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INHIBITION OF CARCINOGENESIS BY DIETARY POLYPHENOLIC COMPOUNDS

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■ **Abstract** Plants consumed by humans contain thousands of phenolic compounds. The effects of dietary polyphenols are of great current interest due to their antioxidative and possible anticarcinogenic activities. A popular belief is that dietary polyphenols are anticarcinogens because they are antioxidants, but direct evidence for this supposition is lacking. This chapter reviews the inhibition of tumorigenesis by phenolic acids and derivatives, tea and catechins, isoflavones and soy preparations, quercetin and other flavonoids, resveratrol, and lignans as well as the mechanisms involved based on studies in vivo and in vitro. Polyphenols may inhibit carcinogenesis by affecting the molecular events in the initiation, promotion, and progression stages. Isoflavones and lignans may influence tumor formation by affecting estrogen-related activities. The bioavailability of the dietary polyphenols is discussed extensively, because the tissue levels of the effective compounds determine the biological activity. Understanding the bioavailability and blood and tissue levels of polyphenols is also important in extrapolating results from studies in cell lines to animal models and humans. Epidemiological studies concerning polyphenol consumption and human cancer risk suggest the protective effects of certain food items and polyphenols, but more studies are needed for clear-cut conclusions. Perspectives on the application of dietary polyphenols for the prevention of human cancer and possible concerns on the consumption of excessive amounts of polyphenols are discussed.

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INTRODUCTION

Phenolic compounds comprise one of the largest and most ubiquitous group of plant metabolites. They are formed to protect the plant from photosynthetic stress, reactive oxygen species, wounds, and herbivores. Phenolic compounds are an important part of the human diet. The most commonly occurring ones in foods are flavonoids and phenolic acids. Early interest in polyphenols was related to their "antinutritional" effects, i.e. decreasing absorption and digestibility of food because of their ability to bind proteins and minerals. The astringency of many fruits and beverages is due to the precipitation of salivary proteins with plant polyphenols. Current interest stems from the observations that dietary polyphenolic compounds have antioxidative, antiinflammatory, and anticarcinogenic activities. This chapter discusses these activities in light of their biochemical properties and bioavailabilities, with the goal of understanding the potential of dietary polyphenolic compounds in cancer prevention.

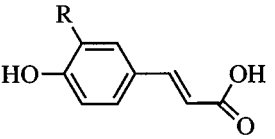
DIETARY SOURCES AND CHEMICAL PROPERTIES

All plant phenolic compounds arise from the common intermediate, phenylalanine, or its close precursor, shikimic acid. They can be divided into at least ten different classes based on their general chemical structures (88). The plant phenolic compounds in the human diet are numerous; we have chosen selected groups of polyphenols for discussion, with emphasis on possible applications for the prevention of cancer. Some representative structures are shown in Figure 1. Many of these compounds are usually glycosylated by sugars such as glucose, rhamnose, galactose, and arabinose.

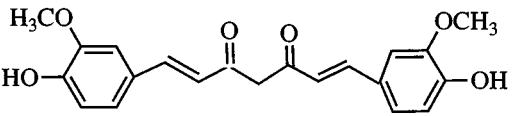
Phenolic Acids and Derivatives

Hydroxybenzoic acids and hydroxycinnamic acids are abundant in food and may account for about one third of the phenolic compounds in our diet. These

Phenolic acids and derivatives



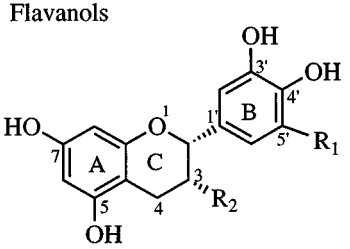
R = OH Caffeic acid
R = OCH_3 Ferulic acid



Curcumin

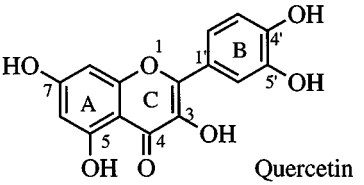
Flavonoids

Flavanols



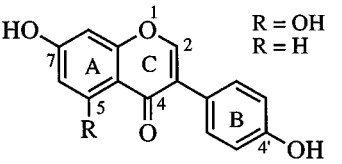
	R1	R2
EGCG	OH	gallate
ECG	H	gallate
EGC	OH	OH
EC	H	OH

Flavonols



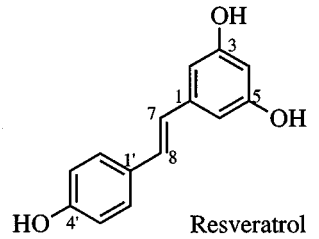
Quercetin

Isoflavones



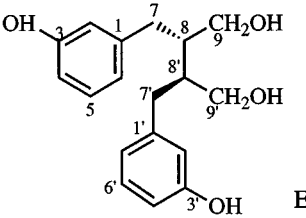
R = OH Genistein
R = H Daidzein

Stilbenes



Resveratrol

Lignans



Enterodiol

Figure 1 Representative structures of selected classes of dietary polyphenols. EGCG, (−)-epigallocatechin-3-gallate; ECG, (−)-epicatechin-3-gallate; EGC, (−)-epigallocatechin; EC, (−)-epicatechin.

compounds are found as esters, which are either soluble and accumulate in vacuoles or insoluble as cell-wall components. The most frequently encountered hydroxycinnamic acids are caffeic acid and ferulic acid. Caffeic acid is found in many fruits such as apple, plum, tomato, and grape. Ferulic acid is linked through ester bonds to hemicellulose of the cell wall, and is found in food sources such as wheat bran (5 mg/g). Derivatives of hydroxycinnamic acid are found in almost every plant. Those of interest include chlorogenic acid (a caffeoyl ester) and curcumin. Chlorogenic acid, which is present in many fruits and vegetables and in coffee (about 7% of the dried beans), is the key substrate for enzymatic oxidation that leads to browning, particularly in apples and pears. Curcumin, which contains two ferulic acid molecules linked by a methylene, with a β-diketone structure in a highly conjugated system, is the major yellow pigment in turmeric and mustard. It is used widely as a food preservative and yellow coloring agent for foods, drugs, and cosmetics.

