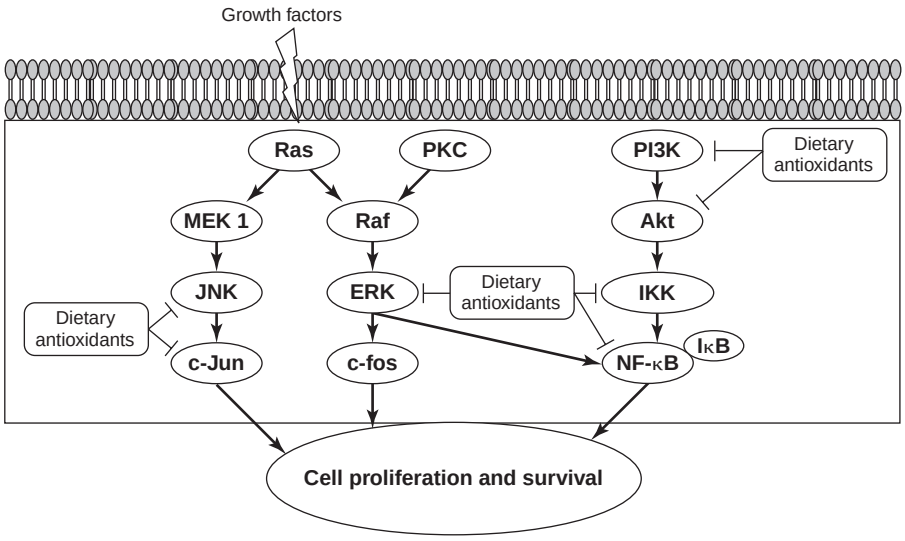

FIG. 4. Alteration of signal transduction pathways by dietary chemopreventive compounds resulting in cell proliferation and survival.

"green tea" is not at all fermented but only steamed. To prepare black and Oolong tea, the young leaves are picked, allowed to wilt, and then rolled. The leaves are then allowed to ferment, converting the polyphenols to phlobaphenes and forming aromatic compounds. During the fermentation process, the enzymes from leaf, including polyphenol oxidase, react with tannins and catechins. For the green tea preparation, the young leaves are not allowed to oxidize by fermentation but are steamed to inactivate the enzymes, thereby preserving as much as 90% of the polyphenols contained in fresh leaves from being degraded (28).

Green tea is manufactured by drying fresh tea leaves. It contains characteristic polyphenolic compounds, (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC). These compounds are commonly known as catechins. Figure 8 shows the major polyphenols present in green tea. A typical tea beverage, prepared in a proportion of 1g leaf to 100 mL water in a 3-min brew, usually contains 250–350 mg tea solids, comprised of 30–42% catechins and 3–6% caffeine (28). The preventive potential of green tea against cancer as evidenced from the several experimental studies is mainly due to these polyphe-

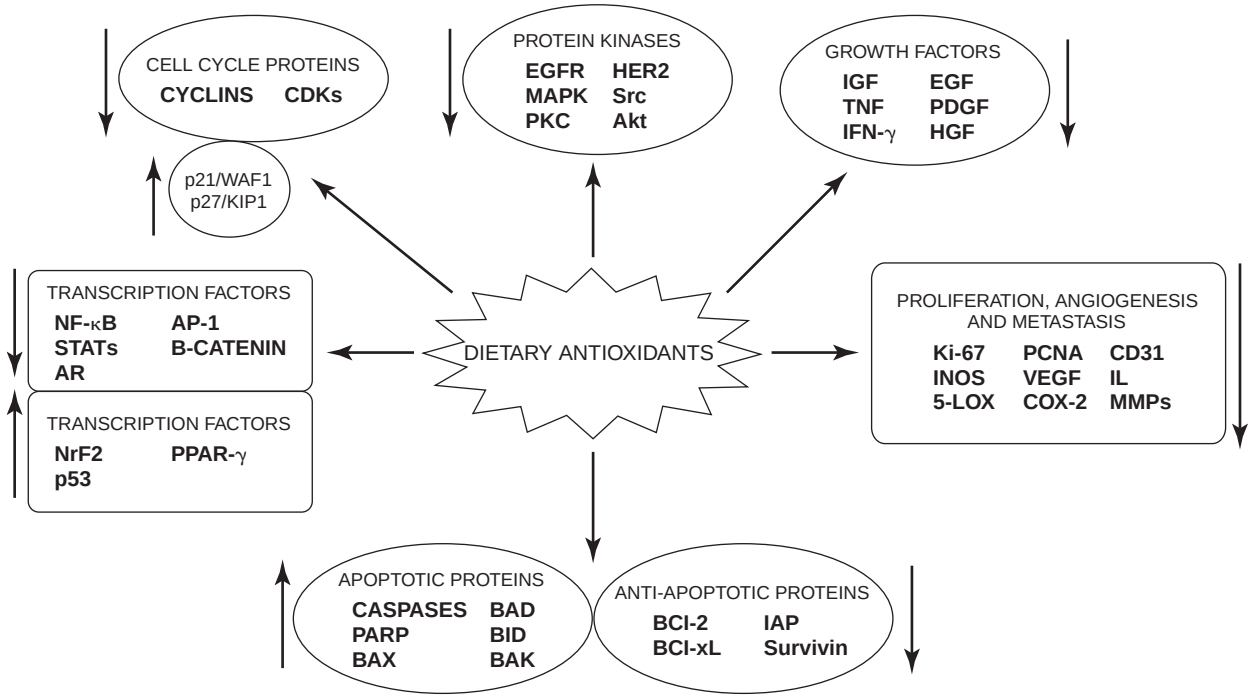

FIG. 5. Molecular targets of dietary antioxidants.

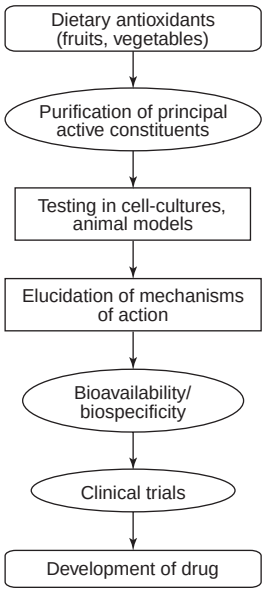

FIG. 6. Drug development through chemopreventive compounds present in the diet.

nols, which are found in green tea in a relatively higher concentration compared to black and Oolong tea, and hence it possesses more anticarcinogenic potential. Of the total amount of tea produced and consumed in the world, 78% is black tea, 20% is green tea, and <2% is Oolong tea. Green tea is consumed mostly in China, Japan, India, and in a few countries in North Africa and the Middle East, while black tea is consumed primarily in Western countries and in some Asian countries, and the Oolong tea consumption is limited to southeastern China and Taiwan (134).

Dried tea leaves are composed mainly of phytochemicals known as polyphenols (30–36%), mainly flavanols (including catechins), flavonoids, and flavondiols. The majority of the polyphenols are flavanols, more commonly known as catechins (14). The catechin in green tea that has gained the most attention with respect to the anticarcinogenic activity is the potent antioxidant EGCG. Much of the anticarcinogenic effect of green tea is mainly attributed to EGCG. EGCG makes up about 10–50% of the total catechin content and appears to be the most powerful of all the catechins with an antioxidant activity ~25–100 times more potent than that of vitamins C and E. EGCG has both antimatrix metalloproteinase and antiangiogenesis activities (49, 88).

Green tea is considered a dietary source of antioxidant nutrients like polyphenols (catechins and gallic acid), carotenoids, tocopherols, ascorbic acid, minerals such as Cr, Mn, Se, Zn, and certain phytochemical compounds. These compounds could increase the GTP antioxidant potential. They may also function indirectly as antioxidants through inhibition of the redox-sensitive transcription factors, inhibition of pro-oxidant enzymes, such as inducible nitric oxide synthase, lipoxygenases, cyclooxygenases, and xanthine oxidase, and induction of antioxidant enzymes, such as glutathione-S-transferases and superoxide dismutases (46).

In a study in humans which compared the pharmacokinetics of equimolar doses of pure EGC, ECG, and EGCG in 10 healthy volunteers, average peak plasma concentrations after a single dose of 1.5 mmol were 5.0 μmol/L for EGC, 3.1 μmol/L for ECG, and 1.3 μmol/L for EGCG. The plasma EGC and EGCG returned to baseline, but plasma ECG remained elevated even after 24 h (106). In black tea, major polyphenols are theaflavin and thearubigens and their structures are given in Fig. 9.

A. Tea polyphenols and skin cancer

Skin has the largest epithelial surface of all organs, and skin cancer is the most common type of cancer in the United States. The incidence of newly diagnosed basal cell carcinoma and squamous cell carcinoma of the skin grouped together as nonmelanoma skin cancer in the United States alone is estimated to exceed 1 million per year.

The activity of tea and tea polyphenols on the inhibition of skin tumorigenesis has been well studied. We have shown that green tea polyphenols (GTP) prevent skin cancer in a chemically-induced skin cancer model when applied topically on Sencar mouse for 7 days before exposure to a single dose of initiating agent. Results showed that GTP had a significant inhibitory effect on tumor induction in this initiation-promotion model (144). Significant protection by GTP against skin tumorigenicity was demonstrated by topical application of GTP in a complete skin tumorigenesis protocol using 3-methylcholanthrene on BALB/c mice, and a two-stage skin tumorigenesis protocol using DMBA as the initiating agent and TPA as tumor promoter with Sencar mice (301). These findings represent the first demonstration of the topical application of GTP for protection from skin cancer and served as a foundation for subsequent studies. EGCG significantly inhibited binding of ^{3}H-labeled polycyclic aromatic hydrocarbons to epidermal DNA. Topical application of EGCG resulted in significant inhibition in TPA-caused induction of epidermal ornithine decarboxylase (ODC) activity. In Sencar mice, the application of

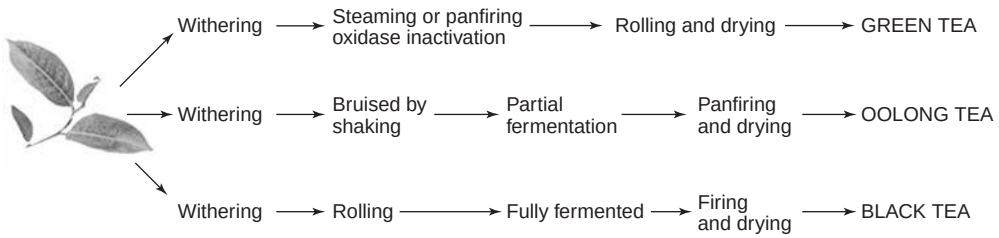

FIG. 7. Processing of different types of tea.

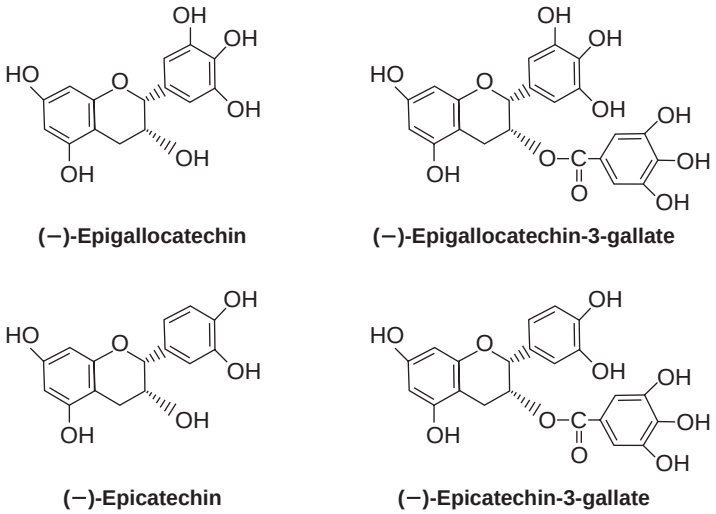

FIG. 8. Chemical structures of major green tea polyphenols.

EGCG before challenge with DMBA also resulted in significant reduction both in percentage of mice with tumors and number of tumors per mouse compared with a non-EGCG-pretreated group of animals (134, 311).

Oral consumption or topical application of brewed green tea, green tea extracts, or GTP showed significant protection against UV or chemical-induced carcinogenesis in hairless mice. One of the earlier studies used brewed green tea as the sole fluid source for SKH-1 mice during carcinogenesis initiated by either UVB or DMBA and promoted by either UVB or TPA, respectively. Oral consumption of brewed green tea at concentrations similar to human consumption (1.25% and 2.5%) significantly inhibited UVB or TPA induced tumorigenesis (299). It is also shown that oral administration of green tea to mice not only inhibited skin tumorigenesis but also reduced fatty tissues in the dermis (70). Mechanistically, oral administration of GTP resulted in decreased UVB-induced ODC and cyclooxygenase (COX) activities (9). Oral administration or intraperitoneal injection of GTP achieved similar effects to inhibit the growth of UV-induced skin papillomas (300) or TPA-induced COX2 in rodent models (160). Conney *et al*., (71) reported that oral administration of green tea, black tea, or EGCG inhibits the growth of well-established skin tumors and, in some cases, tumor regression was also observed. In papilloma-bearing mice, complete regression was observed and the growth of nonmalignant tumors, squamous cell carcinomas, and tumor volume decreased significantly when tumor-bearing mice were administered black tea. Inhibition of DNA synthesis and enhancement of apoptosis were also observed. We have also shown that in SKH-1 hairless mice, topical application of green tea polyphenols resulted in significant decrease in UVB-induced bifold-skin thickness, skin edema, infiltration of leukocytes, and inhibition of MAPK and NFκB pathways (5). Recently, EGCG treatment was found to result in a dose-dependent decrease in the viability and growth of A-375 amelanotic malignant melanoma and Hs-294T metastatic melanoma cell lines (225). Oral administration of GTP reduced UVB-induced skin tumor incidence, tumor multiplicity, and tumor growth in SKH-1 mice. There was also reduced expression of the matrix metalloproteinases (MMP)-2 and MMP-9, CD31, vascular endothelial growth factor (VEGF), and proliferating cell nuclear antigen (PCNA) in the GTP-treated group. Additionally, there were more cytotoxic CD8(+) T cells and greater activation of caspase-3 in the tumors of the GTP group, indicating the apoptotic death of the tumor cells (203).

Green tea and its polyphenolic constituents protect against many of the other damaging effects of UV radiation. In mice, both systemic and topical administration of GTP and EGCG were found to protect against the UV-induced sunburn response (135), UV-induced immunosuppression (135, 136), and photoaging of the skin (289). Similar results with respect to sunburn were observed in human skin that had been pretreated with a crude extract of green tea or with EGCG. In animal models, GTP has an ameliorative effect on photoaging as well (149). In UVA-irradiated SKH-1 hairless mice, there was an observable reduction in the amount of skin wrinkling. Topical application of EGCG has been shown to reduce UV-induced production of MMP-2, -3, -7 and -9, which are known to degrade collagen and lead to photodamage. Moreover, it was associated with a decrease in protein oxidation in the skin which was also seen with photoaged skin (289). As expected, direct examination of UV-irradiated skin that had been pretreated *in vivo* with topical EGCG resulted in a reduction in the number of apoptotic keratinocytes as detected by TUNEL staining (64, 81). The *in vivo* observations are supported by *in vitro* studies in which cultured normal human keratinocytes were exposed to UVB radi-

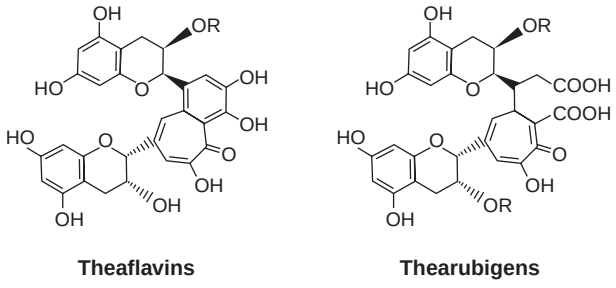

FIG. 9. Chemical structures of black tea polyphenols.

ation *in vitro* (64, 313). Further analysis showed that this anti-apoptotic effect *in vitro* was caused by an EGCG-induced increase in the expression of the anti-apoptotic molecule Bcl-2 and a decrease in the pro-apoptotic protein Bax (64). In contrast to its effect on normal keratinocytes, EGCG stimulates apoptosis in UV-induced pre-malignant papillomas and invasive squamous cell carcinomas in mice (64, 57). GTP also inhibits UVB-induced markers of oxidative stress *in vivo* in animal models. When applied topically or given orally to SKH-1 hairless mice, pretreatment with EGCG or GTP before UVB radiation protects against depletion of glutathione, the antioxidant enzymes glutathione peroxidase and catalase, decreases UV-induced lipid peroxidation and inhibits UVB-induced protein oxidation (288, 289, 133). EGCG protects against UV-induced oxidative stress in humans as well. When it was applied to the skin of volunteers just before exposure to a 4x minimal erythema dose (MED) of UVB radiation, it significantly decreased the production of hydrogen peroxide and nitric oxide production as well as lipid peroxidation in the dermis and epidermis (133). In an *in vitro* study using cultured human cells (lung fibroblasts, skin fibroblasts, and epidermal keratinocytes), EGCG resulted in a dose-dependent reduction in UV-induced DNA damage in all three cell types (215). Green tea polyphenols also significantly inhibited the UVB-induced DNA damage when applied topically to the mouse epidermis, using a ^{32}P-postlabelling technique (55). It has been shown that GTP block the adverse biological effects of UV radiation through the induction of the immunoregulatory cytokine, IL-12, thus preventing UV-induced immune suppression (137).