Flavonoids

Flavonoids are the largest class of phenolic compounds; over 5000 compounds have been described. They are mainly classified into flavones, flavanols (catechins), isoflavones, flavonols, flavanones, and anthocyanins. All are structurally related to the parent compound, flavone (2-phenylbenzopyrone).

Flavanols The main flavanols are catechins, which are abundant in tea, red wine, and chocolate. Grape and chocolate catechins are mainly (+)-catechin and (−)-epicatechin (EC), whereas tea catechins also have galloyl esters of catechins as major components. Proanthocyanidins are polymeric flavanols (4 to 11 units) that are present in plant materials such as grape seeds (reviewed in 80a). Red wine contains more flavonoids than grape juice because the winemaking process extracts some of the flavonoids from the seeds and skins of grapes.

Flavonols Quercetin is the main flavonol in the human diet, present in many fruits, vegetables, and beverages. It is particularly abundant in onions (0.3 mg/g fresh weight) and tea (10–25 mg/L). Quercetin usually occurs as *O*-glycosides, with D-glucose as the most frequent sugar residue. More than 170 different quercetin glycosides have been identified.

Isoflavones Soybeans are the only significant dietary source of isoflavones. The primary isoflavones in soy are genistein and daidzein (approximately 1 mg/g dry bean), which are generally considered as phytoestrogens.

Stilbenes

Stilbenes contain two phenyl compounds connected by a 2-carbon methylene bridge. They occur in nature in a rather restricted distribution. Most stilbenes in plants act as antifungal phytoalexins, compounds that are usually synthesized only in response to infection or injury. The most extensively studied stilbene is

trans-resveratrol (3,5,4′-trihydroxystilbene), which is present in grapes, wine, and peanuts. Red wine contains 1.5 to 3.0 mg resveratrol/L.

Lignans

Lignans are diphenolic compounds that contain a 2,3-dibenzylbutane structure that is formed by the dimerization of two cinnamic acid residues. Most lignans appear to pass through the intestinal tract as fiber. Dietary secoisolariciresinol diglycoside (SDG) and matairesinol, however, can be converted by intestinal microflora to the mammalian lignans, enterodiol and enterolactone, which are absorbed through enterohepatic circulation. Flaxseed meal and flour are the richest source of SDG and matairesinol.

Dietary Intake of Phenolic Compounds

The diversity of the chemical structures and variability in foods make calculating the phenolic content in food difficult. A recent publication has confirmed the previously reported daily phenolic intake of 1 g (81). Other recent calculations of dietary intake were based on only a few specific flavonoids, which, of course, yielded much lower values. One study in Holland on flavonols and flavones estimated the average intake at 23 mg/day (27). A second group in Denmark estimated the intake of flavones, flavonols, and flavanones to be 28 mg/day (54). Another calculation indicated that vegetables (including dry legumes) might provide up to 218 mg of total phenols/day in an average US diet (102). This is likely to be an overestimation based on the use of the Folin assay, which cannot distinguish between phenolics and ascorbic acid. Fruits are usually richer in polyphenols than vegetables, with total phenolic content as high as 1–2 g/100 g fresh weight in certain fruits. Another major source of polyphenols is beverages such as red wine, coffee, tea, and fruit juices. Their consumption varies significantly among individuals. For example, tea drinkers may consume 200 to 800 mg catechins (in 1 to 4 cups of green tea) per day.

Antioxidative Properties

Plant polyphenols are well recognized for their antioxidative activities. They scavenge free radicals, thus breaking the free radical chain reaction of lipid peroxidation. The main structural features for these activities are exemplified by the ortho-dihydroxy structure in the B-ring, 2,3 double bond in conjunction with a 4-keto function, and hydroxyl groups at positions 3 and 5 in flavonols, the di- and trihydroxyphenol structures in catechins, and the side chain double bonds in conjugation with the ortho-dihydroxyphenol structure in caffeic acid. Polyphenols also quench reactive oxygen and nitrogen species generated in biological systems. Another antioxidative mechanism is the chelation of metals such as iron and copper ions, which prevent their participation in Fenton-type reactions and the generation of highly reactive hydroxyl radicals. This ability to react with metal ions, however,

also enables polyphenols to act as pro-oxidants. Using three different oxidation systems, flavonoids were shown to be potent antioxidants against peroxyl and hydroxyl radicals, but to be pro-oxidants with Cu^{2+} (10). The reduction of Cu^{2+} to Cu^{+} by flavonoids may produce the initiation radical. Caffeic acid also showed pro-oxidant activity on Cu^{2+}-induced low-density lipoprotein oxidation during the propagation phase (107). These pro-oxidant actions of polyphenolic compounds may be important in vivo in certain situations, for example, when tissue injury causes the release of free iron or copper.

Many investigators believe that dietary polyphenols have beneficial health effects because they are strong antioxidants. The scientific basis for this thesis is weak. Many of the claimed beneficial effects have not been convincingly demonstrated. Even when the effects are demonstrated in certain animal models, the results may not be due to antioxidative activities. The bioavailability of many dietary polyphenols is rather low and their tissue concentrations may not be high enough to display the effects observed in vitro.

ABSORPTION, BIOAVAILABILITY, AND BIOTRANSFORMATION

The bioavailability of polyphenols is an important determinant in understanding their biological activities. Lack of understanding on this issue has led to excessive claims regarding the in vivo biological activity of polyphenols based on extrapolation from studies in vitro. The bioavailability varies greatly between different polyphenols. Factors influencing bioavailability include the chemical properties of the polyphenols, deconjugation/reconjugation in the intestines, intestinal absorption, and enzymes available for metabolism.

Absorption

The intestinal absorption is the first step to be considered. A commonly accepted concept is that the polyphenols are absorbed by passive diffusion. For this to occur, the glycosylated polyphenols need to be converted to the aglycone by glycosidases in the food or gastrointestinal mucosa, or from the colon microflora. For example, polyphenol glucosides are hydrolyzed by human β-glucosidase in the intestine, whereas polyphenol rhamnosides need to be hydrolyzed by microflora α-rhamnosidases in the colon. There is also evidence for the direct absorption of quercetin-4′-*O*-glucoside and cyanidin-3-glucoside, which have been detected in human plasma after ingestion of food containing these compounds (3, 66). Recent studies suggest that a glucose transport system may be involved in the absorption of quercetin-3-*O*-glucoside, which was more bioavailable than quercetin was in rats (67). Quercetin 3-*O*-rutinoside (rutin) was much less bioavailable than quercetin aglycone was in this study. The bioavailability of quercetin glucoside was also much higher than was quercetin rutinoside in humans, suggesting that the glucoside is actively absorbed in the small intestine (28). Cinnamic acid is absorbed by a Na^{+}-dependent, carrier-mediated transport process in the rat jejunum (104).

Carrier-mediated transport process may be a common process in the absorption of polyphenols. The effects of certain efflux pumps, such as P-glycoprotein and multidrug-resistant associated proteins, on the bioavailability of dietary polyphenols require more investigation.

Biotransformation

The polyphenols are readily conjugated by glucuronidation, sulfation, and methylation in the small intestine, liver, and other organs. This concept is illustrated in Figure 2, using (−)-epigallocatechin (EGC) as an example. Glucuronidation is catalyzed by microsomal UDP-glucuronosyltransferases (UGT) utilizing UDP-glucuronic acid as the cofactor. Among the isoforms of UGT, the UGT1A family is the main source of enzymes for the glucuronidation of polyphenols (81), but the UGT enzymes responsible for the conjugation of different polyphenols still need to be characterized. Sulfation is catalyzed by cytosolic sulfotransferases (SULT) with 3′-phosphoadenosine 5′-phosphosulfate (PAPS) as the sulfate donor. Although phenol SULT (SULT1A) catalyzes the sulfation of phenols, the roles of different SULT isoforms in the conjugation of different types of polyphenols require further investigation. Catechol-*O*-methyltransferase (COMT) catalyzes the transfer of a methyl group to polyphenols from S-adenosylmethionine (SAM). The polyphenol molecule provides multiple potential sites for these reactions. For example, the molecule can be methylated followed by glucuronidation or sulfation at other sites. The sequence and extent of these reactions depends on several factors: (*a*) substrate specificity of the enzyme that determines the reactivity and the position of the conjugation; (*b*) the availability of the conjugating enzymes and

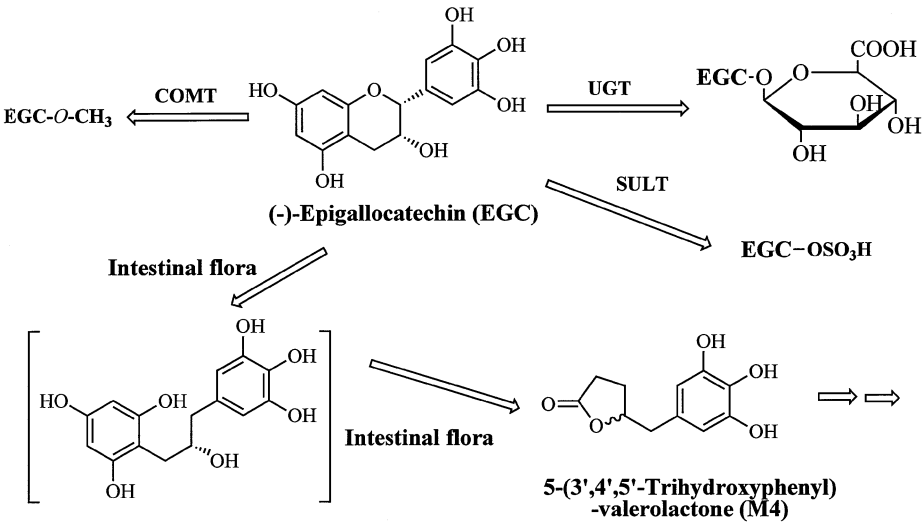


Figure 2 Biotransformation of polyphenols using (−)-epigallocatechin as an example.

their respective cofactors that are affected by species differences, genetic polymorphism, enzyme induction, diet, and metabolic state; (*c*) the doses of dietary polyphenols and competing substrates such as medication that may saturate the enzyme system or deplete the cofactors, and thus affect the extent of conjugation. The extent of conjugation is dose- and time-dependent and has large individual variabilities. Conjugation of polyphenols affects their biological fate; for example, administration of piperine (an inhibitor of UGT) markedly increases the level of serum curcumin in rats and humans (83).

Phase I metabolism is important for some polyphenols. Compounds containing double bonds are subject to reductive metabolism. For example, curcumin is converted to tetrahydrocurcumin in the intestinal tract. Cytochrome P450 enzymes can oxidize and create additional phenolic groups on the ring or to catalyze the *O*-demethylation of the methylated polyphenols. These reactions may take place only with compounds having a low number of phenolic groups. Extensively hydroxylated polyphenols may be too hydrophilic to be substrates of cytochrome P450 enzymes.

Microbial Degradation and Enterohepatic Circulation

Dietary polyphenols refractory to absorption in the upper gastrointestinal tract enter into the colon. Conjugated polyphenol metabolites excreted in the bile also reach the colon and are deconjugated by microflora hydrolases. The colon microflora can form reductive and ring-fission metabolites, which can be absorbed. For example, dietary lignans are converted to enterodiol and enterolactone in the colon and undergo enterohepatic circulation in which they are absorbed, transported to the liver, and secreted in bile. Ring fission compounds of EGC such as trihydroxyphenyl-γ-valerolactone (Figure 2) (55) have been found in human plasma and urine (mostly in glucuronide and sulfate forms). Further degradation of the valerolactone moiety to propionic acid and carboxylic acid is also expected based on the results from (+)-catechin (30). The variability in the populations of intestinal microflora adds to the individual and species differences in the absorption and biotransformation of dietary polyphenols.

A survey of the published bioavailability studies shows that human plasma concentrations of intact flavonoids do not exceed 1 μM when the polyphenols are given in doses similar to those consumed in our diets (81). Our estimation on plasma levels of tea catechins of moderate tea drinkers agrees with this assessment. The peak value of plasma genistein after ingesting 60 g of baked soybean powder is reported to be 2.4 μM (103).