Studies have demonstrated that oral administration of green tea to SKH-1 hairless mice enhanced UV-induced increases in the number of p53- and p21/WAF1-positive cells in the epidermis following UV exposure (196). This implies that the photoprotective effect of green tea on UV-induced carcinogenesis may be mediated through stimulation of UV-induced increases in the levels of p53, p21/WAF1. Administration of EGCG in the drinking water significantly decreased both tumor number and total tumor burden compared with untreated ODC/Ras mice without decreasing the elevated polyamine levels present in the ODC/Ras mice. EGCG selectively decreased both proliferation and survival of primary cultures of ODC overexpressing transgenic keratinocytes but not keratinocytes from normal littermates or ras-infected keratinocytes (233).

B. Tea polyphenols and prostate cancer

We have demonstrated that EGCG dose-dependently reduced the cell number of both androgen-dependent LNCaP and androgen-independent DU145 cells (98). We have also reported that EGCG-induced apoptosis in human prostate carcinoma LNCaP cells is mediated via stabilization of p53 by phosphorylation on critical serine residues and p14ARF-mediated down-regulation of murine double minute 2 (MDM2) protein, and negative regulation of NF-κB activity, thereby decreasing the expression of the proapoptotic protein Bcl-2 (103). We have also provided evidence for the involvement of cdk inhibitor-cyclin-cdk machinery during cell cycle arrest and apoptosis of human prostate carcinoma cells by EGCG (100). Recently, we have shown that treatment of human prostate cancer cells LNCaP, PC-3, and CWR22Ru1, with combination of EGCG and Cox-2 inhibitor, resulted in enhanced cell growth inhibition, apoptosis induction, and inhibition of NF-κB. In athymic nude mice, implanted with CWR22Ru1 cells, combination treatment with GTP and celecoxib resulted in enhanced tumor growth inhibition, lowering of PSA and IGF-1 levels, and increase in IGFBP-3 levels (2).

Employing TRAMP (transgenic adenocarcinoma of the mouse prostate) mice, we have shown that oral infusion of GTP at a human achievable dose (equivalent to six cups of green tea per day) significantly inhibits CaP development and increases tumor free and overall survival of mice. GTP, provided as the sole source of drinking fluid to TRAMP mice from 8 to 32 weeks of age, resulted in significant delay in primary tumor incidence and tumor burden as assessed sequentially by MRI, significant decrease in prostate and genitourinary weight, inhibition in serum insulin-like growth factor-I (IGF-1), and restoration of insulin-like growth factor binding protein-3 (IGFBP-3) levels and reduction in the protein expression of proliferating cell nuclear antigen (PCNA) in the prostate, compared with water-fed TRAMP mice (99). Treatment of athymic nude mice with GTP, water extract of black tea, EGCG, and theaflavins resulted in significant inhibition in growth of implanted prostate tumors, reduction in the level of PSA, induction of apoptosis, and decrease in the levels of VEGF protein. GTP also caused a significant regression of tumors at human achievable concentrations (262). EGCG has also been shown to inhibit FAS activity, which inhibits growth and induces apoptosis *in vitro* and in tumor xenografts *in vivo*. This inhibition is as effective as that by presently known synthetic inhibitors, and strengthens the molecular basis for the use of EGCG as a chemopreventive and antineoplastic agent (42). It has been shown that green and black tea significantly reduced tumorigenicity. The combination of soy phytochemical concentrate (SPC) and green tea synergistically inhibited final tumor weight and metastasis, and significantly reduced serum concentrations of both testosterone and dihydrotestosterone *in vivo*. Inhibition of tumor progression was associated with reduced tumor cell proliferation and tumor angiogenesis (329). GTP feeding to TRAMP mice resulted in marked inhibition of prostate cancer progression which was associated with reduction of S100A4 and restoration of E-cadherin (247). Continuous GTP administration for 24 weeks to TRAMP mice resulted in reduction in the levels of IGF-I and increase in the levels of IGFBP-3 in the dorso-lateral prostate with an inhibition of protein expression of PI3K, Akt, and ERK 1/2. There was also inhibition of VEGF, uPA, and MMPs 2 and 9 (3). In a recent study, green tea catechins given in the form of capsules to men with high-grade prostate intraepithelial neoplasia (PIN) demonstrated cancer preventive activity by inhibiting the conversion of high grade PIN lesions to cancer. After one year, there was 3% incidence of prostate cancer in men given green tea catechin capsules, whereas 30% incidence in placebo-treated men (37). Evidence from a case-control study conducted in south-east China assessing 130 patients with histologically confirmed incidental prostate cancer and 274 patients without cancer matched by age, showed that the prostate cancer risk declined with increasing frequency, duration, and quantity of green tea consumed. This reduction was statistically significant, suggesting that green tea protects against prostate cancer (124).

C. Tea polyphenols and breast cancer

EGCG induces apoptosis in many human cancer cell lines. Mechanisms through which EGCG-induced apoptosis may be mediated include cell cycle arrest and changes in intracellular signaling cascades. Liang *et al*. (181) demonstrated that following treatment with EGCG, both p21/WAF1 and p27 proteins were overexpressed in MCF-7 cells. This correlated well with cell cycle studies, which demonstrated that EGCG increased the proportion of cells arrested in G(1) phase of the cell cycle. Studies in the ER negative cell line, MDA-MB-231, showed a very similar trend, with increased protein expression of p21/WAF1 and p27, and inhibition of both basal and transforming growth factor (TGF)-α-induced EGFR auto-phosphorylation following EGCG treatment. (204). EGCG modulated the hepatocyte growth factor (HGF)/met signaling pathway involved in proliferation, survival, and motility/invasion. EGCG treatment inhibited HGF-induced Met phosphorylation, and subsequent AKT and ERK activation (39). EGCG was found to suppress Wnt signaling in invasive breast cancer cells (150). Recently, green tea extract was found to increase the anticancer effect of *Ganoderma lucidum* extract on cell proliferation as well as colony formation of breast cancer cells. This effect was mediated by the downregulation of expression of oncogene c-myc and by the suppression of secretion of urokinase plasminogen activator (uPA) in MDA-MB-231 cells (282). Green tea also increased the inhibitory effect of tamoxifen on the proliferation of the MCF-7, ZR75, and T47D human breast cancer cells *in vitro*. Recently, it has been reported that green tea catechins and black tea theaflavins decrease tumor size and tumor levels of the malondialdehyde-DNA adduct M1dG in mice (139). Mice treated with both green tea and tamoxifen had the smallest MCF-7 xenograft tumor size, and the highest levels of apoptosis in tumor tissue, as compared with either agent administered alone and the suppression of angiogenesis *in vivo* correlated with larger areas of necrosis and lower tumor blood vessel density in treated xenografts. It was observed that green tea blocked ER-dependent transcription, as well as estradiol-induced phosphorylation and nuclear localization of mitogen-activated protein kinase (MAPK) (249). Various studies using either green tea extracts or purified EGCG have also been conducted using breast cancer cell xenografts in mice (184, 281). EGCG reduced tumor size in female athymic nude mice inoculated with MCF-7 cells (184). Treatment of athymic nude mice inoculated with MDA-MB-231 human breast cancer cells, with GTP in the drinking water or EGCG by oral gavage suppressed tumor growth and burden (281). Green tea consumption decreased tumor growth, tumor weight, and endothelial vessel density in SCID mice inoculated with MDA-MB-231 breast cancer cells (248). There was also delayed tumor growth onset, rate of tumor growth, tumor volume and metastasis after consumption of GTP mixture in the drinking water in BALB/c mice inoculated with 4T1 mouse mammary carcinoma cells. These effects were associated with an increase in the Bax/Bcl_2 ratio and caspase-3 activation (29). In a case control study, conducted in southeast China in 2004–2005 on 1,009 female patients aged 20–87 years with histologically confirmed breast cancer, green tea consumption was found to be associated with a reduced risk of developed breast cancer (324).

D. Tea polyphenols and lung cancer

Recently, it has been reported that EGCG caused suppression of NF-kappaB/PI3K/AKT/mTOR and MAPKs in normal human bronchial epithelial cells, which may contribute to its ability to suppress inflammation, proliferation, and angiogenesis induced by cigarette smoke (276). Lung cancer is the predominant cause of cancer mortality in developed countries. Five-year survival is $<10\%$ (43). It was reported that Oolong and green tea administered to Kumming mice inhibited urethane-induced lung neoplasia (316). Green tea greatly reduced tumor incidence and multiplicity in *N*-methyl-N9-nitro-*N*-nitrosoguanidine (MNNG)-induced lung cancers and precancerous lesions in LACA mice (197). Green tea and EGCG have been shown to inhibit NNK- induced mouse lung tumorigenesis by 63% and 28%, respectively (165, 317). Similarly, green tea significantly inhibited B(a)P-induced lung tumorigenesis in A/J mice (297). Green tea and decaffeinated green tea reduced lung tumor incidence and multiplicity in *N*-nitrosodiethylamine (NDEA)-treated A/J mice (298). The administration of green tea as the sole drinking source beginning 1 week after NNK administration significantly reduced tumor multiplicity in both $p53^{wt/wt}$ and $p53^{val135/wt}$ mice (328). In addition to the effect of green tea, black tea, EGCG, and caffeine have also been demonstrated to be protective against lung tumorigenesis in A/J mice treated with the tobacco-related carcinogens (165, 317). When administered during the NNK treatment period, green and black teas appeared to have the same effectiveness. When administered after the carcinogen treatment period, green tea seemed to be more effective than black tea (298).

Decaffeinated black tea decreased lung tumor multiplicity but did not significantly decrease tumor incidence (298). Decaffeinated green and black tea showed a dose-dependent chemoprevention of lung tumors in dimethylnitrosamine-treated C3H mice (48). Theaflavin and EGCG exhibited a protective effect against BP-induced lung tumorigenesis in strain A mice (31). Exposure to tobacco is involved in 90% of lung carcinomas. It has been shown that administration of polyphenon E, a standardized green tea polyphenol preparation, significantly reduced the NNK-induced lung tumor incidence (52%) and multiplicity (63%) in female A/J mice. Polyphenon E treatment inhibited cell proliferation and enhanced apoptosis in adenocarcinomas and adenomas, and lowered levels of c-Jun and extracellular signal-regulated kinase (Erk) 1/2 phosphorylation (194).

A prospective cohort study over 10 years in Japan showed that the daily consumption of green tea delayed the onset of cancer in both smokers and nonsmokers (221).

E. Tea polyphenols and liver cancer

EGCG has been shown to reduce the incidence of hepatoma in mice and also reduced the average number of hepatomas per mouse. EGCG also inhibited the growth and secretion of alpha-fetoprotein by human hepatoma-derived PLC/PRF/5 cells without decreasing their viability. These results indicate that EGCG acts as a preventive agent against human hepatoma (226). Green and black tea treatment caused a significant decrease in the diethylnitrosamine (DEN)-induced liver tumors in C3H mice (48). All four tea catechins [(−)-epicatechin, (−)-epigallocat-

echin, (−)-epicatechin gallate and (−)-epigallocatechin gallate], black tea extract, and Oolong tea extract significantly decreased DEN and phenobarbital-induced number and area of preneoplastic glutathione S-transferase placental form-positive foci in the liver (205). Treatment with green tea resulted in decrease in 2-nitropropane-induced serum glutamic-oxaloacetic transaminase (GOT) activity and hepatic lipid peroxidation, together with an increase in hepatic glycogen and serum triglyceride. A dose-related decrease was observed in oxidative DNA damage and cell proliferation in the liver by treatment with green tea in drinking water (244). Drinking green tea significantly protected mice against pentachlorophenol-induced gap junctional intercellular communication inhibition, the reduction in connexin32 (Cx32) plaques in the plasma membrane, and the elevation of the cell proliferation index in male B6C3F1 mice (245). Tea polyphenols and tea pigments significantly decreased the number and area of GST-Pi-positive foci cyclin D1, cdk4, and induction of p21/WAF1 in liver of rats (95, 123). Recently, EGCG was found to inhibit hepatic glucose-6-phophatase system mediated through an elevated luminal glucose level (72). Administration of green tea was able to prevent the increase in incidences and multiplicities of DEN-induced hepatocellular tumors and also arrest the progression of cholangiocellular tumors in mice (286).

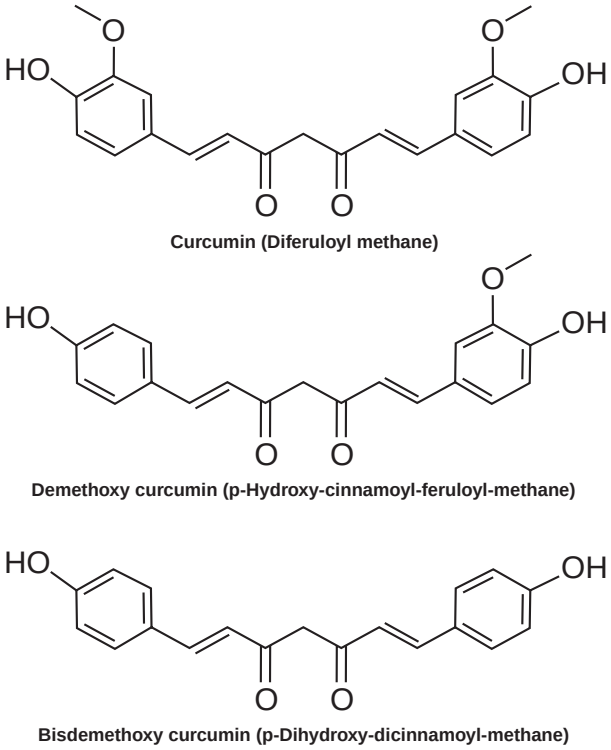

FIG. 10. Chemical structures of curcuminoids curcumin, demethoxy curcumin, and bisdemethoxy curcumin.