INHIBITION OF TUMORIGENESIS AND MECHANISMS INVOLVED

Many publications have described the inhibition of tumorigenesis by plant polyphenols. With an interest on dietary prevention of cancer, we rate the evidence the strongest if the polyphenols were given in the diet, rather than by topical application

or injection. Polyphenols that are effective when given during the postinitiation period, i.e. by inhibiting tumor promotion and progression, are believed to be more useful in preventing cancer in humans than are polyphenols, which are effective only when given before and during the carcinogen treatment. Transplanted tumor models may be more relevant to therapy than carcinogenesis. Although the inhibition of carcinogenesis by dietary polyphenols has been studied extensively, the molecular mechanisms of action and their applicability to human cancer prevention are unclear. The relevance of many of the in vitro studies is uncertain, because of the much higher concentrations of polyphenols used in comparison to the tissue levels attainable via dietary intake. For many polyphenols, bioavailability and tissue levels are key factors in determining whether the agent is effective in specific target organs. Recently, many in vitro studies have been published on the modulation of oncogenes, tumor suppressor genes, cell cycle, apoptosis, angiogenesis, and related signal transduction pathways by polyphenols. In this review, we include only mechanistic studies that are relevant to the inhibition of carcinogenesis in vivo.

Phenolic Acids and Their Derivatives

The inhibitory effect of topically applied caffeic acid, ferulic acid, chlorogenic acid, and curcumin on tumor promotion by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) has been demonstrated (37). The test compound (1–20 μmol) was applied together with 5 nmol of TPA twice weekly for 20 weeks to the skin of mice previously initiated with 7,12-dimethylbenz[a]anthracene (DMBA), and dose-dependent reduction of tumor multiplicity (number of tumors per mouse) was observed. Among these compounds curcumin was most active. Additional studies indicated that desmethoxycurcumin and caffeic acid phenethyl ester (a constituent of the propolis of honey bee hives) were also active in this model (reviewed in 15). Caffeic acid, ellagic acid, chlorogenic acid, and ferulic acid (0.02–0.05% in the diet) also inhibit 4-nitroquinoline-1-oxide (4-NQO)-induced tongue carcinogenesis in rats (93). More recent studies indicate that curcumin (0.2% and 0.6% in the diet), administered to azoxymethane (AOM)-treated rats during the promotion/progression stage, inhibited colon tumorigenesis (46). The multiplicity of both the invasive and noninvasive adenocarcinomas was lower, and the apoptosis of colonic tumor cells was higher, in the curcumin-treated group. Curcumin (0.1% in the diet) also inhibited intestinal tumorigenesis in the APC^{min} mice (60). Increased enterocyte apoptosis and proliferation as well as decreased expression of the oncoprotein β-catenin were observed in the curcumin-treated group. A similar inhibitory effect was found with caffeic acid phenethyl ester (0.03% in the diet), but not with quercetin or rutin (2% in the diet).

Curcumin (0.2% in the diet) also inhibited diethylnitrosamine (DEN)-induced hepatocarcinogenesis in mice; both tumor multiplicity and tumor incidence were significantly inhibited (12). Orally administered curcumin (0.5–4% in the diet) inhibited benzo(a)pyrene-induced forestomach, *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine-induced duodenal, and AOM-induced colon tumorigenesis (33). Orally administered curcumin, however, had little or no effect on chemically induced lung

and mammary carcinogenesis in mice (26, 35, 36). In DMBA-induced mammary carcinogenesis in mice and rats, inhibition was demonstrated with dibenzoylmethane (which has a β-diketone structure similar to curcumin) but not with curcumin (35*, 84). Apparently, the bioavailability of the agent to the target tissues is a major determining factor. On the other hand, 1% curcumin in the diet reduced the incidence of γ-ray-initiated and diethylstilbestrol-promoted mammary tumors in rats (40). In the rat serum, low levels of tetrahydrocurcumin (300 nM) and curcumin (16 nM) were observed; these bioavailable compounds may cause the inhibition directly or by modulating estrogen actions.

Antiinflammatory activity, due mainly to the inhibition of arachidonic acid metabolism, is thought to be a key mechanism for the anticarcinogenic action of curcumin and perhaps other polyphenolic compounds. Curcumin inhibits cyclooxygenase (COX)-2 expression in human colon epithelial cells, and the activity is proposed to be due to inhibition of NF-κB via blocking the phosphorylation of IκB by IKKs (76). Curcumin (5–50 μM) also down-regulates epidermal growth factor receptor (EGF-R) and inhibits its activation by ligands in human prostate cancer cell lines (21). The importance of these mechanisms in cancer prevention remains to be demonstrated in vivo.

Tea, Catechins, and Related Compounds

The inhibitory activity of tea against carcinogenesis has been demonstrated in different animal models for organ sites such as skin, lung, esophagus, stomach, liver, small intestine, pancreas, colon, bladder, and mammary gland (reviewed in 16, 45, 111, 113, 115). Both green and black tea preparations (2–4 mg tea solids/ml), when given to mice as the sole source of drinking fluid, inhibited UVB-induced skin tumorigenesis in DMBA-treated mice and in the UVB-induced complete skin tumorigenesis model (15). In the UVB-induced complete skin tumorigenesis model, caffeine was inhibitory, but decaffeinated tea only decreased the tumor volume. Green and black tea (in drinking fluid) and EGCG (given i.p.) also inhibited the growth of established skin papillomas in mice previously treated with DMBA/TPA or UVB/TPA.

Inhibition of lung tumorigenesis by tea preparations has been demonstrated in A/J mice (reviewed in 112). Administration of decaffeinated green or black tea to mice (as the sole source of drinking fluid) for 3 weeks starting 2 weeks before the 4-(methylnitrosamine)-1-(3-pyridyl)-1 butanone (NNK) treatment, or for 15 weeks starting 1 week after the NNK treatment, markedly reduced the number of tumors formed in the mice. In mice that had already developed adenomas at 16 weeks after the NNK injection, the progression of adenomas to adenocarcinomas was significantly inhibited by the administration of black tea from weeks 16 to 52. These experiments indicate that tea has broad inhibitory activity against lung carcinogenesis, and it is effective when administered during the initiation, promotion, or progression stages of carcinogenesis. A similar conclusion for the inhibition of skin carcinogenesis is also supported by strong experimental

evidence. The protective effect of tea against colon carcinogenesis in other models, however, is less conclusive. Inhibitory activity has been demonstrated in some studies but not in others. Many studies did not show a protective effect against chemically induced breast cancer formation, except when a high-fat diet was used (80).