IV. CURCUMIN

Curcumin is a major yellow pigment in turmeric that imparts a yellow color to food and is widely used as a spice. It is derived from the root of the plant *Curcuma longa* Linn. and has been used for centuries in indigenous medicine for the treatment of a variety of inflammatory conditions and other diseases. The chemical structures of the curcumin and curcuminoids are given in Fig. 10. In 1988, curcumin was first shown to have antimutagenic activity in the Ames *Salmonella* test (256). It has a wide range of pharmacological activities including anti-inflammatory, anti-cancer, anti-oxidant, wound healing, and antimicrobial effects (198). It also exhibits strong antioxidant activity, comparable to vitamins C and E. It has been shown to have several clinical applications due to its anti-inflammatory and anti-oxidant properties. Curcumin is also a potent scavenger of a variety of ROS, including superoxide anion radicals, hydroxyl radicals, and nitrogen dioxide radicals. Local application of turmeric is a household remedy in India for several conditions such as skin diseases, insect bites, and chicken pox (198). The molecular basis of anti-carcinogenic and chemopreventive effects of curcumin is attributed to its effect on several targets including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators, and cellular signaling molecules (11). Curcumin has been shown to downregulate the production of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and IL-1β, and to inhibit the activation of transcription factors NF-κB and activator protein-1 (AP-1), which regulate the genes for pro-inflammatory mediators and protective antioxidant genes (274). In a phase-I study in Taiwan, the tolerability of curcumin in 25 subjects from Taiwan with high risk or premalignant lesions was assessed by giving curcumin as a 500 mg tablet for 3 months. The serum concentration of curcumin usually peaked at 1–2 h after oral intake of crucumin and gradually declined within 12 h. A trend was seen with an increase in the area under the curve (AUC, nMole h/ml), maximum concentration (C_{max}, μM), and T_{max} (time at maximum concentration, h) as dose increased. Five subjects receiving 4000 mg of curcumin had an AUC of 2.55 $\pm$ 1.76, C_{max} of 0.51 $\pm$ 0.11, and a T_{max} of 1.67 $\pm$ 0.58. Two subjects received 8000 mg of curcumin had an AUC of 13.74 $\pm$ 5.63, C_{max} of 1.77 $\pm$ 1.87, and a T_{max} of 1.75 $\pm$ 0.35 (58, 125).

A. Curcumin and skin cancer

The mouse models used to test curcumin involved prophylactic treatment with either oral or topical doses followed by exposure to topical chemical carcinogens or UVA. Curcumin was reported to decrease induction of epidermal ODC activity, epidermal cyclooxygenase and lipoxygenase enzyme levels, epidermal glutathione content, arachidonic acid-induced epidermal edema, oxidation of DNA bases, and the numbers of tumors per mouse and tumor volume per mouse. A dose-dependent relationship of chemoprevention was established as well as determination of the equivalent efficacy of commercial-grade curcumin versus pure curcumin (113, 115). Curcumin was also found to cause cell death in eight melanoma cell lines, four with wild-type, and four with mutant p53. It leads to activation of caspase-3 and -8, induced Fas receptor aggregation in a FasL-independent manner, and that low-temperature incubation, previously shown to inhibit receptor aggregation, prevented curcumin-induced cell death. The expression of dominant negative FADD significantly inhibited

curcumin-induced cell death. Curcumin also blocked the NF-κB cell survival pathway and suppresses the apoptotic inhibitor, XIAP (44). Treatment with curcumin of highly metastatic murine melanoma cells B16F10 significantly inhibited MMP-2 activity. Expression of membrane type-1 matrix metalloproteinase (MT1-MMP) and focal adhesion kinase (FAK), an important component of the intracellular signaling pathway, were also reduced to almost background levels (32). Curcumin-treated B16F10 melanoma cells formed eight-fold fewer lung metastases in C57BL6 mice. Curcumin-treated cells showed a dose-dependent reduction in their binding to four extracellular matrix (ECM) proteins in the cell adhesion assays. The binding to fibronectin, vitronectin, and collagen IV decreased by over 50% in 24 h, and by 100% after 48 h of curcumin treatment; it persisted at this level even after 15 days of cultivating cells in curcumin-free medium. Cells treated with curcumin also showed a marked reduction in the expression of $\alpha5\beta1$ and $\alpha5\beta3$ integrin receptors. In addition, curcumin treatment inhibited pp125 FAK and collagenase activity. There was also enhanced expression of antimetastatic proteins, tissue inhibitor metalloproteinase (TIMP)-2, nonmetastatic gene 23 (Nm23), and E-cadherin (240). Treatment of JB6 cells with curcumin inhibited the formation of TPA-induced anchorage-independent colonies that grow in soft agar. Topical application of curcumin together with TPA once a day for 5 days strongly inhibited TPA-induced epidermal hyperplasia and *c-Jun* and *c-Fos* expression in CD-1 mice (195). Recently, it has been shown that on treatment of HaCaT cells with UVB and curcumin, there was induction of apoptosis as evidenced by DNA laddering. Combination of UVB irradiation with curcumin also synergistically induced apoptotic cell death in HaCaT cells through activation of caspase-8, -3, and -9, followed by release of cytochrome *c* (232). It has been reported recently that curcumin suppresses the differentiation agent-dependent activation of involucrin gene expression and that an AP1 transcription factor DNA binding site in the involucrin gene is required for this regulation. Curcumin treatment inhibited the novel protein kinase C, Ras, and MEKK1-dependent activation of involucrin promoter activity and reduces the differentiation agent-dependent increase in AP1 factor level and DNA binding. In addition, curcumin treatment reduced cell number, which is associated with a reduction in cyclin, cdk1, and Bcl-xL, leading to reduced mitochondrial membrane potential and increased cleavage of PARP protein (27).

Curcumin treatment significantly reduced the number of tumors and tumor volume when given in diet to animals in which skin tumors had been initiated with DMBA and promoted with TPA. Also, the dietary consumption of curcumin resulted in a significantly decreased expression of *ras* and *fos* proto-oncogenes in the skin tumors (186). Curcumin inhibited the mean values of TPA-induced formation of the oxidized DNA base 5-hydroxymethyl-2′-deoxyuridine (HMdU) formation in epidermal DNA, and only the two highest doses of curcumin strongly inhibited TPA-induced tumor promotion (62–79% inhibition of tumors per mouse and tumor volume per mouse). Topical application of curcumin together with TPA twice a week for 18 weeks markedly inhibited TPA-induced tumor promotion. Curcumin had a strong inhibitory effect on DNA and RNA synthesis in cultured HeLa cells (114). Topical application on the dorsal side of the skin with curcumin before TPA treatment inhibited the TPA-induced expression of *c-fos*, *c-jun*, and *c-myc* (129). Topical application of curcumin prior to the application of [^{3}H]B(a)P inhibited the formation of [^{3}H]B(a)P-DNA adducts in epidermis. The number of tumors per mouse and the percentage of tumor-bearing mice was decreased in animals treated with curcumin prior to each application of B(a)P. Topical application of curcumin prior to each application of DMBA once weekly for 10 weeks, followed a week later by promotion with TPA twice weekly for 15 weeks decreased the skin tumor incidence in mice (116). Curcumin inhibited B(a)P-induced forestomach tumors in female Swiss mice and DMBA-induced skin tumors in Swiss bald mice. There was also inhibition of DMBA-initiated and TPA promoted skin tumors in female Swiss mice. *In vitro* [^{3}H]B(a)P-DNA interaction studies and *in vivo* carcinogen metabolizing enzyme studies revealed that curcumins exert anticarcinogenic activity by altering the activation and/or detoxification process of carcinogen metabolism. Curcumin also exhibited dose-dependent *in vitro* cytotoxicity against human chronic myeloid leukemia (218).

B. Curcumin and prostate cancer

Curcumin has been shown to induce apoptosis in both androgen-dependent and androgen-independent prostate cancer cells; this was accomplished by downregulating apoptosis suppressor proteins and other crucial proteins such as the androgen receptor (79). Curcumin significantly altered microfilament organization and cell motility in PC-3 and LNCaP human prostate cancer cells *in vitro*. Pretreatment of cells with curcumin suppresseed changes in microfilament organization caused by cytochalasin B (CB) and blocked PC-3 membrane blebbing. Treatment with the PKC inhibitor bisindolylmaleimide inhibited the ability of curcumin to block CB-induced membrane blebbing (108). In PC-3, human prostate cancer cell line, curcumin reduced MDM2 protein and mRNA in a dose- and time-dependent manner, and enhanced the expression of the tumor suppressor p21/WAF1. Curcumin induced apoptosis and inhibited proliferation of PC-3 cells in culture, but both MDM2 overexpression and knockdown reduced these effects. Curcumin downregulated the expression of homeobox gene NKX3.1 and the activity of the NKX3.1 1040 bp promoter in LNCaP cells. Curcumin inhibited AR-mediated induction of NKX3.1 expression and decreased the expression of AR and the binding activity to antioxidant response element (ARE) directly (323). It has been shown recently that curcumin sensitizes LNCaP and PC-3 prostate cancer cells to TRAIL-induced apoptosis by suppression of NF-κB through inhibition of Akt signaling pathway (76). Curcumin and PEITC have been reported to suppress phosphorylation of EGFR (Y845 and Y1068), Akt, and PI3K induced by EGF in PC-3 cells (151). It has been reported that the expressions of Bcl-2, and Bcl-xL were downregulated and the expression of p53, Bax, Bak, PUMA, Noxa, and Bim were upregulated on treatment of cells with curcumin. Curcumin upregulated the expression of p53 as well as its phosphorylation at serine 15, and acetylation in a concentration-dependent manner. Acetylation of histone H3 and H4 was also increased in cells treated with curcumin. Treatment of LNCaP cells with curcumin also resulted in transloca-

tion of Bax and p53 to mitochondria, production of reactive oxygen species, drop in mitochondrial membrane potential, release of mitochondrial proteins (cytochrome c, Smac/DIABLO, and Omi/HtrA2), activation of caspase-3 and induction of apoptosis (257). Curcumin also inhibited the growth of cells and enhanced the cytotoxic effects of gemcitabine, which is a drug used in various carcinomas. Administration of curcumin to tumor-bearing nude mice inhibited growth of PC-3 xenografts and enhanced the antitumor effects of gemcitabine and radiation, and curcumin reduced the expression of MDM2 in these tumors (175). Continued i.p. injection of curcumin or phenyl isothiocyanate (PEITC), beginning a day before tumor implantation using NCr immunodeficient (nu/nu) mice bearing s.c. xenografts of PC-3 human prostate cancer cells significantly retarded the growth of PC-3 xenografts. Combination of i.p. administration of PEITC and curcumin showed stronger growth-inhibitory effects and inhibition of Akt and NF-κB signaling pathways (145). Curcumin treatment of DU145 prostate cancer cells resulted in significant reduction in the expression of MMP-2 and MMP-9, and effected the inhibition of invasive ability. Curcumin was also shown to induce a marked reduction of tumor volume, and MMP-2 and MMP-9 activity in the tumor-bearing site in xenogfraft model. The metastatic nodules *in vivo* were significantly fewer in the curcumin-treated group than untreated group (109).

C. Curcumin and breast cancer

In MCF-7 breast cancer cells, telomerase activity decreased with increasing concentrations of curcumin, may be due to downregulation of hTERT expression. Curcumin caused a steady decrease in the level of human telomerase reverse transcriptase (hTERT) mRNA in MCF-7 cells, whereas there was no effect on the levels of hTER and c-myc mRNAs expression (237). Curcumin inhibited the expression of ER downstream genes, pS2 and transforming growth factor (TGF)-β in ER-positive MCF-7 cells. ERE (estrogen responsive element)-CAT activities induced by 17-beta estradiol were also decreased on treatment with curcumin. In addition, it was also demonstrated that curcumin exerts strong anti-invasive effects *in vitro* that are not estrogen dependent in the ER-negative MDA-MB-231 breast cancer cells. These anti-invasive effects appear to be mediated through the downregulation of MMP-2 and the upregulation of TIMP-1 (258). Curcumin-induced apoptosis in the breast cancer cell line MCF-7 which was accompanied by an increase in p53 level as well as its DNA-binding activity, followed by Bax expression at the protein level. Using p53-null MDAH041 cells and low and high p53-expressing TR9-7 cells, in which p53 expression is under tight control of tetracycline, established that curcumin induced apoptosis in tumor cells via a p53-dependent pathway in which Bax is downstream effector of p53 (60). Curcumin dose and time dependently downregulated expression of cyclin E that correlated with decrease in the proliferation of human prostate and breast cancer cells. Curcumin also enhanced the expression of cdk inhibitors p21/WAF1 and p27 as well as tumor suppressor protein p53, but suppressed the expression of retinoblastoma protein and induced the accumulation of the cells in G1 phase of the cell cycle (10). Treatment of breast cancer cells MDA-MB-435 cells with curcumin inhibited paclitaxel-activated NF-κB through inhibition of IκBα kinase activation and IκBα phosphorylation and degradation. Curcumin also suppressed the paclitaxel-induced expression of antiapoptotic (XIAP, IAP-1, IAP-2, Bcl-2, and Bcl-xL), proliferative (cyclooxygenase 2, c-Myc, and cyclin D1), and metastatic proteins (VEGF, MMP-9, and ICAM-1). Curcumin has been reported to induce apoptosis in MCF-7 and MCF-10A breast cancer cells. Microarray hybridization of apoptotic arrays with labeled first-strand probes of total RNA was performed to identify and characterize the genes regulated by curcumin in tumor cells, and curcumin was found to alter 104 genes out of the 214 apoptosis-associated genes examined in the array. Curcumin upregulated 22 genes and downregulated 17 genes in the MCF-7 cell line. (238). Curcumin selectively increases p53 expression at G(2) phase of carcinoma cells and releases cytochrome *c* from mitochondria. Further experiments using p53-null as well as dominant-negative and wild-type p53-transfected cells have established that curcumin induces apoptosis in carcinoma cells via a p53-dependent pathway. Curcumin reversibly inhibits normal mammary epithelial cell cycle progression by downregulating cyclin D1 expression and blocking its association with cdk4 and 6, as well as by inhibiting phosphorylation and inactivation of retinoblastoma protein, and upregulates cell cycle inhibitory protein p21/WAF1 in normal cells and arrests them in G(0) phase of cell cycle (61).

Curcumin inhibited camptothecin, mechlorethamine, and doxorubicin-induced apoptosis of MCF-7, MDA-MB-231, and BT-474 human breast cancer cells. Treatment with curcumin inhibited both JNK activation and mitochondrial release of cytochrome c in a concentration-dependent manner. Using an *in vivo* model of human breast cancer, dietary supplementation with curcumin was found to significantly inhibit cyclophosphamide-induced tumor regression which was accompanied by a decrease in activation of apoptosis by cyclophosphamide and decreased JNK activation (265). In a human breast cancer xenograft model, dietary administration of curcumin significantly decreased the incidence of breast cancer metastasis to the lung and suppressed the expression of NF-κB, COX-2 and MMP-9 (12). It has been reported recently that curcumin strongly induced apoptosis in MDA-MB-231 breast cancer cells in correlation with reduced activation of the survival pathway NF-κB. Curcumin also reduces the expression of major MMPs due to reduced NF-κB activity and transcriptional downregulation of AP-1. Reduced NF-κB/AP-1 activity and MMP expression lead to diminished invasion through a reconstituted basement membrane and to a significantly lower number of lung metastases in immunodeficient mice after intercardiac injection of MDA-MB-231 cells. Curcumin-treated animals showed no or very few lung metastases, most likely as a consequence of downregulation of NF-κB /AP-1 dependent MMP expression and direct apoptotic effects on circulating tumor cells (25).