Many authors have considered (−)-epigallocatechin gallate (EGCG) as the active component of green tea because EGCG is the most abundant catechin, and cancer inhibitory activity of EGCG has been demonstrated. The inhibition of EGCG against skin, stomach, colon, and lung carcinogenesis (13, 106, 108) as well as the growth of human prostate and breast tumors in athymic mice (56) have been reported. Other catechins, theaflavins, and caffeine may also contribute to the inhibition of carcinogenesis. Theaflavins (a mixture of theaflavin and theaflavin gallates) inhibit lung and esophageal carcinogenesis (68, 116). Based on studies in the UV light-induced complete mouse skin carcinogenesis model with green tea, decaffeinated green tea, and caffeine, Conney et al postulated that the "lowering of body fat levels," mainly by caffeine, is a key factor in the inhibition of tumorigenesis (16, 38, 57). This concept may also be applicable to other models. In the inhibition of spontaneous lung tumorigenesis in A/J mice by brewed black tea and green tea infusions, mice in the tea-treated groups had significantly lower (10–16%) body weights than the control group, and the fat-pad weights were even more dramatically decreased (53). The inhibitory action of caffeine against lung tumorigenesis has been demonstrated previously in mice (106) and in rats (13).

Quercetin and Other Flavonoids

When 30 μmol of quercetin was applied topically to mouse skin 2 h before or 1 h after each TPA application in a DMBA-initiated two-stage skin carcinogenesis model, the multiplicity of papillomas and incidence of carcinomas were markedly decreased (100). Oral administration of quercetin, however, did not prevent UVB-induced skin carcinogenesis in mice (87). Apparently, the bioavailability of the orally administered quercetin to the target organ is a key issue. When given i.p., quercetin and apigenin inhibited melanoma cell (B16-BL6) growth and metastatic potential in syngenetic mice (9). Feeding rats with quercetin or chalcone and 2-hydroxychalcone (0.05% in the diet), during either the initiation or promotion stage, inhibited 4-NQO-induced carcinoma formation in the tongue. These compounds also decreased cell proliferation and polyamine levels (61). Dietary quercetin inhibited DMBA-induced tumorigenesis in hamster buccal pouch (4). Quercetin and ellagic acid, when given during the initiation stage, also inhibited DEN-induced lung tumorigenesis in mice (48). Inhibition of DMBA-induced mammary tumorigenesis in rats by quercetin was observed in one study (101), but not in another (75).

The effects of quercetin and rutin on intestinal carcinogenesis have been studied by many investigators but the results are not consistent. In the AOM-induced colon carcinogenesis model, inhibitory action by quercetin and rutin has been observed in mice (20), but the lack of such an inhibitory effect (22) and enhancement of colon carcinogenesis (75) have also been observed in rats. In the APC^{min} mouse

model, quercetin and rutin (2% in the diet) also did not inhibit intestinal tumorigenesis (60). In a medium-term multiorgan carcinogenesis model in rats, quercetin (1% in the diet) inhibited tumor promotion in the small intestine (2). Treatment of colon cancer cell lines and primary human colorectal tumors with quercetin (10 μM) reduced the level of Ras protein (79). Apigenin, fisetin, and kaempferol were less active in this experimental system. In another study, quercetin and luteolin (20 μM) inhibited the proliferation and induced apoptosis of skin cancer cell lines A431 and other cell lines (38). Inhibition of EGF mediated EGF-R tyrosine kinase activity, the phosphorylation of EGF-R and other proteins, and the secretion of matrix metalloproteinase-2 (MMP-2) and MMP-9 were also observed. Orange juice, which is rich in flavonoids, or a naringin-supplemented diet inhibited the development of mammary tumors in DMBA-treated female rats on a high-fat diet (85).

The possible enhancement of carcinogenesis by quercetin is a concern. In addition to the enhancement of colon carcinogenesis by quercetin (75) as mentioned above, promotion of nitrosomethylurea (NMU)-induced mammary tumors in rats has been suggested (5).

Isoflavones and Soybean

Soybean is rich in genistein and daidzein, which are commonly regarded as phytoestrogens. They have weak estrogenic activity, but can be estrogen antagonists at higher concentrations. Many studies have demonstrated an inhibitory effect against mammary tumorigenesis by soybean or soybean products (reviewed in 64, 95). Daily injection of genistein (0.8 mg/day) to rats starting at 35 days of age for 6 months reduced MNU-induced mammary tumor multiplicity, but daidzein was less effective (17). Exposure to genistein neonatally or prepubertally reduced the number of terminal end buds, and this may be a major factor for the reduced mammary tumorigenesis observed in animal models (52). A recent study showed that fermented soy milk (which contains larger amounts of genistein and daidzein than unfermented soy milk) and isoflavone mixtures, given to rats starting at 7 weeks of age, inhibited mammary tumorigenesis induced by 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) (72). Although genistein is an inhibitor of protein tyrosine kinase and topoisomerase in vitro, its effect on these enzymes has not been demonstrated in these animal models.

A high-isoflavone diet inhibits MNU-induced prostate-related cancer in Lobund-Wistar rats (77). A soy protein–based diet also inhibited the growth and enhanced apoptosis of transplanted LNCaP prostate adenocarcinomas in nude mice (8). Inhibition of growth and enhanced apotosis of LNCaP cells by genistein were observed in vitro with an IC_{50} of 40 μM (74). This concentration was much higher than the expected levels in the prostate. Genistein injection reduced the growth of tumor implanted in the dorsolateral prostate of rats, and this effect may be due in part to the down-regulation of the expression of EGF and HER2/Neu receptors (18). Dietary genistein (50 mg/kg body weight/day), soy phytochemical concentrate (0.2% of the diet), and soy protein isolates (20% of the diet) reduced the volume of transplanted murine bladder cancer in C57BL/6 mice (118). Reduced angiogenesis

and increased apoptosis by the treatment were also observed. In a separate study with seven human bladder cancer cell lines, genistein (3–20 μg/ml) caused G2-M cell cycle arrest and inhibition of cdc2 kinase activity; daidzein and biochanin-A were less effective (91). Genistein (200 μmol/kg body weight), administered orally on 10 alternative days, inhibited lung tumor nodule formation in mice injected with B16F-10 melanoma cells (63).