D. Curcumin and lung cancer

Treatment of A549 cells with curcumin inhibited IFN-α-induced activation of NF-κB and COX-2 (169). It has been suggested that curcumin has the potential to act as an adjuvant chemotherapeutic agent and enhance chemotherapeutic efficacy of vinorelbine in squamous cell lung carcinoma H520 cells *in vitro*. Curcumin and vinorelbine caused apoptosis by increas-

ing the protein expression of Bax and Bcl-xs while decreasing Bcl-2 and Bcl-xL, releasing apoptogenic cytochrome *c*, and augmenting the activity of caspase-9 and 3. Expression of Cox-2, NF-κB, and AP-1 was also affected (255). Curcumin inhibited the growth of human lung cancer cell lines A549 and H1299 in a concentration-dependent manner and caused induction of apoptosis. Growth inhibition of H1299 cell lines was both time and concentration dependent. A decrease in expression of p53, Bcl-2, and Bcl-xL was observed after treatment of cells with curcumin. This suggested a p53 independent induction of apoptosis in lung cancer cells by curcumin (236). Chen *et al*. (56) used microarray analysis of gene expression profiles to characterize the anti-invasive mechanisms of curcumin in CL1-5, highly invasive lung adenocarcinoma cells. It was shown that curcumin significantly reduces the invasive capacity of CL1-5 cells in a concentration range far below its levels of cytotoxicity and that this anti-invasive effect was concentration dependent. Using microarray analysis, 81 genes were downregulated and 71 genes were upregulated after curcumin treatment. Below sublethal concentrations of curcumin (10 μM), several invasion-related genes were suppressed, including MMP-14, neuronal cell adhesion molecule and integrins α6 and β4. In addition, several heat-shock proteins (Hsp) such as Hsp27, Hsp70, and Hsp40-like protein were induced by curcumin. By gelatin zymographic analysis, it was further shown that curcumin reduced the MMP14 expression in both mRNA and protein levels and also inhibited the activity of MMP2, the downstream gelatinase of MMP14 (56). It has been reported recently that the inhibitory effect of curcumin on the survival of lung and pancreatic adenocarcinoma cell lines is associated with simultaneous downregulation of COX-2 and EGFR and inhibition of Erk1/2 signaling pathway (171). The IFN-α-induced COX-2 expression and STAT1 activation were markedly inhibited by the addition of curcumin to the IFN-α-pretreated A549 human non-small cell lung cancer cell line which was associated with downregulation of cdks 2, 4, and 6 and upregulation of p27 (170).

Oral administration of polyphenols such as curcumin and catechin inhibited the lung metastasis maximally as seen by the reduction in the number of lung tumor nodules. Consequent to the inhibition of the lung tumor nodules, the lifespan of animals treated with curcumin was also found to be increased (207). Curcumin when given orally, significantly inhibited the mediastinal lymph node metastasis of orthotopically implanted Lewis lung carcinoma (LLC) cells in a dose-dependent manner, but did not affect the tumor growth at the implantation site. Combined treatment with curcumin and an anti-cancer drug, cis-diamine-dichloroplatinum (CDDP), resulted in a marked inhibition of tumor growth at the implanted site and of lymphatic metastasis and a significant prolongation of the survival time. The downregulation of transcriptional AP-1 activity by curcumin caused inhibition of LLC cell invasion through the repression of expression of the mRNAs for urokinase-type plasminogen activator (u-PA) and its receptor (u-PAR) (118).

E. Curcumin and liver cancer

Recently, it has been shown that curcumin significantly decreases hypoxia-induced HIF-1α protein levels in HepG2 hepatocellular carcinoma cells. Treatment with curcumin also suppressed the transcriptional activity of HIF-1 under hypoxia, leading to a decrease in the expression of vascular endothelial growth factor (VEGF), a major HIF-1 target angiogenic factor. Curcumin also blocked hypoxia-stimulated angiogenesis *in vitro* and downregulated HIF-1alpha and VEGF expression in vascular endothelial cells (26). Intravital fluorescence videomicroscopy was performed to monitor neocapillaries in hepatocellular carcinoma (HepG2) cell-inoculated tumors on days 3, 7 and 14 post-tumor inoculation, using RITC-dextran. The increased tumor neocapillary density (NCD) was attenuated significantly by daily treatment of curcumin solution. The curcumin treatment also reduced the tumor-induced overexpression of COX-2 and serum VEGF in HepG2 groups significantly, indicating that curcumin could inhibit tumor angiogenesis (321). Treatment with curcumin and embelin prevented the *N*-nitrosodiethylamine (DENA) and phenobarbital (PB) induced decrease in hepatic glutathione antioxidant defense, decreased lipid peroxidation, minimized the histological alterations induced by DENA/PB, but showed toxic effects on the hematopoietic cells (269). Curcumin prevented methylglyoxal (MG)-induced cell death and apoptotic biochemical changes such as mitochondrial release of cytochrome c, caspase-3 activation, and cleavage of PARP. Using the cell permeable dye 2′,7′-dichlorofluorescein diacetate (DCF-DA) as an indicator of reactive oxygen species generation, it was found that curcumin abolished MG-stimulated intracellular oxidative stress (54). Curcumin inhibited cellular migration and invasion of highly invasive SK-Hep-1 cell line of HCC. Further, it also inhibited MMP-9 secretion in SK-Hep-1 in a dose-dependent fashion. The authors concluded that curcumin has a significant anti-invasion activity in SK-Hep-1 cells and that this effect is associated with its inhibitory action on MMP-9 secretion (187). Curcumin, along with other food additives, was found to inhibit the mutagenesis induced by aflatoxin B1 (AFB1) in *Salmonella* tester strains TA98 and TA100. Turmeric and curcumin, which were the most active, inhibited mutation frequency by >80%. Administration of curcumin by gavage effectively suppressed DEN-induced liver inflammation and hyperplasia in rats. Curcumin inhibited DEN-mediated increased expression of oncogenic p21/WAF1(ras), p53, PCNA, cyclin E, and p34(cdc2) proteins and NF-κB in liver tissues of rats (62). Treatment with curcumin in diet caused 81% reduction in multiplicity and a 62% reduction in incidence of development of hepatocellular carcinoma (HCC) induced by DEN in C3H/HeN mice. There was reduction in the levels of p21/WAF1(ras), PCNA, and cdc2 proteins in the hepatic tissues of mice (63). Administration of curcumin for 6 consecutive days to rats bearing the highly cachectic Yoshida AH-130 ascites hepatoma resulted in an important inhibition of tumor growth (45). Dietary administration of curcumin to rats significantly reduced the number of gamma glutamyl transpeptidase-positive foci induced by AFB1 which is considered as the precursor of hepatocellular neoplasm (266). Daily oral administration of curcumin suppressed intrahepatic metastasis in a dose-dependent manner, whereas the growth of hepatocellular carcinoma, CBO140C12 cells implanted tumors was not affected. Curcumin inhibited the invasion of tumor cells through matrigel-coated filters, the production of MMP-9 and also inhibited adhesion and haptotactic

migration to fibronectin and laminin without affecting the expression of integrins on the cell surface. These results suggested that curcumin suppressed the intrahepatic metastasis mediated by the inhibiton of several metastatic properties, in which the functional alteration of cytoskeletal organization could play an important role (228).

V. GENISTEIN

Genistein (5,7,4′-trihydroxyisoflavone) is an isoflavone that was first isolated from soybeans in 1931 with diverse biological activities (307). In recent years, increasing evidence has accumulated that this natural ingredient shows preventive and therapeutic effects for cancers, osteoporosis, and cardiovascular diseases in animals and humans. Genistein and its related isoflavones lack mutagenicity in *Salmonella* strains at a wide range of concentrations. It has been reported that genistein displays a moderate antimutagenicity in B(a)P 7,8-diol-9,10-epoxide-induced mutagenesis in *Salmonella* strain TA100 and it is the most potent inhibitor of P450-mediated activation of B(a)P of all tested isoflavones. Although soybeans contain a number of ingredients with demonstrated anticancer activities, genistein is the most important agent that has been extensively investigated and studied. Genistein inhibits the activities of tyrosine protein kinase, topoisomerase II (318), and ribosomal S6 kinase in cell culture (188). It has been reported to inhibit the growth of *ras*-oncogene transfected NIH 3T3 cells without affecting the growth of normal cells (229) and diminishes the platelet-derived growth factor-induced c-*fos* and c-*jun* expression in CH310T1/2 fibroblasts (330). Genistein potently inhibits the production of certain cytokines and eicosanoid biosynthesis, suggesting that genistein can modulate the inflammatory responses that are commonly involved in the promotional stage (93). It displays many anticancer properties which includes suppression of the proliferation of a variety of human gastrointestinal cancer cell lines, induction of differentiation of leukemia cells, and inhibition of endothelial cell angiogenesis relevant to tumor metastasis (86). Genistein treatment also leads to inhibition of topoisomerase II and ribosomal S6 kinase by stabilizing a cleavable topoisomerase-DNA complex and modulating mRNA translation *in vitro*, which may lead to protein-linked DNA strand breaks, cell growth suppression, differentiation and induction of several malignant cell lines (302). Genistein was also found to exhibit antioxidant properties, preventing the hemolysis of red blood cells by dialuric acid or by H_2O_2 and inhibiting microsomal lipid peroxidation induced by an Fe^{2+}-ADP complex and NADPH. Genistein and its related isoflavones were also reported to inhibit the NADH oxidase and respiratory chain in rat liver mitochondria (304 and references therein).

To study their bioavailability, seven women consumed 3.4, 6.9, or 10.3 μmol isoflavones/kg body wt in soymilk in each of three meals of a liquid diet on one of three feeding days that were separated by 2-wk washout periods. The plasma concentration of daidzein and genistein was significantly increased at 6.5 h after dosing, compared with the concentration at other times, although at 24 h after dosing, plasma concentration of isoflavones was still about half or two-thirds of the level of 6.5 h. Among the two subjects excreting large amounts of fecal isoflavones, plasma concentration of genistein at 24 h was significantly greater than that among the five subjects excreting small amounts of fecal isoflavones at each dosage (315).

Soy and its constituents have been consumed at high levels in Asian populations without toxic effects, but concern has been raised of potential adverse effects due to estrogenic activities of the isoflavones. In the mouse lymphoma assay, genistein induced an increase of predominantly small colonies, indicating that genistein acts as a clastogen. There is also published data on the inhibitory action of genistein on topoisomerase II, which is known to lead to chromosomal damage with a threshold dose response (209).

A. Genistein and skin cancer

Treatment of human keratinocyte cell line NCTC 2544 with genistein prevented UV-induced enhancement of the DNA-binding activity of signal transducer and activator of transcription (STAT)-1 by acting as a tyrosine kinase inhibitor, thus limiting lipid peroxidation and increase in ROS formation (206). Genistein dose dependently preserved cutaneous proliferation in human reconstituted skin as evidenced by the preservation of proliferating cell populations with increasing genistein concentrations and noticeable paucity in PCNA immunoreactivity in the absence of genistein. Genistein inhibited UV-induced DNA damage, evaluated with pyrimidine dimers (PD), demonstrated an inverse relationship with increasing topical genistein concentrations. A dose-dependent inhibition of UVB-induced PD formation was observed relative to increasing genistein concentrations (214). Pretreatment of hairless mice with genistein 1 h prior to UVB exposure significantly inhibited UVB-induced H_2O_2 and MDA in skin and 8-hydroxy-2′-deoxyguanosine (8-OHdG) in epidermis as well as internal organs. Suppression of 8-OHdG formation by genistein has been corroborated in purified DNA irradiated with UVA and B (305). Genistein substantially inhibits skin carcinogenesis and cutaneous aging induced by UV light in mice and photodamage in humans (304). In estrogen receptor alpha wild-type (ERα WT) mice, dietary intake of genistein influenced tumor development, enhancing anaplasia of mammary cancer induced by oral administration of DMBA, and subscapular implantation of medroxyprogesterone acetate. Mice consuming genistein expressed malignant mammary adenocarcinoma, whereas benign adenomas were observed in mice fed the control diet. No tumors were observed in estrogen receptor-alpha knockout (ER alpha KO) mice (75). Topical application of genistein before UV-B radiation reduced *c-fos* and *c-jun* expression in the SENCAR mouse skin in a dose-dependent manner (296). Genistein showed synergistic effect with cyclophosphamide against B16F-10 melanoma cells injected intraperitoneally, intravenously, or intradermally (308). Two promotion studies using DMBA and TPA protocol were conducted using CD-1 and SENCAR mice. Both studies consistently showed that genistein substantially inhibited TPA-promoted skin tumorigenesis by reducing the tumor multiplicity. However, the tumor incidence appeared to be less affected. Genistein inhibited DMBA-induced bulky DNA adduct formation and substantially sup-

pressed TPA-stimulated H_2O_2, inflammatory responses, and ODC activity in mouse skin (303).

B. Genistein and prostate cancer

Genistein inhibited cell growth and induced apoptosis in PC-3 prostate cancer cells but not in nontumorigenic CRL-2221 human prostate epithelial cells. Genistein also inhibited Akt kinase activity and abrogated the EGF-induced activation of Akt in prostate cancer cells. Akt transfection resulted in the induction of NF-κB activation and was completely inhibited by genistein treatment. Genistein treatment also abrogated the EGF-induced activation of NF-κB which was mediated via Akt signaling pathway (177). Genistein caused significant inhibition of basal VEGF expression and hypoxia-stimulated VEGF expression in both human prostate cancer PC-3 cells and human umbilical vein endothelial cells (HUVECs). Genistein treatment reduced VEGF and HIF-1α in PC-3 cells (97). Genistein caused sustained G2/M arrest in TRAMP-C2 cells which was associated with increased p-cdc2, decreased cdc2 protein, cytoplasmic retention of cyclinB1, resulting in decreased cdc2 kinase activity independently of p21/WAF1. Genistein treatment also increased Myt-1 levels and decreased Wee-1 phosphorylation. Downregulation of Myt-1 and Wee-1 by siRNA restored cdc2 levels, its kinase activity, cyclinB1 nuclear localization, and partially restored cell proliferation of genistein-treated cells (285). Pretreatment with genistein potentiated radiation induced cell killing in human PC-3 prostate cancer cells. Genistein combined with prostate tumor irradiation caused greater inhibition of primary tumor growth and increased control of spontaneous metastasis to para-aortic lymph nodes, increasing mouse survival in orthotopic xenograft in nude mice. Treatment with genistein alone increased metastasis to lymph nodes. The combination of genistein with radiation in orthotopic RM-9 prostate tumors in syngeneic C57BL/6 mice also caused a greater inhibition of primary tumor growth and spontaneous metastasis to regional para-aortic lymph nodes, whereas treatment with genistein alone showed a trend to increased lymph node metastasis (295). This observation is of concern in relation to soy-based clinical trials for cancer patients, as treatment with genistein alone was found to promote metastatic spread to regional lymph nodes. It has been demonstrated that genistein-mediated inhibition of cell invasion rests upon blocking activation of the MAP kinase-activated protein kinase 2 (MAPKAPK2) and the HSP27 pathway in PC-3 and PC3-M cells (314). It was shown that genistein-induced inhibition in cell proliferation is associated with a reduction in telomerase activity in prostate cancer cells. Genistein decreased hTERT expression and transcriptional activity along with decrease in c-myc protein expression (119). Genistein strongly suppressed basal expression of androgen-responsive gene (ARG) mRNAs, including PSA and Ste20-related proline-alanine-rich kinase (SPAK). The synthetic androgen R1881-induced expression of PSA, SPAK, B2M, and SEPP1 genes was uniformly blocked by genistein (277). Genistein reduced MDM2 protein and mRNA levels in human cell lines of breast, colon, and prostate cancer, primary fibroblasts, and breast epithelial cells in a dose- and time-dependent manner. The inhibitory effects were found at both transcriptional and post-translational levels and were independent of tyrosine kinase pathways. At the post-translational level, genistein induced ubiquitination of MDM2, which led to its degradation and also induced apoptosis, G2 arrest, and inhibited proliferation in a variety of human cancer cell lines, regardless of p53 status. It was also shown that MDM2 overexpression abrogated genistein-induced apoptosis *in vitro* and genistein inhibited MDM2 expression and tumor growth in PC-3 xenografts (174). Genistein had a dose-dependent, significant inhibitory effect on osteopontin (OPN) transcript levels in prostates of TRAMP mice displaying advanced prostate cancer and it was reported that dietary genistein may delay the progression from benign to malignant tumors by inhibiting OPN expression (208). Genistein in the diet significantly downregulated cell proliferation, EGFR, IGF-1R, ERK-1, and ERK-2, but not AR, ER-α, ER-β, ErbB2, EGF, TGF-α, IGF-1, VEGF, and VEGFR in prostates of TRAMP mice (293). Treatment of TRAMP mice with genistein at 12–28 weeks and at 1–35 days postpartum caused resulted in 29% and 6% decrease in poorly-differentiated cancerous lesions compared with controls, respectively. The most significant effect was seen in the TRAMP mice exposed to genistein throughout life (1–28 weeks) with a 50% decrease in poorly differentiated cancerous lesions. In castrated TRAMP mice, dietary genistein suppressed the development of advanced prostate cancer. There were 100% poorly differentiated tumors in castrated TRAMP mice and 37% in noncastrated TRAMP mice. Genistein and estrogen also downregulated AR, ER-α, and PR in the prostates of C57BL/6 mice and acted independently of ER (294). Genistein significantly potentiated the antitumor, anti-invasive, and antimetastatic activities of docetaxel both in culture and in severe combined immunodeficient (SCID)-human model of experimental prostate cancer bone metastasis. It was also found that the expression of osteoprotegerin (OPG) was induced by genistein and inhibited by docetaxel, whereas genistein significantly downregulated the expression and secretion of receptor activator of NF-κB (RANK) ligand (RANKL), inhibited osteoclast formation, MMP-9 activity, and invasion of PC-3 cells (178). Genistein in the diet downregulated the EGF and ErbB2/Neu receptors in the rat prostate with no apparent adverse toxicity in Lobound–Wistar rats (73). In a population-based prospective study in Japanese men aged 45–74 years, intakes of genistein, daidzein, miso soup, and soy food decreased the risk of localized prostate cancer (162).