The effects of genistein and soybean preparations on colon tumorigenesis are uncertain (reviewed in 95). In carcinogen-treated rats, both inhibition and no effect on ACF formation have been reported. Genistein was reported to increase the noninvasive and total adenocarcinoma multiplicity, but to have no effects on the multiplicity of invasive adenocarcinoma (78). In APC^{min} mice feeding on a high-fat/low-fiber/low-calcium diet, treatment with soy isolates (with high isoflavone content) had no significant effect on the incidence, multiplicity, and size of intestinal tumor (86).

These studies indicate that dietary intake of soy preparations or genistein has the potential to inhibit experimental mammary and prostate carcinogenesis, probably due to its modulation of estrogenic activity. Again the bioavailability is a problem, as the injected genistein is more effective in inhibiting transplanted tumors.

Resveratrol and Other Grape Constituents

Because of its presence in red wine, the biological activity of resveratrol has received considerable attention. When resveratrol (1–25 μmol) was topically applied together with TPA to mice in a two-stage carcinogenesis model, marked inhibition of the tumor incidence and multiplicity was observed. Resveratrol also inhibited the development of preneoplastic lesion in DMBA-treated mouse mammary glands in culture (42). In the AOM-induced colon carcinogenesis model, resveratrol administration (200 μg/kg/day) to rats reduced ACF formation and the expression of *Bax* and $p21^{CIP}$ in the mucosa surrounding the ACF (94). Resveratrol administration (i.p., 1 mg/kg/day) to rats inhibited the growth of innoculated Yoshida AH-130 ascites hepatoma (11). Administration of an extract of the herb *Polygonum cuspidatum* (which contained 8% resveratrol and derivatives) in the diet (1.2%) inhibited AOM-induced colon tumorigenesis and DMBA-induced mammary tumorigenesis in mice (M-T Huang, unpublished). On the other hand, resveratrol (and curcumin) was not effective in inhibiting mouse lung tumorigenesis induced by benzo(a)pyrene plus NNK (26).

The mechanisms of the inhibitory activity against tumorigenesis by resveratrol are not clear. Resveratrol was reported to be an estrogen agonist and antagonist, but only the antagonist action was demonstrated in growing rats (99). Inhibition of the expression and function of the androgen receptor in LNCaP cells by resveratrol was reported, but only at concentrations of 100 μM or higher (65). The suppression of prostate-specific antigen expression by resveratrol in these cells, however, was reported to be androgen receptor-independent (31).

The antiinflammatory activity of resveratrol is likely to be important in inhibiting carcinogenesis. Inhibition of COX activity (43) and suppression of COX-2

expression by resveratrol in different cell lines have been reported (69, 92). Resveratrol (2–5 μM) suppressed the transformation of mouse epidermal JB6P+ cells and induced apoptosis via a p53-dependent pathway (32). It induced apoptosis in THP-1 human monocytic leukemia cells by a Fas-independent signaling pathway (98).

A polyphenolic fraction from grape seeds, which contain catechins, procyanidins, and procyanidin gallates, inhibited TPA-promoted skin tumorigenesis in mice previously treated with DMBA (117). A diet enriched with red wine solids (solids from 750 ml of red wine per kg diet), which contained catechins, gallic acid, and other polyphenols, delayed the onset of tumors in the HTLV-1 transgenic mouse (14).

Lignans and Flaxseed

The effects of lignans and flaxseed on tumorigenesis have been reviewed by Thompson (95). The mammalian enterodiol and enterolactone are produced in the colon from plant precursors such as SDG. Therefore, these compounds may exert a direct effect on colon tumorigenesis. Flaxseed or defatted flaxseed (2.5% or 5% in the diet) or SDG equivalent to that in the 5% flaxseed, when given to AOM-treated rats for 100 days, lowered the number of ACF and the number of aberrant crypts per ACF (44). The results suggest that the inhibitory effect of flaxseed is partially due to SDG.

Administration of flaxseed (5% in the diet) to rats for 4 weeks prior to injection of DMBA, or continuously until sacrifice, decreased the incidence and multiplicity of mammary tumors (82). Enterodiol and enterolactone have estrogenic activities. Similar to the effect of genistein, early life exposure to lignans apparently affected the mammary gland development, which caused the reduction of tumorigenesis. When 5% flaxseed or an equivalent amount of SDG was given in the diet to dams during pregnancy and lactation, the off-springs had a reduction in the number of terminal bud structures in the mammary glands (97). Feeding of flaxseed (2.5% or 5% in the diet) for 7 weeks, beginning 13 weeks after DMBA-treatment, to rats that already developed mammary tumors ($\sim$1-cm diameter), decreased the tumor size by over 50% as well as the number and volume of new tumors formed (96). Similar effects were observed with purified SDG or flaxseeed oil (rich in α-linolenic acid) fed at levels equivalent to those in 5% flaxseed; but flaxseed oil appeared to be only effective in inhibiting the growth of preformed tumors. Feeding flaxseed (2.5%, 5%, or 10% in the diet) to mice, for two weeks before and two weeks after injection of the melanoma cell line B16B26, reduced the number of metastatic lung tumors by 32%, 34%, or 63%, respectively (109).

STUDIES IN HUMANS

Tea and Catechins

A major constraint in extrapolating results from cell lines and animal models to humans is the bioavailability and tissue levels of the effective components. The pharmacokinetics of tea polyphenols have been studied in humans (110). The total

peak plasma concentrations of EGCG, EGC, and EC (free plus conjugated forms) were around 2 to 3 μM or lower. These are much lower than the concentrations used in many studies with cell lines (reviewed in 113). If only the nonconjugated forms of tea polyphenols are considered, the concentrations are even lower. The biological activities of glucuronide, sulfate, and methylated derivatives and ring fission metabolites remain to be determined.