C. Genistein and breast cancer

Treatment of the non-neoplastic, immortalized human breast epithelial MCF-10A cells with physiologically-relevant levels of genistein was associated with decreased cell proliferation, downregulation of the protooncogene MET, upregulation of the breast tumor suppressor gene EGR-1, immediate-early response genes FOS and JUN and Egr-1 binding to the transcription factor Sp1 (264). Treatment of breast cancer MDA-MB-231, MCF-7, and BT-20 cells caused arrest of cells in the G2/M phase. Both normal and breast cancer cell lines express the genes of MMP-2, 9, MT1, MT2, MT3-MMP, and TIMP-1, 2 and 3. MCF-7 express notably less MMPs than MDA-MB-231 cell line. Genistein resulted in downregulation of the transcription of MMP genes in MDA-MB-231 and MCF-7 cells. Genistein also significantly reduced the invasion properties of cancer cells (157). Recently, it has been shown that the combination treat-

ment of tamoxifen and genistein inhibited the growth of ER+/HER2-overexpressing BT-474 human breast cancer cells in a synergistic manner. This inhibitory effect might be contributed in part from combined effects on cell-cycle arrest at G-1 phase and on induction of apoptosis by downregulation of survivin, EGFR, HER2, and ERα expression (199). It was shown that genistein treatment depleted the G1 population of Brca1 mutant mammary tumor cells, which was accompanied by an accumulation of cells at G2. Some genistein-treated cells entered mitosis; however, they exhibited chromosome abnormalities and maintained tetraploidy owing to abortive mitotic exit. A fraction of G2 cells underwent endoreduplication and became polyploid, which was accompanied by increased cell death through activating DNA damage response (284). Genistein induced dose-dependent spindle-cell morphology and significantly reduced motility in F3II mammary carcinoma cells. Genistein inhibited uPA secreted by F3II cell monolayers, while inducing an increase in the proteolytic activity of B16 cells. *In vivo*, i.p. administration of genistein reduced tumor-induced angiogenesis in syngeneic mice implanted with F3II mammary carcinoma cells (83). Genistein inhibited cell proliferation in estrogen receptor-positive MCF-7 and estrogen receptor-negative MDA-MB-231 human breast carcinoma cell lines. Treatment with genistein also inhibited cytochrome P450 (CYP) 1A1-mediated ethoxyresorufin-*O*-deethylase (EROD) activity and TPA-induced COX-2 activity and protein expression (261). Recently, it was reported that genistein and quercetin increased connexin43 and suppress MDA-MB-231 cells proliferation at physiologically relevant concentrations (69).

Genistein inhibited invasion *in vitro* of MCF-7 and MDA-MB-231 cells characterized by downregulation of MMP-9 and upregulation of TIMP-1. In these xenograft studies in athymic nude mice implanted with MCF-7 cells, genistein inhibited tumor growth, stimulated apoptosis, and upregulated p21/WAF1 expression. In the MDA-MB-231 xenograft, genistein also inhibited angiogenesis by decreasing vessel density and decreasing the levels of VEGF and TGFβ1 (259). However, dietary genistein was shown to stimulate mammary gland growth and enhanced the growth of MCF-7 cell tumors in ovariectomized athymic mice (111). It was also shown that dietary treatment with genistein at physiological concentrations stimulates estrogenic effects such as breast tumor growth, cellular proliferation, and pS2 expression in athymic mice (127). Genistein induced the upregulation of p53 protein, phosphorylation of p53, activation of the sequence-specific DNA binding properties of p53, and phosphorylation of the hCds1/Chk2 protein kinase in ataxia-telangiectasia mutated protein (ATM) dependent manner (319). Genistein significantly increased tumor cross-sectional area and tumor multiplicity but not the tumor incidence and latency period in NMU-induced tumorigenesis in adult female rats (146). Mammary glands of young adult female rats exposed to casein supplemented with genistein or soy protein isolate (SPI) had increased apoptosis, relative to rats fed CAS diet devoid of genistein. The increased apoptotic index in mammary glands of genistein-treated rats was accompanied by increased levels of the tumor suppressor protein PTEN (phosphatase and tensin homolog deleted in chromosome ten), and increased expression of the pro-apoptotic p21/WAF1, Bax, and Bok genes. Genistein-induced apoptosis in MCF-7 cells was concomitant with increased PTEN expression and this was abrogated by PTEN siRNA (74). It has been reported that treatment with dietary genistein reduced the metastasis in a postsurgical orthotopic breast cancer model (287). Genistein increased the weight of estrogen-dependent adenocarcinomas in ovariectomized rats compared with the negative control animals. Genistein treatment also resulted in a higher percentage of proliferative cells in tumors and increased uterine weights when compared with ovariectomized rats (17). Female Balb/c mice fed diets supplemented with genistein exhibited a significant reduction in tumor weight compared to controls. Genistein significantly inhibited F3II cell proliferation and caused a G2/M block in cell cycle progression *in vitro* associated with a significant increase in the protein expression of p-cdc2 and cyclin B1 (105). It has also been reported that weakly estrogenic genistein negated the inhibitory effect of tamoxifen on the growth of estrogen-dependent breast tumors. Treatment with tamoxifen suppressed estrogen-stimulated MCF-7 tumor growth in ovariectomized athymic mice. Genistein when given in diet to mice negated the inhibitory effect of tamoxifen on MCF-7 tumor growth, lowered estrogen level in plasma, and increased expression of estrogen responsive genes such as pS2, PR, and cyclin D1 (128). Tamoxifen and bioactive soy components, genistein and soy phytochemical concentrate (SPC), delayed the growth of MCF-7 tumors in nude mice. The combination of tamoxifen with genistein or SPC, at the lower dose of tamoxifen had synergistic effects on delaying the growth of MCF-7 tumors. The combination of genistein and tamoxifen synergistically delayed the growth of breast tumors via decreased estrogen level and activity and downregulation of EGFR expression (200).

D. Genistein and lung cancer

Genistein was found to inhibit cell growth in H460 cells, which harbor wild-type p53, and H322 cells, which possess mutated p53 in a dose-dependent manner. Genistein caused cell death via apoptotic pathway with upregulation of p21/WAF1 and Bax in wild-type and mutant p53 cell lines. Furthermore, cells treated with genistein showed an increased expression of endogenous wild-type p53, while the level of the mutant p53 protein remained unchanged (180). Genistein induced p21/WAF1 expression mainly in a p53-dependent manner in A549 human lung cancer cell line (77). In male F344 rats, the total incidences of adenomas and carcinomas in the lungs of animals treated with genistein were significantly higher than in the control group. There was elevation of 5-bromo-2′-deoxyuridine labeling indices, reflecting cell proliferation in the lungs of rats given genistein. There was significant increase in the level of 8-OHdG, a marker of oxygen radical-mediated DNA damage in the lungs of rats treated with genistein after DHPN initiation (254). It has been shown recently that genistein pretreatment inactivates NF-κB and may contribute to increased growth inhibition and apoptosis induced by cisplatin, docetaxel, and doxorubicin in prostate, breast, lung, and pancreatic cancer cells (176). Dietary supplementation with genistein and diadzein reduced pulmonary metastasis of B16BL6 murine melanoma cells in C57BL/6 mice. The number and size of the tumors in isoflavone-supplemented group were less than in the control group and this showed that isoflavones reduced experimental metastasis of melanoma cells in mice (173). The treatment with genistein resulted in the reduction of the lung

tumors in Lewis lung cancer LL2 implanted subcutaneous tumors in mice (308, 309).

E. Genistein and liver cancer

Genistein was able to inhibit EGF-induced EGF receptor degradation and tyrosine phosphorylation in human hepatoma HepG2 cells and this inhibition was increased with increasing genistein concentration. With treatment of HepG2 cells with genistein, the amount of internalized EGF was remarkably decreased (318). Genistein and daidzein increased apo A-I secretion in a dose-dependent fashion in human hepatoma cell line Hep G2. The effect of genistein on apo A-I secretion was similar to that observed with 17-beta-estradiol. Treatment of cells with genistein also increased the transcriptional activity of the apo A-I gene (164). Genistein and dexamethasone have been shown to block cell cycle checkpoint with a selective induction of cdk inhibitor p21/WAF1 in a tumor suppressor p53-independent manner and abolishment of cdk2 phosphorylation. Genistein also strongly increased the expression of p21/WAF1 protein and activated p21/WAF1 promoter reporter constructs (231). Genistein, biochanin-A, and daidzein inhibited growth of the human hepatoma cell lines, HepG2, Hep3B, Huh7, PLC, and HA22T in a dose-dependent manner. The isoflavones caused tumor cell death by induction of apoptosis by activation of caspase-3, cleavage of PARP, downregulation of Bcl-2 and Bcl-xL expression. Genistein induced progressive and sustained accumulation of hepatoma cancer cells in the G2/M phase as a result of inhibition of Cdc2 kinase activity (273). Genistein significantly inhibited the growth of Bel 7402 hepatocellular carcinoma (HCC) cells and caused G2/M cell cycle arrest with significant decrease in S phase and increase in apoptosis. The expression of p125FAK in the genistein group was significantly lower than that in the control group. Tumor growth in genistein-treated nude mice was significantly retarded in comparison to control mice and it also inhibited the invasion of Bel 7402 cells into the renal parenchyma of nude mice with xenograft transplant (96). Genistein caused inhibition of cell proliferation, induction of apoptosis, and activation of caspase-3 in DEN induced and phenobarbital promoted cancer-bearing rats (59).

VI. RESVERATROL

Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene), a phytoalexin found in grape skins, peanuts, and red wine, has been reported to exhibit a wide range of biological and pharmacological properties. It exists in two isoforms; *trans*-resveratrol and *cis*-resveratrol where the *trans*-isomer is the more stable form. Resveratrol-glucuronide is the major form absorbed when compared to the very minute amounts of unconjugated resveratrol and resveratrol sulfate. Resveratrol is glucuronated in the human liver and sulfated in both the liver and the duodenum (Fig. 11). It was first detected in the dried roots of *Polygonum cuspidatum*, traditionally used in Chinese and Japanese medicines as an anti-inflammatory agent. It has gained considerable attention because of its potential cancer chemopreventive properties. There have also been extensive studies demonstrating that resveratrol possesses an ability to intervene in multistage carcinogenesis. In addition, resveratrol may be beneficial in the control of atherosclerosis, heart disease, arthritis, or autoimmune disorders. Numerous biological activities have been ascribed to resveratrol, which may explain its antiinflammatory, anticarcinogenic, or anticancer properties. Among its various actions, resveratrol has been demonstrated to inhibit cellular survival signaling (21). The chemopreventive activity of resveratrol was first demonstrated in a seminal report published by John Pezzuto and colleagues, who reported that resveratrol was effective in all three major stages (*i.e*., initiation, promotion, and progression) of carcinogenesis. According to their study, resveratrol significantly reduced the number of tumors per mouse in a two-stage skin carcinogenesis model (120). That report has been followed with a battery of *in vitro* investigations reporting that resveratrol can prevent or slow the progression of various diseases including cancer, cardiovascular disease, and ischemic injuries (34). In a study in healthy volunteers, resveratrol was administered at a dose of 360 μg/kg either dissolved in grape juice, vegetable juice, or white wine. By the gas chromatography-mass spectrometry method, plasma peak levels of 20 nm authentic resveratrol and 2 μM "total" resveratrol (*i.e*., genuine resveratrol plus resveratrol generated by hydrolysis of its conjugates) 30 min after ingestion, irrespective of dietary matrix were found. Results from preclinical studies in rats, using high-performance liquid chromatography methods, suggest consistent attainment of plasma peak levels 5–10 min post-oral administration and a rapid plasma elimination half-life of 12–15 min (94).

A. Resveratrol and skin cancer

Resveratrol, along with sesamol, sesame oil, and sunflower oil, showed a profound inhibitory effect on the Epstein–Barr virus early antigen induction. Resveratrol showed a remarkable cytotoxic activity in brine shrimp lethality assays, as well as profound free radical scavenging activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging bioassay. In the *in vivo* assay resveratrol offered a 60% reduction in the DMBA and TPA-induced skin papillomas in mouse at 20 weeks (131). Single topical application of resveratrol to SKH-1 hairless mice resulted in significant inhibition of UVB-mediated increase in bifold skin thickness and skin edema. The resveratrol treatment to mouse skin also resulted in significant inhibition of UVB-mediated induction of COX and ODC enzyme activities and protein expression of ODC, which are well-established markers for tumor promotion. It was also observed that resveratrol inhibited UVB-mediated increased level of lipid peroxidation, a marker of oxidative stress (4). Topical application of resveratrol resulted in significant decrease in UVB-induced bi-fold skin thickness, hyperplasia, and infiltration of leukocytes. It was also suggested that the antiproliferative effects of resveratrol might be mediated via modulation in the expression and function of cell cycle regulatory proteins cyclin-D1 and D2, cdk2, 4, and 6, and WAF1/p21/WAF1, and may be associated with inhibition of the MAPK pathway (241). In NHEK, 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

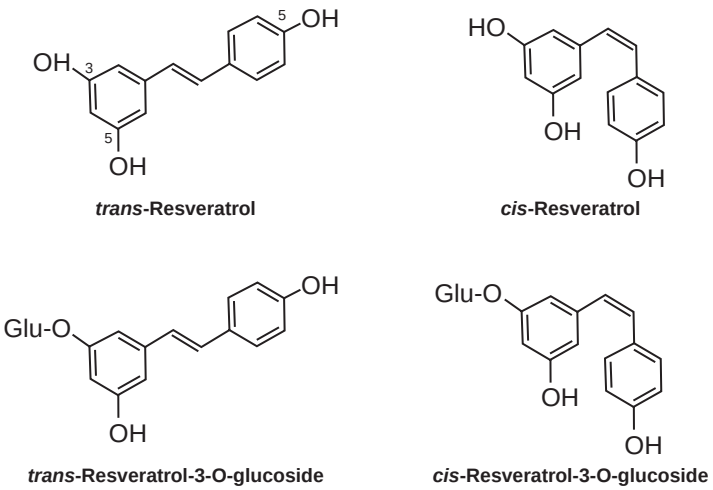

FIG. 11. Chemical structures of resveratrol and resveratrol glucosides.

(1). It has been shown that the topical application of skin with resveratrol resulted in inhibition of UVB-radiation induced tumor incidence and delay in the onset of skin tumorigenesis. The post-treatment of resveratrol was found to impart equal protection than the pretreatment, suggesting that resveratrol-mediated responses may not be sunscreen effects. It was also demonstrated that resveratrol caused downregulation of survivin, phospho-survivin protein, and upregulation of proapoptotic Smac/DIABLO protein in skin tumors and enhancement of apoptosis (24).

B. Resveratrol and prostate cancer

Resveratrol has been shown to induce apoptosis in LNCaP and DU145 prostate cancer cell lines through different PKC-mediated and MAPK-dependent pathways (260). Resveratrol treatment to DU-145 cells reduced cell viability and increased membrane breakdown in a dose-dependent way, without interfering with ROS production or NO synthesis. Furthermore, at low concentration, resveratrol was able to raise heat shock proteins (HSP70) levels, but at high concentration, the measured levels of protective HSP70 were unmodified (51). The growth-inhibitory concentrations of resveratrol suppressed EGFR-dependent Erk1/2 activation pathways stimulated by EGF and TPA in PC-3 cells *in vitro*. It was also demonstrated that resveratrol abrogation of a PKC-mediated Erk1/2 activation response in PC-3 cells correlates with isozyme-selective PKCα inhibition (272). The treatment of androgen-sensitive prostate cancer cells LNCaP with resveratrol downregulated PSA, AR co-activator ARA24, and NF-κB/p65. Altered expression of these genes was associated with an activation of p53-responsive genes such as p53, PIG 7, p21/WAF1, p300/CBP, and Apaf-1 (222). Treatment of LNCaP cells with resveratrol caused induction of apoptosis through inhibition of PI3K/Akt activation and modulations in Bcl-2 family proteins (23). Resveratrol caused modulation of a number of important genes in the androgen pathway, including PSA and AR in LNCaP cells. Resveratrol also downregulated 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-G1 and S phases of the cell cycle, and inhibited cell proliferation in a time- and dose-dependent manner (126). Recently, it has been shown that resveratrol and EGCG-induced apoptosis is associated with a significant downregulation of casein kinase 2 (CK2) activity and protein expression in both the androgen-sensitive (ALVA-41) and androgen-insensitive (PC-3) prostate cancer cells. Overexpression of CK2alpha protected prostatic cancer cells against resveratrol and EGCG-induced apoptosis. Relatively low doses of resveratrol and EGCG induced a modest proliferative response in cancer cells that could be switched to cell death by moderate inhibition of CK2 (13). Resveratrol induced a decrease in proliferation rates and an increase in apoptosis in prostate-derived cells nontumorigenic line PZ-HPV, androgen-sensitive cancer line LNCaP, and androgen-insensitive cancer line PC-3 in a dose- and time-dependent manner. These effects were coincident with cell accumulation at the G0/G1 phase of the cell cycle. In LNCaP and PC-3, the apoptosis induced by resveratrol was mediated by activation of caspase-9 and -3, and a change in the ratio of Bax/Bcl-2. Expressions of cyclin D1, E, and cdk4, as well as cyclin D1/cdk4 kinase activity, were reduced and p53, p21/WAF1, and p27 were increased by resveratrol only in LNCaP cells. In contrast, resveratrol decreased cyclin B1 and cdk1 expression and cyclin B/cdk1 kinase activity were decreased in both cell lines (36).

C. Resveratrol and breast cancer

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. Cells treated with resveratrol, but lacking aberrant Stat3 activity, show reversible growth arrest and minimal loss of viability (156). Resveratrol induced apoptosis in MCF-7 cells in a time- and concentration-depen-

dent manner. The growth-inhibitory effect of resveratrol on malignant cells was mainly due to its ability to induce S-phase arrest and apoptosis in association with reduced levels of telomerase activity. Resveratrol treatment downregulated the telomerase activity of target cells and the nuclear levels of hTERT, the reverse transcriptase subunit of the telomerase complex (167). Treatment with resveratrol significantly decreased tumor growth, angiogenesis, and increased apoptotic index in ER$\alpha-$ ER$\beta+$ MDA-MB-231 tumors in nude mice. There was also a significant increase in apoptosis and reduced extracellular levels of VEGF in resveratrol-treated MDA-MB-231 cells (89). It has been reported recently that resveratrol-induced actin structures called filopodia formation is time-dependent and concentration-dependent. In contrast to resveratrol at 50 μM, resveratrol at 5 μM acts in a manner similar to estrogen by increasing lamellipodia, as well as cell migration and invasion. Resveratrol at 50 μM decreases Rac and Cdc42 activity, whereas estrogen and 5 μM resveratrol increase Rac activity in breast cancer cells. MDA-MB-231 cells expressing dominant-negative Cdc42 or dominant-negative Rac retain filopodia response to 50 μM resveratrol (22). Resveratrol affected the growth of human breast cancer cell lines MCF7, MDA-MB-231, SK-BR-3, and Bcap-37 in a dose-dependent manner and has been shown to exert its growth-inhibitory/apoptotic effect on the breast cancer cells via the Akt-caspase-9 pathway (179). Resveratrol induced nuclear accumulation of COX-2 protein in human breast cancer MCF-7 and MDA-MB-231 cell cultures and this induction is MAPK and AP-1 dependent. Nuclear COX-2 in resveratrol-treated cells colocalized with p53 and with p300, a coactivator for p53-dependent gene expression (278). It has been demonstrated that resveratrol regulates IGF-II and that IGF-II mediates RSV effect on cell survival and growth in breast cancer cells (291). Resveratrol induced apoptosis in MCF-7 cells and involve an oxidative, caspase-independent mechanism, whereby inhibition of PI3K signaling converges to Bcl-2 through NF-κB and calpain protease activity (235). Resveratrol treatment enhances CD95L expression in T47D breast carcinoma cells and it was shown that resveratrol-mediated cell death is specifically CD95-signaling dependent (67). Resveratrol acts as a potent sensitizer of tumor cells for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through p53-independent induction of p21/WAF1 and p21/WAF1-mediated cell cycle arrest associated with survivin depletion (87).

In MCF-7, T47D, and LY2 cells, resveratrol showed a weak estrogenic response, but when resveratrol was combined with 17β-estradiol (E2), a clear dose-dependent antagonism was observed. Using the mouse mammary organ culture model, resveratrol induced progesterone receptor (PR) when administered alone, but expression was suppressed in the presence of E2. Furthermore, resveratrol inhibited the formation of estrogen-dependent preneoplastic ductal lesions induced by DMBA in mammary glands and reduced *N*-methyl-*N*-nitrosourea-induced mammary tumorigenesis when administered by gavage to female Sprague Dawley rats (38). In DMBA-treated 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. DMBA induced ductal carcinomas and focal microinvasion *in situ*, whereas treatment with resveratrol suppressed DMBA-induced ductal carcinoma. Treatment with resveratrol also suppressed the DMBA-induced COX-2, MMP-9, and NF-κB expression in the breast tumor and inhibited proliferation at S-G(2)-M phase of the cell cycle in MCF-7 cells (30). Administration of grape seed extract (GSE) in AIN-76A diet did not show any protective activity of GSE against DMBA-induced breast cancer. However, administration of GSE in a laboratory dry food diet resulted in a 50% reduction in tumor multiplicity (148). Resveratrol modulated the expression of BRCA1, BRCA2, ER alpha, ER beta, p53, p21/WAF1, CBP/P300, RAD51, pS2, and Ki67 genes in a pattern dependent on the status of alpha and beta estrogen receptors in three human breast tumor cell lines HBL100, MCF7, and MDA-MB-231 and one breast cell line MCF 10A derived from a fibrocystic disease. These results show that resveratrol regulates gene expression via the estrogen receptor pathway (168). Resveratrol suppressed DMBA-induced mammary carcinogenesis in Sprague–Dawley CD rats (fewer tumors per rat and longer tumor latency). Resveratrol treatment resulted in more differentiated lobular structures and caused a significant reduction in proliferative cells in mammary terminal ductal structures making them less susceptible to carcinogen insult (308).

D. Resveratrol and lung cancer

Resveratrol was found to inhibit the growth of A549, EBC-1 and Lu65 lung cancer cells. Although simultaneous exposure to resveratrol plus paclitaxel, an essential chemotherapeutic agent against lung cancer, 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, and resveratrol enhanced the subsequent apoptotic effects of paclitaxel and induced levels of p21/WAF1waf1, p27kip1, E-cadherin, EGFR, and Bcl-2 in EBC-1 cells (158). 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 p21/WAF1. In addition, resveratrol treatment resulted in induction of apoptosis, activation of caspase-3, a shift in Bax/Bcl-xL ratio more towards apoptosis, and inhibited the transcriptional activity of NF-κB (153). It has been demonstrated that resveratrol enhances the radiosensitivity of human non-small cell lung cancer NCI-H838 cells accompanied by NF-κB inhibition and S-phase cell cycle arrest (182). Resveratrol significantly reduced the tumor volume, tumor weight, and metastasis to the lung in mice bearing highly metastatic Lewis lung carcinoma (LLC) tumors. In addition, resveratrol inhibited DNA synthesis, induced apoptosis, and decreased the S phase population in LLC cells. Resveratrol inhibited tumor-induced neovascularization at in an *in vivo* model. Moreover, resveratrol significantly inhibited the formation of capillary-like tube formation from human umbilical vein endothelial cells (HUVEC) and inhibited the binding of vascular endothelial growth factor (VEGF) to HUVEC (154). Resveratrol also exerted lung cancer chemopreventive activity through altering the expression of genes involved in the metabolism of

polycyclic aromatic hydrocarbons (PAH), resulting in altered formation of carcinogenic B(a)P metabolites in human bronchial epithelial cell line BEP2D (213). The BPDE-DNA adduct induction by B(a)P in the lungs of Balb-C mice was abrogated significantly by resveratrol. A similar pattern was found by immunohistochemistry for apoptosis and CYP1A1. Resveratrol also prevented BaP-induced CYP1A1 expression the lung tissues of mice (242).

E. Resveratrol and liver cancer

Resveratrol inhibited cell growth in p53-positive HepG2 cells. This anticancer effect was a result of cellular apoptotic death induced by resveratrol via the p53-dependent pathway. Resveratrol-treated cells were arrested in G1 phase and were associated with the increase in p21/WAF1 and Bax expression (161). Resveratrol inhibited CYP1A1 expression in human HepG2 hepatoma cells, by preventing the binding of the aryl hydrocarbon receptor (AHR) to promoter sequences that regulate CYP1A1 transcription (65). 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 seems to involve a gradually shortened half-life of HIF-1α protein caused by enhanced protein degradation through the 26S proteasome system. In addition, resveratrol remarkably inhibited hypoxia-mediated activation of ERK 1/2 and Akt, leading to a marked decrease in hypoxia-induced HIF-1α protein accumulation and VEGF transcriptional activation (325). Resveratrol treatment caused induction of apoptosis as well as an increase in nuclear size and granularity in a concentration-dependent manner in human leukemia cell line HL-60 and the human hepatoma-derived cell line HepG2. Resveratrol also inhibited cell proliferation in a concentration- and time-dependent manner by interfering with different stages of the cell cycle (271). Resveratrol inhibited cell proliferation, reduced the production of reactive oxygen species, and induced apoptosis, through cell cycle arrest in G1 and G2/M phases in HepG2 cells. Furthermore, it also modulated the NO/NOS system, by increasing iNOS and eNOS expression, NOS activity, and NO production. Inhibition of NOS enzymes attenuates its antiproliferative effect (227). Treatment with resveratrol caused cell death via induction of apoptosis in metabolically active H4IIE rat hepatoma cells as detected by caspase activation, oligonucleosomal DNA fragmentation, and formation of apoptotic nuclei. Following DNA damage, resveratrol led to an activation of caspases-2, -3, -8, and -10 (211).

The administration of resveratrol to rats inoculated with a fast growing tumor, Yoshida AH-130 ascites hepatoma, caused a very significant decrease in tumor cell content. The effects were found to be associated with an increase in the number of cells in the G2/M cell cycle phase. Flow cytometric analysis of the tumor cell population revealed the existence of an aneuploid peak, suggesting that resveratrol causes apoptosis in the tumor cell population, resulting in a decreased cell number (50). Resveratrol treatment inhibited the growth of murine hepatoma H22 cells, after the mice bearing H22 tumor were treated with resveratrol for 10 days. Resveratrol induced the S phase arrest of H22 cells and increased the percentage of cells in S phase in a dose-dependent manner. The enhanced inhibition of tumor growth by 5-FU was also observed in H22 bearing mice when 5-FU was administered in combination with resveratrol (312). Following treatment of H22 tumor bearing mice with resveratrol, the growth of murine transplantable liver cancer was inhibited. The level of expression of cyclin B1 and p34cdc2 protein was decreased in the transplantable murine hepatoma 22 treated with resveratrol (322). Resveratrol treatment leads to inhibition of 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 (190).

VII. LYCOPENE

Lycopene is a natural pigment synthesized by plants and microorganisms but not by animals. It is a carotenoid, an acyclic isomer of β-carotene which is a highly unsaturated, straight chain hydrocarbon containing 11 conjugated and two nonconjugated double bonds. The antioxidant properties of lycopene are a focus of interest these days. However, other mechanisms such as modulation of intercellular gap junction communication, hormonal and immune systems, and metabolic pathways are also beginning to be investigated (18). Lycopene ingested in its natural *trans* form found in tomatoes, is poorly absorbed. Recent studies have shown that heat processing of tomatoes and tomato products induces isomerization of lycopene to the *cis* form which in turn increases its bioavailability (239, 270). The most common sources of lycopene include red fruits and vegetables, such as tomatoes, watermelons, pink grapefruit, apricots, and pink guavas. Tomatoes and processed tomato products such as juice, ketchup, paste, sauce, and soup all are good sources of lycopene and may account for $>$85% of dietary lycopene in the North American diet. The lycopene content of tomatoes varies with the variety and increases with fruit ripening. Lycopene is one of the most potent antioxidants and has been suggested to prevent carcinogenesis and atherogenesis by protecting critical biomolecules including lipids, low-density lipoproteins (LDL), proteins, and DNA (221). Several studies have indicated that lycopene is an effective antioxidant and free radical scavenger. Lycopene, because of its high number of conjugated double bonds, exhibits higher singlet oxygen quenching ability compared to β-carotene or α-tocopherol (18).

A clinical study was conducted in which 25 men ingested a single dose of a tomato beverage that was composed of tomato paste, olive oil, and water. The men were divided into five groups and received one of five treatment levels: 10, 30, 60, 90, or 120 mg lycopene. Serial plasma samples were drawn for 1 month after the dose, and plasma samples were analyzed for lycopene by HPLC. The compartmental model was developed and it revealed that saturation of lycopene absorption occurs with increasing dose. The absorption efficiency at the 10 mg dose was on average 34%, whereas the absorption efficiency of the 120 mg dose was $\sim$5.5% (78).

A. Lycopene and skin cancer

Mouse models have demonstrated chemopreventive effects of lycopene against photo-induced tumors. In these studies, topical application of lycopene prior to UVB exposure reduced photoinjury in a dose-dependent relationship, as measured by decreases in both the inflammatory response and ODC activity, an enzyme linked to the development of skin tumors (16, 84). In addition, the topical application of lycopene was shown to help maintain normal levels of epidermal markers associated with proliferation, which are increased in cutaneous malignancy (219). To investigate the relationship between melanoma and dietary factors in this case-control study, subjects were requested to complete a food frequency questionnaire, which assessed diet over the previous year. Newly diagnosed patients with melanoma ($n = 502$) were recruited from pigment lesion clinics and controls ($n = 565$) were recruited from outpatient clinics. Persons in high versus low quintiles of energy-adjusted vitamin D, alpha-carotene, beta-carotene, cryptoxanthin, lutein, and lycopene had significantly reduced risk for melanoma, which remained after adjustment for presence of dysplastic nevi, education, and skin response to repeated sun exposure (212).