Many ecological, case-control, and cohort studies have investigated the effects of tea consumption on human cancer incidence (reviewed in 6, 7, 45, 50, 114, 115). The reduction of human cancer risk by tea consumption has been demonstrated in some studies but not in others. For example, several studies in Japan and China suggest that green tea consumption is associated with lower incidence of gastric cancer, but such an association was not observed in many other studies. Studies in Saitama, Japan, have shown that women consuming more than 10 cups of tea daily are likely to have a lower risk for cancer (all sites combined), and increased tea consumption was associated with lower risk for breast cancer metastasis and recurrence (39, 70). In a case-control study in Shanghai, frequent consumption of tea (green tea) was shown to be associated with a lower incidence of esophageal cancer, especially among nonsmokers and nonalcohol-drinkers (24). On the other hand, in the Netherlands Cohort Study on Diet and Cancer, consumption of (black) tea was not found to affect the risk for colorectal, stomach, lung, and breast cancers (25). A preliminary report associated with NHANES I follow-up study (10 years) indicated a general inverse association between tea consumption (>1.5 cups/day) and colon cancer in both males and females (90). This potentially very important study needs to be expanded.

The quantity of tea consumed and other lifestyle-related factors such as smoking and diet are likely to be important confounding factors. The different results on tea and cancer may be due to different etiological factors involved in different populations. Tea may be only effective against certain types of cancer caused by specific etiological factors. Additional research on the mechanisms of action of tea constituents and the development of useful exposure biomarkers for human studies, such as urinary and blood levels of tea constituents, are key to our understanding of the relationship between tea consumption and human cancer risk (114).

Dietary Flavonoids

In a 25-year follow-up study on 9959 Finnish men, dietary intake of flavonoids was inversely associated with the incidence of cancer at all sites combined (49). The association was mainly due to lung cancer, with relative risk of 0.54 (highest versus lowest quartiles), and was not attributed to the intake of vitamin E, vitamin C, β-carotene, or total calories. Of the major dietary flavonoid sources, the consumption of apples showed an inverse association with lung cancer incidence. In a population-based case-control study in Hawaii involving 582 lung cancer patients, after adjusting for smoking and intake of saturated fat and β-carotene, an inverse association was observed between lung cancer risk and the consumption of onions, apples, or white grapefruits as well as the calculated total intake of quercetin (62).

Onions and apples are the main food sources of quercetin. Since onions are also rich in organosulfur compounds and apples are rich in phenolic acids and derivatives, the involvement of nonflavonoid compounds cannot be eliminated. It would be useful if biomarkers for the dietary intake of specific flavonoids were used in future studies. An approach in this direction was made by measuring plasma and urine levels of quercetin and kaempferol after ingestion of tea and onion (19). The plasma and urinary levels were low and the variations were large; more work in this area is needed.

The bioavailability, metabolism, and excretion of quercetin have been studied. In a study in ileostomized patients, 52% of quercetin glycosides from onions, 24% of pure quercetin, and 17% of rutin were absorbed without microbial degradation (29). The rate of urinary excretion of total quercetin in these subjects was highest after ingestion of the glycosides. A recent study found that, of the ingested quercetin glucosides, approximately 50% is absorbed probably as glucosides in the small intestines and subsequently metabolized (73). In a clinical trial, quercetin was injected i.v. to human subjects (23). Inhibition of lymphocyte protein tyrosine phosphorylation was observed during the period of 1 to 16 h after quercetin administration. Renal toxicity was observed when the dosage went up to 945 mg/m^2 (at 1-week or 3-week intervals). Quercetin pharmacokinetics were described by a first-order two-compartment model with median $t_{1/2\alpha}$ and $t_{1/2\beta}$ of 6 and 43 min, respectively.

Isoflavone- and Lignan-Rich Foods

Many epidemiological studies have investigated the relationship between cancer risk and the consumption of food items that are rich in isoflavones and lignans (reviewed in 1, 51, 64, 95, 105). The lower breast and prostate cancer rates in Japan and China (as compared to Western countries) have been associated with the higher levels of consumption of foods rich in isoflavones and lignans (or higher urinary excretion of metabolites of these compounds). Because these two groups of populations are also very different in other dietary practices (such as the high meat and high fat content in the Western diet) and other habits, these cross section studies should be interpreted with caution.

Case-control studies are generally more informative, but the results on breast cancer from different studies are inconsistent (reviewed in 105). In studies in Singapore and Japan, high soy intake ($\geq$55 g/day) or frequent consumption of bean curd ($\geq$3 time/week) was associated with reduced breast cancer risks in women, but such an association was not observed in a large study in China. Bean curd consumption was inversely associated with risk for breast cancer in both premenopausal and postmenopausal Asian-American women who were foreign born, but not in Asian-American women born in the United States. In an Australian study, the risk of breast cancer was inversely associated with urinary excretion of equol (an isoflavone metabolite) and enterolactone. In a study in China, women with high levels of urinary isoflavones appeared to be associated with lower risk for breast cancer, and the association was stronger if the urinary excretion of both isoflavones and total phenols was taken into consideration.

In a prospective study with Seventh-Day Adventist men in California, frequent consumption of soy milk was associated with a reduced risk of prostate cancer (41). Bean curd has been associated with lower risk of prostate cancer among Japanese men, of gastric cancer among Japanese men and women, and of lung cancer among Chinese men. A reduced risk for gastric cancer was also associated with consumption of soybean ($\geq$5 kg/year) in China and Japan (reviewed in 51).