B. Lycopene and prostate cancer

Lycopene more potently inhibited the growth of the androgen-independent DU145 and PC-3 cells than androgen-dependent LNCaP cells. The tumor growth rate of DU145 tumor xenografts in BALB/c male nude mice was inhibited by 55–75% in mice treated with lycopene. Flow cytometry revealed that lycopene caused G0/G1 phase cell cycle arrest and apoptosis in DU145 cells in a dose-dependent manner (279). Lycopene has been shown to elevate levels of IGF-I and decreased levels of IGFBP-3 in prostate cancer PC-3 cells (130). A study compared the effects of AIN-93G diets containing 10% tomato powder, 0.025% lycopene, and 20% dietary energy restriction on the development of prostate cancer in the NMU-androgen-induced prostate cancer model. Compared with the control group, rats fed tomato powder experienced a significant 26% decrease in prostate cancer-specific mortality, whereas the 9% decrease of mortality by lycopene consumption did not reach significance (41). There was a substantial inhibition of cancer risk in a study which evaluated a combination of vitamin E, selenium, and lycopene in the *Lady* transgenic model (290). The effects of lycopene and vitamin E, two components of tomatoes, were tested on the growth of prostate tumors using the Dunning MatLyLu subline, a less differentiated and aggressive transplantable rat prostate cancer cell line (263). The authors observed no significant effect of lycopene, vitamin E, or dietary supplementation of both on overall tumor growth. However, changes in tumor composition with rats fed lycopene, vitamin E, and their combination, demonstrating tumor necrotic areas of 36%, 36%, and 29%, respectively, were observed by *in vivo* analysis of tumors by MRI. The changes in tumor composition of the rats fed lycopene and vitamin E were significantly different from the untreated and vehicle-treated animals, which had tumor necrotic areas of 20% and 23%, respectively. Using microarray analysis on the tumor tissue, the authors found that vitamin E reduced androgen signaling, whereas lycopene downregulated 5 α-reductase 1, IGF-1, and IL-6 expression (263). Diets containing broccoli, tomato, lycopene, and a combination of tomato plus broccoli reduced Dunning R-3327H prostate tumor growth rate compared with the control diet (47).

The large prospective Health Professionals Follow-up Study report in 1995 revealed that men with higher consumption of tomato products have a substantially lower risk of prostate cancer (92, 310). A meta-analysis found that compared with nonfrequent users of tomato products, the relative risk of prostate cancer among consumers of high amounts of raw tomato was 0.89 (95% CI 0.8-1.0). For high intake of cooked tomato products, the relative risk was 0.81 (95% CI 0.71-0.92). They concluded that the effect of tomato consumption was modest and restricted to high-intake consumers (82). The meta-analysis indicates that results from cohort studies and serum- or plasma-based studies support about a 25–30% reduction in the risk of prostate cancer. A study conducted in The Netherlands found no appreciable association between tomato consumption and prostate cancer risk. The consumption of tomato appeared to be low in this population (251). A study published by Kucuk and colleagues involved 26 men diagnosed with presumed localized prostate cancer that were scheduled to undergo a radical prostatectomy and were randomized to consume 30 mg of lycopene per day from two tomato oleoresin capsules or to continue their normal diet for 3 weeks before surgery. Post-surgical prostate tissue specimens were then compared between the two groups. Men consuming the lycopene supplement had 47% higher prostatic tissue lycopene levels than the control group, however, plasma lycopene levels were not significantly different between the groups, nor did they change significantly within each group. Men who consumed the lycopene supplement were less likely to have involvement of surgical margins. Additionally, they were less frequently found to have high-grade prostatic intraepithelial neoplasia (HGPIN) in the prostatectomy specimen. The intervention group was found to have smaller tumors, a greater reduction in PSA, and a higher expression of connexin 43; however, none of these differences were statistically significant (159). A longer follow-up period from the Health Professionals Follow-up Study cohort was evaluated to confirm the association between frequent intakes of tomato products and decreased prostate cancer risk. In the population, 2,481 of the 47,365 men were diagnosed with prostate cancer and tomato sauce consumption was associated with a 23% reduction in prostate cancer risk when two or more servings were compared with <1 serving per wk. Higher lycopene intake was also significantly associated with a 16% reduced risk for prostate cancer incidence when high vs. low quintile of lycopene intake were compared (median quintile intakes of 3.4 and 18.8 mg/d, respectively). In a nested case-control study within this cohort, there was a significant inverse association between plasma lycopene concentrations and prostate cancer risk that appeared to be strongest in men >65 years of age and individuals without a prior family history of prostate cancer incidence (312). Barber *et al*. have reported the inhibitory effect(s) of lycopene in primary prostate epithelial cell cultures, and the results of a pilot phase II clinical study investigating whole-tomato lycopene supplementation on the behavior of established CaP, demonstrating a significant and maintained effect on PSA velocity over 1 year (33). It has been reported that there was 10.77% decrease in PSA levels in patients with benign prostate hyper-

plasia who were submitted to daily ingestion of tomato paste. Dietary ingestion of 50 g of tomato paste per day for 10 weeks significantly reduced mean plasma PSA levels in patients with benign prostate hyperplasia, probably as a result of the high amount of lycopene in tomato paste (80). In a dose-escalating, Phase I–II trial of lycopene supplementation, 36 men with biochemically relapsed prostate cancer were enrolled. Six consecutive cohorts of 6 patients each received daily supplementation of lycopene for 1 year and the serum levels of PSA and plasma levels of lycopene were measured at baseline and every 3 months. It was concluded that lycopene supplementation in men with biochemically relapsed prostate cancer is safe and well tolerated. The plasma levels of lycopene were similar for a wide dose range and plateaued by 3 months. There was no discernible response in serum PSA by lycopene supplementation at the doses used in this study (66). Combined treatment of lycopene and vitamin E suppressed orthotopic growth of PC-346C prostate tumors by 73% at 42 days and increased median survival time by 40% from 47 to 66 days. The PSA index (PSA: tumor volume ratio) did not differ between experimental groups, indicating that PSA levels were not selectively affected (185). In a recent Phase II study evaluating 46 patients with androgen-independent prostate cancer, lycopene did not appear effective for androgen-independent prostate cancer (121). In a multicenter study designed to examine methods of early detection and risk factors for cancer, no association was observed between serum lycopene and total prostate cancer (234).

C. Lycopene and breast cancer

Lycopene delivered in cell culture medium from stock solutions in tetrahydrofuran, strongly inhibited proliferation of endometrial (Ishikawa), mammary (MCF-7), and lung (NCI-H226) human cancer cells. In addition to its inhibitory effect on basal endometrial cancer cell proliferation, lycopene also suppressed IGF-I-stimulated growth (172). Growth stimulation of MCF-7 mammary cancer cells by IGF-I was markedly reduced by physiological concentrations of lycopene. The inhibitory effect of lycopene on IGF signaling was associated with suppression of IGF-stimulated cell cycle progression of serum-starved, synchronized cells (132). It has been shown that there is an increase of BRCA1 and BRCA2 mRNA in the estrogen receptor (ER)-positive cell lines (MCF-7 and HBL-100) and a decrease or no change in the ER-negative cell lines (MDA-MB-231 and MCF-10A). Flow cytometry analysis showed a G1/S phase cell cycle arrest after treatment of the cells with 10 μM lycopene (52). In transiently transfected cancer cells, lycopene transactivated the expression of reporter genes fused with ARE sequences (35). Human breast (MCF-7) and endometrial (ECC-1) cancer cells were treated with lycopene and all-trans retinoic acid (atRA) inhibited IGF-I-stimulated cell cycle progression from G1 to S phase and decreased retinoblastoma protein (pRb) phosphorylation. These events were associated with a reduction in cyclin D1 and p21/WAF1 level. It was further shown that attenuation of cyclin Dl levels by lycopene and atRA is an important mechanism for the reduction of the mitogenic action of IGF-I (220). Recently, a subset of 391 genes was found to be differentially modulated by lycopene between estrogen-positive cells (MCF-7) and estrogen-negative cells (MDA-MB-231, MCF-10A). Hierarchical clustering revealed 726 discriminatory genes between breast cancer cell lines (MCF-7, MDA-MB-231) and the fibrocystic breast cell line (MCF-10A). Modified gene expression was observed in various molecular pathways, such as apoptosis, cell communication, MAPK, and cell cycle, as well as xenobiotic metabolism, fatty acid biosynthesis, and gap junctional intercellular communication (53). However, neither pure lycopene nor lycopene in the form of a mixed carotenoid oleoresin exerted an inhibitory effect on mammary tumor incidence, latency, multiplicity, volume, or total tumors induced by *N*-methylnitrosourea (NMU) in rats (68).

In a case-control study in Uruguay, including 400 cases and 405 controls, total vegetable, total fruit, dietary fiber, vitamin C, vitamin E, lycopene, folate, and total phytosterol intakes were inversely associated with breast cancer risk (243). In a large cohort study of Canadian women examining the relations between dietary intakes of beta-carotene, alpha-carotene, beta-cryptoxanthin, lycopene, and lutein + zeaxanthin, and breast cancer risk, there was no clear association between intakes of any of the studied carotenoids and breast cancer risk in the study population (280). To investigate the association between serum and plasma concentrations of micronutrients with subsequent development of breast cancer, a nested case control study was conducted among female residents of Washington County, Maryland, who had donated blood for a serum bank in 1974 or 1989. Median concentrations of beta-carotene, lycopene, and total carotene were significantly lower in cases compared with controls in the 1974 cohort and the risk of developing breast cancer in the highest fifth was approximately half of that of women in the lowest fifth for beta-carotene lycopene and total carotene in the 1974 cohort (250).

D. Lycopene and lung cancer

Lycopene strongly inhibited proliferation of lung human cancer cells and also suppressed IGF-I stimulated growth (172). Lycopene treatment has been reported to significantly decrease the incidences and multiplicities of lung adenomas and carcinomas induced by combined treatment with DEN, MNU, and 1,2-dimethylhydrazine (DMH) in B6C3F1 mice (147). However, enhancement of B(a)P-induced-mutagenesis was observed in colon and lung on treatment of LacZ mice with lycopene-rich tomato oleoresin (101). It has been shown that ferrets supplemented with lycopene and exposed to cigarette smoke had significantly higher plasma IGFBP-3 levels and a lower IGF-I/IGFBP-3 ratio than ferrets exposed to smoke alone, and lycopene supplementation substantially inhibited smoke-induced squamous metaplasia and PCNA expression in the lungs of ferrets (189).

In a study to examine the relation between lung cancer risk and intakes of alpha-carotene, beta-carotene, lutein, lycopene, and beta-cryptoxanthin in two large cohorts, alpha-carotene and lycopene intakes were significantly associated with a lower risk of lung cancer (210). The association between lung cancer risk and intakes of specific carotenoids using the primary data from seven cohort studies in North America and Europe was analyzed. Carotenoid intakes were estimated from dietary questionnaires administered at baseline in each study. During follow-up of up to 7–16 years across studies, 3,155 incident lung cancer cases were diagnosed among 399,765 participants. The

relative risks for alpha-carotene, lutein/zeaxanthin, and lycopene were also close to unity (202).

E. Lycopene and liver cancer

Lycopene inhibited liver cancer cells metastasis by upregulating the expression of nm23-H1, a metastasis suppressor gene, in SK-Hep-1 cells, a highly invasive hepatoma cell line (112). The antimetastatic properties of lycopene in inhibiting the adhesion, invasion, and migration of SK-Hep1 human hepatoma cells were reported recently (117). Feeding of rats with lycopene significantly decreased the size of gamma-glutamyl transpeptidase- and glutathione S-transferase-positive foci induced by DEN (by 64% and 65%, respectively), as well as the fraction of liver volume occupied by foci (by 84% and 79%, respectively), but did not significantly reduce their number (20). In Wistar rats, lutein and lycopene treatment caused lower number of hepatic placental glutathione S-transferase-positive preneoplastic lesions in the liver and lower hepatic DNA strand breakage (283).

VIII. POMEGRANATE

The pomegranate (*Punica granatum* L.) fruit has been used for centuries in ancient cultures for its medicinal purposes. Pomegranate fruits are widely consumed in fresh and beverage forms as juice. Employing a novel technique of Matrix Assisted Laser Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS), pomegranate juice was found to contain six anthocyanins (pelargonidin 3-glucoside, cyanidin 3-glucoside, delphinidin 3-glucoside, pelargonidin 3,5-diglucoside, cyanidin 3,5-diglucoside, and delphinidin 3,5-diglucoside), ellagitannins, and hydrolysable tannins. The chemical structures of anthocyanins present in pomegranate are given in Fig. 12. The other flavonoids present include quercetin, kaempferol, and luteolin glycosides (91). Recently, there have also been numerous reports on the *in vitro* and *in vivo* anticancer properties of pomegranates (252). Pomegranate juice (PJ) shows potent antioxidant properties attributed to its high content of polyphenols, including ellagic acid (EA), in its free and bound forms, gallotannins, anthocyanins, and other flavonoids. The most abundant of these polyphenols is punicalagin, which is implicated as the bioactive constituent responsible for >50% of the juice's potent antioxidant activity (252).

Pomegranate juice concentrate was given to 18 healthy volunteers and blood samples were obtained for 6 h afterwards. Twenty-four hour urine collections were obtained on the day before (−1), the day of (0), and the day after (+1) the study. Ellagic acid (EA) was detected in plasma of all subjects with a maximum concentration of 0.06 ± 0.01 micromol/L, area under concentration time curve of 0.17 ± 0.02 (micromol × h) × L(-1), time of maximum concentration of 0.98 ± 0.06 h, and elimination half-life of 0.71 ± 0.08 h. EA metabolites, including dimethylellagic acid glucuronide (DMEAG) and hydroxy-6H-benzopyran-6-one derivatives (urolithins), were also detected in plasma and urine in conjugated and free forms (253).

A. Pomegranate and skin cancer

We have shown that the treatment of normal human epidermal keratinocytes (NHEK) with pomegranate fruit extract (PFE) before UV-B exposure dose dependently inhibited UV-B-mediated phosphorylation of ERKl/2, JNK1/2, and p38 proteins in a time-dependent manner. We also found that PFE treatment to NHEK resulted in a dose- and time-dependent

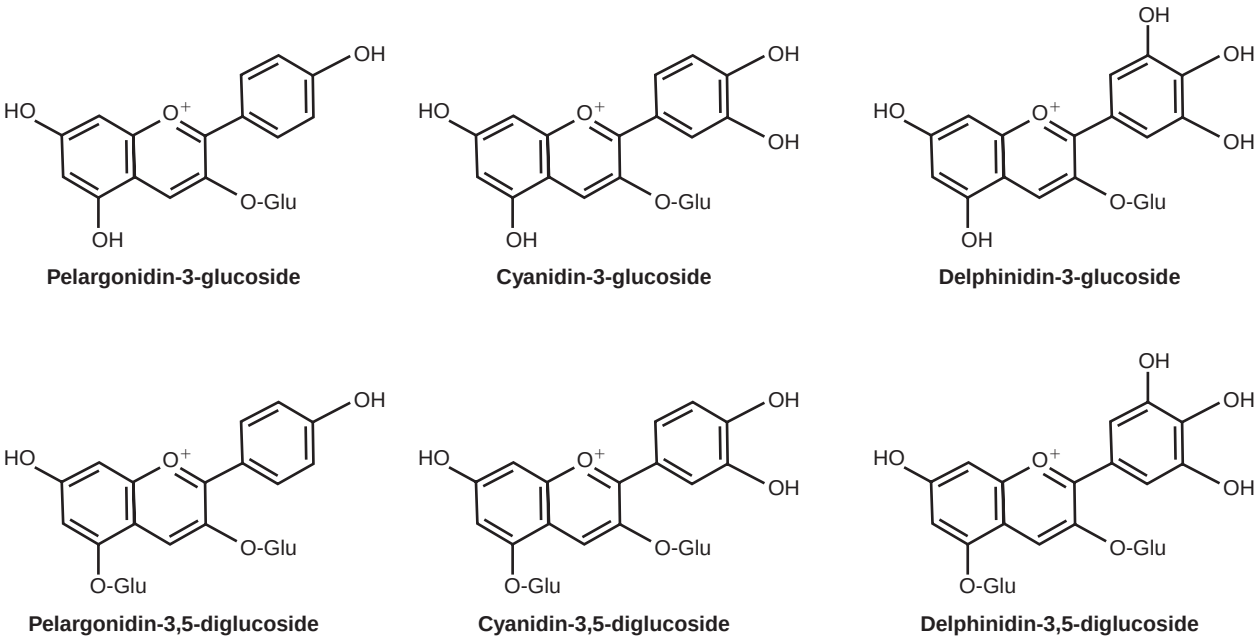

FIG. 12. Chemical structures of anthocyanins present in pomegranate.

inhibition of UV-B-mediated NF-κB pathway (6). Pomegranate seed oil has also been shown to significantly decrease skin tumor incidence, multiplicity, and TPA-induced ODC activity in CD-1 mice (110). In our earlier study, we have reported that topical application of PFE prior to TPA application on mouse skin afforded significant inhibition against TPA-mediated increase in skin edema and hyperplasia, epidermal ODC activity, and protein expression of ODC and cyclooxygenase-2 in a time-dependent manner. We also found that topical application of PFE resulted in inhibition of TPA-induced phosphorylation of MAPK and NF-κB pathways. Topical application of PFE resulted in inhibition of TPA-induced skin tumor promotion in DMBA-initiated CD-1 mouse. The animals pretreated with PFE showed substantially reduced tumor incidence and lower tumor body burden when assessed as total number of tumors per group, percent of mice with tumors, and number of tumors per animal as compared to animals that did not receive PFE. Skin application of PFE prior to TPA application also resulted in a significant delay in latency period from 9 to 14 weeks and afforded protection when tumor data were considered in terms of tumor incidence and tumor multiplicity (7). Recently, we have reported that delphinidin, a major anthocyanidin in pomegranate, protected against UVB-mediated decrease in cell viability and induction of apoptosis by increase in lipid peroxidation, formation of 8-OHdG, decrease in PCNA, increase in PARP, and activation of caspases. Topical application of delphinidin to SKH-1 hairless mouse skin inhibited UVB-mediated apoptosis and markers of DNA damage like cyclobutane pyrimidine dimers and 8-OHdG (8).

B. Pomegranate and prostate cancer

Ellagic acid, caffeic acid, luteolin, and punicic acid, all important components of the aqueous compartments or oily compartment of pomegranate fruit were reported to inhibit *in vitro* invasion of human PC-3 prostate cancer cells in an assay employing matrigel artificial membranes (166). Cyanidin reduced the level of prostaglandin E2 (PGE2) in LNCaP cells and also attenuated the effect of arachidonic acid on increasing the amount of PGE2. Cyanidin reduced the levels of COX-2 protein in a dose- and time-dependent fashion and also lowered the PPAR-γ mRNA levels (217). We have shown that PFE treatment of human prostate cancer PC-3 cells resulted in a dose-dependent inhibition of cell growth/cell viability and induction of apoptosis. PFE treatment of PC-3 cells resulted in induction of proapoptotic and downregulation of antiapoptotic proteins and induction of cell cycle regulatory molecules. Oral administration of PFE to athymic nude mice implanted with androgen-sensitive CWR22Ru1 cells resulted in a significant inhibition in tumor growth concomitant with a significant decrease in serum PSA levels (201). Recently, a phase II study determined the effects of pomegranate juice consumption on PSA progression in men with a rising PSA following primary therapy. Patients were treated with 8 ounces of PJ daily until disease progression. Mean PSA doubling time significantly increased with treatment from a mean of 15 months at baseline to 54 months post treatment. *In vitro* assays comparing pretreatment and post-treatment patient serum on the growth of LNCaP showed a 12% decrease in cell proliferation, 17% increase in apoptosis, 23% increase in serum nitric oxide, and significant reductions in oxidative state and sensitivity to oxidation of serum lipids after versus before pomegranate juice consumption (230).

C. Pomegranate and breast cancer

Recently, it has been reported that pomegranate extract and genistein inhibited the growth of MCF-7 breast cancer cells through induction of apoptosis, with combination treatment being more efficacious than single treatments (122). Recently, fractions of the pomegranate (*i.e.*, crude seed oil, crude fermented and unfermented juice, and peel extract) were shown to exert antiproliferative effects on human breast cancer cells *in vitro*. In a murine mammary gland organ culture, fermented juice polyphenols effected 47% inhibition of cancerous lesion formation induced by the carcinogen DMBA (152). It has also been shown that cyanidin, delphinidin, and petunidin inhibited the growth of MCF-7 breast cancer cells (326).

D. Pomegranate and lung cancer

We have shown that treatment of PFE was found to result in a decrease in the viability of human lung carcinoma A549 cells. PFE treatment of A549 cells also resulted in dose-dependent arrest of cells in G0–G1 phase of the cell cycle, induction of cell cycle regulatory proteins, inhibition of MAPK and NF-κB pathways, and inhibition of NF-κB DNA-binding activity. Oral administration of PFE to athymic nude mice implanted with A549 cells resulted in a significant inhibition in tumor growth (143). Recently, we have shown the chemopreventive effect of PFE on lung tumorigenesis induced by benzo(a)pyrene [B(a)P] and *N*-nitroso-tris-chloroethylurea (NTCU) in A/J mice. Mice exposed to B(a)P and NTCU and treated with PFE had statistically significant lower lung tumor multiplicities than mice treated with carcinogens only. PFE treatment also caused inhibition of activation of MAPK and NF-κB pathways, activation of mTOR signaling, phosphorylation of c-met and markers of cell proliferation, and angiogenesis in lungs of B(a)P and NTCU-treated mice (140).

E. Pomegranate and liver cancer

Delphinidin induced apoptotic cell death characterized by internucleosomal DNA fragmentation, induction of caspase-3 activity, c-Jun and JNK phosphorylation expression at mRNA and protein levels, upregulation of Bax, and downregulation of Bcl-2 protein in human hepatoma HepG2 cells (320). Pomegaranate juice (PJ) has been shown to inhibit azoxymethane (AOM)-induced aberrant crypt foci in Fisher 344 male rats. Total glutathione-S-transferase (GST) activity in the liver of the rats fed PJ was significantly higher in the rats than compared with the control groups (40). Pretreatment with pomegranate flower extract dose dependently protected against ferric nitrilotriacetate (Fe-NTA) induced oxidative stress as well as hepatic injury. The extract afforded protection against hepatic lipid peroxidation and preserved glutathione (GSH) levels and activities of antioxidant enzymes as well as inhibition in the modulation of liver toxicity markers in serum (138).

IX. LUPEOL

Lup-20(29)-en-3h-ol (Lupeol), a triterpene found in fruits such as such as olive, mango, strawberry, grapes, and figs, in many vegetables, and in several medicinal plants, is used in the treatment of various diseases. It possesses strong anti-inflammatory, antiarthritic, antimutagenic, and antimalarial activity *in vitro* and *in vivo* systems (90). Lupeol has been shown to act as a potent inhibitor of protein kinases and serine proteases (107) and to inhibit the activity of DNA topoisomerase II, a target for anticancer chemotherapy (292). It has also been reported to improve the epidermal tissue reconstitution and induces differentiation and inhibits the cell growth of melanoma cells (104).

A. Lupeol and skin cancer

We have shown that topical application of lupeol prior to TPA application onto the skin of CD-1 mice afforded significant inhibition against TPA-mediated increase in skin edema and hyperplasia, epidermal ODC activity, and inhibition of TPA-induced NF-κB pathways. Lupeol also possesses antitumor-promoting effects in a mouse skin tumorigenesis model. The animals pretreated with lupeol showed significantly reduced tumor incidence, lower tumor body burden, and a significant delay in the latency period for tumor appearance (246).

B. Lupeol and prostate cancer

Lupeol treatment resulted in significant inhibition of cell viability in a dose-dependent manner and caused apoptotic death of prostate cancer cells. Lupeol was found to induce the cleavage of PARP protein and degradation of acinus protein with a significant increase in the expression of FADD protein and Fas receptor. The small interfering RNA-mediated silencing of the Fas gene and inhibition of caspase-6, -8, and -9 by their specific inhibitors confirmed that lupeol specifically activates the Fas receptor-mediated apoptotic pathway in androgen-sensitive prostate cancer cells. The treatment of cells with a combination of anti-Fas monoclonal antibody and lupeol resulted in higher cell death compared with the additive effect of the two compounds alone, suggesting a synergistic effect. Lupeol treatment also resulted in a significant inhibition in growth of tumors with concomitant reduction in PSA secretion in athymic nude mice implanted with CWR22Ru1 cells (247).

C. Lupeol and breast cancer

Lambertini *et al*. (163) evaluated the potential of the selected plant extracts to affect proliferation and differentiation of ERα-negative MDA-MB-231 breast cancer cells, which become ERα-positive after treatment with a decoy molecule against a regulatory region of the human ERα gene. By gas-chromatography/mass-spectrometry analysis, they identified lupeol as the major bioactive component of *Aegle marmelos* plant extract. Lupeol was found to stimulate the decoy effect of RA4 DNA sequence, increasing at a high level ERα gene expression in MDA-MB-231 ERα -negative breast cancer cells and inhibited proliferation of breast cancer cells (163).

X. CONCLUSIONS AND FUTURE DIRECTIONS

Various laboratory studies both in cell culture systems and in animal models convincingly argue for a definitive role of selected dietary natural occurring products for prevention and treatment of cancer. It is noteworthy that many of these agents are antioxidants in nature. Many of these agents inhibit or induce many pathways in complex cancer surviving pathways by modulating one or more signal transduction pathways. The challenge is how best to use this information for cancer prevention in populations with differing cancer risk. A major advancement of cancer prevention research is to integrate new molecular findings into clinical practice. Identification of molecular targets or biomarkers, whose changes are associated with inhibition of malignantly transformed cell properties, is vital to cancer prevention and will greatly assist in a better understanding of anticancer mechanisms by chemopreventive/chemotherapeutic compounds. At the molecular level, it has become clear that cancer results from alterations and aberrations in several hundred genes, indicating that a tumor cell uses multiple pathways to survive and thrive. Phytochemical extracts from fruits and vegetables have potent antioxidant and antiproliferative activities, and the major part of total antioxidant activity is from the combination of phytochemicals. The additive and synergistic effects of phytochemicals in fruits and vegetables are beginning to be studied, which may lead to designing potent antioxidant phytococktails with superior cancer preventive effects for humans. Thus, in addition to building an armamentarium of cancer preventive agents, scientists could utilize a phytococktail approach, in which various natural and synthetic products can be used in a mixture in concentrations that could easily be consumed by humans. Such agents in cocktails are expected to act on different molecular pathways that will have greater likelihood for producing cancer chemopreventive effects in humans. They may even have synergistic preventive and/or anticancer effects. This approach can be explored in laboratory, animal, clinical, and epidemiological studies in the future.

It is extremely important to consider seriously the issue of bioavailability and metabolism of the dietary phytochemicals, since the biological properties of agents depend on their presence at the time of the damage. It is crucial to study this issue before discussing their chemopreventive efficacy. Since the biological properties of polyphenols depend on their bioavailability, it is important to discuss this issue. In fact, the different chemical structures of polyphenols determine their selective gut absorption. Urine and plasma levels represent good markers to establish bioavailability of polyphenols and their metabolites. Generally, $<10\%$ of ingested polyphenols, or their metabolites, are found in urine and plasma, where concentrations barely reach 1 μM. Polyphenols are usually present in the gut as glycosyl-derivatives, and removal of the sugar moiety by glycosidases is required to pass the small intestine barrier. After hydrolysis to the free aglycone, polyphenols undergo modifications similar to common drugs: they are conjugated by methylation, sulfation, glucuronidation, or a combination of them. This is a crucial point in terms of chemopreventive activity. In fact, conjugates can significantly change biological properties of the original compounds. The general low bioavail-

ability of single compounds, together with the complex transformation reactions they undergo, makes difficult a cause–effect analysis. Another issue of concern is whether purified phytochemicals have the same protective effects, as do the whole food or mixture of foods in which these compounds are present. The current knowledge base teaches us that they are generally more effective when consumed as whole foods.

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ABBREVIATIONS

AFB1, aflatoxin B1; AOM, azoxymethane; AP-1, activator protein-1; ARE, antioxidant response element; ARG, androgen-responsive gene; ATM, ataxia-telangiectasia mutated protein; atRA, all-trans retinoic acid; B(a)P, benzo(a)pyrene; CB, cytochalasin B; CDDP, cis-diamine-dichloroplatinum; COX-2, cyclooxygenase-2; Cx32, connexin32; CYP, cytochrome P450; DCF-DA, 2′,7′-dichlorofluorescein diacetate; DEN, diethylnitrosamine; DENA, *N*-nitrosodiethylamine; DMBA, dimethylbenz(a)anthracene; DMH, 1,2-dimethylhydrazine; DPPH, 1,1-diphenyl-2-picrylhydrazyl; E2, 17β-estradiol; EC, (−)-epicatechin; ECG, (−)-epicatechin-3-gallate; ECM, extracellular matrix; EGC, (−)-epigallocatechin; EGCG, (−)-epigallocatechin-3-gallate; ER alpha KO; estrogen receptor-alpha knockout; ERE, estrogen responsive element; ERK, extracellular signal-regulated kinase; EROD, ethoxyresorufin-*O*-deethylase; ERα WT, estrogen receptor alpha wild type; FAK, focal adhesion kinase; GOT, glutamic-oxaloacetic transaminase; GSE, grape seed extract; GST, glutathione-S-transferase; GTP, green tea polyphenols; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HGPIN, high-grade prostatic intraepithelial neoplasia; HMdU, 5-hydroxymethyl-2′-deoxyuridine; Hsps, heat-shock proteins; hTERT, human telomerase reverse transcriptase; HUVECs, human umbilical vein endothelial cells; IGF-1, insulin-like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; LLC, Lewis lung carcinoma; MALDI-TOF MS, Matrix Assisted Laser Ionization Time of Flight Mass Spectrometry; MAPK, mitogen-activated protein kinase; MAPKAPK2, MAP kinase-activated protein kinase 2; MDM2, murine double minute 2 protein; MED, minimal erythema dose; MG, methylglyoxal; MMPs, matrix metalloproteinases; MNNG, *N*-ethyl-9-nitro-N-nitrosoguanidine; MT-1MMP, membrane type-1 matrix metalloproteinases; NCD, neocapillary density; NDEA, *N*-nitrosodiethylamine; NF-κB, nuclear factor-kappa B; NHEK, normal human epidermal keratinocytes; Nm23, nonmetastatic gene 23; NMU, *N*-methylnitrosourea; NTCU, *N*-nitroso-tris-chloroethylurea; ODC, ornithine decarboxylase; OPG, osteoprotegerin; OPN, osteopontin; PB, phenobarbital; PCNA, proliferating cell nuclear antigen; PD, pyrimidine dimers; PEITC, phenyl isothiocyanate; PFE, pomegranate fruit extract; PGE2, prostaglandin E2; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; PIN, prostate intraepithelial neoplasia; PJ, pomegranate juice; pRB, retinoblastoma protein; PSA, prostate specific antigen; PTEN, phosphatase and tensin homolog deleted in chromosome ten; RANK, receptor activator of NF-κB; ROS, reactive oxygen species; SPC, soy phytochemical concentrate; SPI, soy protein isolate; Stat 3, signal transducer and activator of transcription 3; Stat-1, signal transducer and activator of transcription; TIMP-2, tissue inhibitor metalloproteinases; TNF-α, tumor necrosis factor-α; TPA, 12-*O*-tetradecanoyl-phorbol-13-acetate; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TRAMP, transgenic adenocarcinoma of the mouse prostate; uPA, urokinase plasminogen activator; u-PAR, urokinase-type plasminogen activator receptor; UVR, ultraviolet radiation; VEGF, vascular endothelial growth factor.

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