One of the proposed mechanisms by which isoflavones affect mammary tumorigenesis is through their effects on estrogens. Consumption of a 36-ounce portion of soymilk (113–207 mg total isoflavones) per day, starting on day 2 of a menstrual cycle until day 2 of the next cycle, by healthy normal cycling women reduced circulating levels of 17β-estradiol and progesterone, but had no effect on luteinizing hormone or follicle-stimulating hormone (58, 59). The mean menstrual cycle length did not change. The mean daily serum levels of genistein and daidzein (free and conjugated forms at 15 h after soymilk ingestion) were 3.14 and 11.37 μM, respectively. The urinary recovery of isoflavones varied from 9% to 37% of the intake among the subjects. Consumption of soymilk also increased the excretion of 2-hydroxyestrone, but not that of 16β-hydroxyestrone. When 60 g of baked soybean powder (containing 112 μmol genistein and 103 μmol daidzein) was given to volunteers, plasma levels of genistein and daidzein peaked after 6 h with values of 2.44 and 1.56 μM, respectively. The half-life in the blood was 8 h for genistein and 6 h for daidzein. Most of the subjects showed 2 or 3 peaks in urinary excretion over 3 days, probably due to enterohepatic recirculation. Total recovery from urine and feces was 54.7% for daidzein and 20.1% for genistein (103).

Daily feeding of soy preparations containing 45 mg isoflavones for 16 days, or 37.4 mg genistein for 6 months, to premenopausal women has been reported to increase proliferation of breast epithelium as well as plasma estradiol levels and the volume of nipple aspirate fluid. These results are suggestive of estrogenic effects and their implications in cancer risk needs to be studied carefully. The consequence of feeding infants with soy milk, thereby exposing them to high levels of phytoestrogens (95), needs to be investigated.

After consumption of flaxseed, more than 2 days are needed for enterodiol and enterolactone to return to baseline concentrations in plasma and urine (71), apparently due to enterohepatic circulation. Feeding 10 g raw flaxseed per day for 3 months to women did not change the menstrual cycle length, but lengthened the luteal phase length. No significant changes in sex hormones were observed, except for a decreased plasma estrodiol to progesterone ratio (95). The effect of consumption of flaxseed on human cancer risk is not clear.

PERSPECTIVES ON CANCER PREVENTION BY DIETARY POLYPHENOLS

Numerous laboratory studies have demonstrated the inhibition of carcinogenesis by polyphenols. Nevertheless, these results should be interpreted with caution in assessing the contribution of dietary polyphenols to the reduction of human cancer

risk. Some polyphenols identified in animals may have direct application, limited use, or no use in cancer prevention in humans based on the following mechanistic considerations.

1. Some polyphenols are considered cancer chemopreventive agents because they inhibit carcinogen activation, commonly catalyzed by cytochrome P450 enzymes, in vivo or in vitro. If the carcinogen used in the animal model is not a human carcinogen, then the agent may not be useful in humans. General inhibitors of cytochrome P450 enzymes are not useful, because they may affect their normal physiological functions such as in steroid metabolism.
2. Many polyphenols are considered chemopreventive agents because they induce phase II enzymes. In theory, induction of phase II enzymes may facilitate the elimination of certain carcinogens or their reactive intermediates. Caution is needed, however, in applying this concept to humans. The induction of phase II enzymes is probably an adaptive response to potentially harmful agents. For example, some phase II enzymes are electrophiles or pro-oxidants; at moderate doses, the effects may be beneficial, but toxic effects may be produced at high doses. In addition, some phase II enzymes participate in the activation of certain carcinogens.
3. Certain polyphenols inhibit arachidonic acid metabolism. Metabolism of arachidonic acid (and linoleic acid) leads to the production of many pro-inflammatory or mitogenic metabolites such as certain prostaglandins and reactive oxygen species. The inhibition of phospholipase A_2, COX, and lipooxygenase are potentially beneficial, and have been proposed as a mechanism in the chemopreventive action of curcumin and other polyphenols. Verification of such activities in human tissues will further substantiate this concept for cancer prevention.
4. Isoflavones and lignans are phytoestrogens and have been demonstrated to modulate hormone-dependent carcinogenesis in animals. As discussed previously, the time of administration of these agents during animal development is a key factor. In human applications, the possible estrogenic activity of high doses is a concern, especially in premenopausal women and infants.
5. Modulation of different oncogenes, tumor suppressor genes, and signal transduction pathways, leading to inhibition of cell proliferation, transformation, and angiogenesis as well as to the induction of apoptosis, has been proposed by many investigators as mechanisms for the chemopreventive activities of many polyphenolic compounds. As our understanding of the signal transduction pathways and the molecular events leading to carcinogenesis increases, more results in this area will become available from studies in cell cultures. These studies should be

integrated with studies in vivo in order to evaluate the applicability of these mechanisms in cancer prevention in humans. Comparison of the effective concentration of a polyphenol in cell lines with the levels achievable in animal and human tissues is of great importance.

6. Polyphenols are well recognized for their antioxidative properties. They are considered cancer chemopreventive by some authors, because polyphenols can quench or prevent the formation of reactive oxygen and nitrogen species, which play important roles in carcinogenesis. Evidence for these mechanisms, however, has been mostly circumstantial and more investigations are needed.

As is true with many agents, excessive amounts of polyphenols can be toxic, even though they are from dietary sources. The limited absorption of most of the dietary polyphenols may be considered as a protective mechanism. Strategies to boost tissue levels by using supplements or by manipulation of absorption should be implemented with caution. Flavonoids are reported to induce cleavage in the MLL gene and may contribute to infant leukemia (89). Again, it is not known whether this in vitro study can be extrapolated to human situations, because of the dose and bioavailability issue. More research in this area is needed and this publication calls attention to the possible problems with intake of excessive amounts of flavonoids.

Evidence on the prevention of human cancers has to come from human studies; both observational epidemiological studies and intervention trials are needed. Many epidemiological studies have demonstrated that reduced cancer risk is associated with frequent consumption of vegetables and fruits in general. Certain studies have reported the association with a specific type of food item such as apple, onion, or soybean. Although these food items are rich in polyphenols, the contribution by other compounds cannot be eliminated. For more precise information on the role of dietary polyphenols in cancer prevention in humans, reliable biomarkers for the consumption of specific polyphenols are needed, in addition to the use of dietary questionnaires. The association between the consumption of a specific type of polyphenol (or food item) and lowered cancer risk needs to be observed consistently in different studies, before dietary recommendations can be made. The National Cancer Institute and other institutions are pursuing human cancer chemoprevention trials. This subject has been reviewed (47). We hope discussions in this chapter are informative to the readers and useful to researchers in this area.

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