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Antioxidative and anti-carcinogenic activities of tea polyphenols

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Abstract

Tea (*Camellia sinensis*, Theaceace), a popular beverage consumed world-wide, has been studied for its preventive effects against cancer as well as cardiovascular, neurodegenerative, and other diseases. Most of the proposed beneficial effects have been attributed to the polyphenolic compounds in tea, but the nature of these activities and the molecular mechanisms of their actions remain unclear. Tea polyphenols are known to be strong antioxidants. Prevention of oxidative stress, modulation of carcinogen metabolism, and prevention of DNA damage have been suggested as possible cancer preventive mechanisms for tea and tea polyphenols. In this chapter, we discuss these topics in the light of biotransformation and bioavailability of tea polyphenols. We also review the preventive effects of tea polyphenols in animal models of carcinogenesis and some of the possible post-initiation mechanisms of action. Finally, we discuss the effects of tea consumption on cancer risk in humans. It is our aim to raise some of the unanswered questions regarding cancer prevention by tea and to stimulate further research in this area.

Introduction

Tea (*Camellia sinensis*, Theaceae) is a popular beverage worldwide (Yang et al. 2002). Depending on the technology of manufacturing, tea can be classified into three major types: green tea, black tea, and Oolong tea (Balentine et al. 1997; Lambert and Yang 2003). The different production methods alter the chemical composition of the dried tea leaves. Green tea, which accounts for 20% of world tea consumption, is prepared by pan-frying or steaming the tea leaves to inactivate polyphenol oxidase. This process preserves the characteristic tea catechins, which account for 10–15% of the weight of the dried leaves. The major catechins are epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) (Fig. 1). Black tea, representing 78% of world tea consumption, is prepared by crushing the tea leaves and causing enzyme-catalyzed oxidation and polymerization of tea catechins in a process commonly known as “fermentation”. This process results in the formation of oligomers such as theaflavins as well as large polymeric compounds known as thearubigins. Oolong tea is made by a delicate process to crush only the rim of the tea leaf. The product retains higher levels of catechins and contains newly formed oligomers

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of catechins such as theasinensins. A typical cup of green tea, brewed with 2.5 g tea leaves in 250 mL hot water, contains 620–880 mg of water-extractable materials, of which about one-third are catechins. EGCG is the most abundant catechin and may account for 50–75% of the catechins.

The possible beneficial effects of tea in the prevention of cancer as well as cardiovascular, neurodegenerative, and other diseases have been studied extensively. Most of the activities have been attributed to tea polyphenols. In this chapter, we review the antioxidative activities of tea polyphenols, their bioavailability and biotransformation, their effects on oxidative stress, and their inhibitory activities against carcinogenesis. Most of the reviewed studies are on catechins, particularly EGCG.

Redox properties and antioxidative activities of tea polyphenols

Tea catechins are characterized by the di- or tri-hydroxyl groups on the B-ring and the meta-5,7-dihydroxyl groups on the A ring. These structures provide strong antioxidative activities. The antioxidative activity is further increased by the presence of the trihydroxyl structure in the D-ring (gallate) in EGCG and ECG (Wiseman et al. 1997; Rice-Evans 1999). Tea preparations have been shown to react with reactive oxygen species (ROS), such as superoxide radical, singlet oxygen, hydroxyl radical, peroxyl radical, nitric oxide, nitrogen dioxide, and peroxynitrite. Among tea catechins, EGCG is most effective in reacting with most ROS. The B-ring appears to be the principal site of antioxidant reactions (Valcic et al. 2000; Sang et al. 2002). The polyphenolic structure allows electron delocalization, conferring high reactivity to quench free radicals. During the reaction of tea polyphenols with free radicals, several oxidation products are formed (Sang et al. 2007). Reactions of EGCG and other catechins with peroxyl radicals lead to the formation of anthocyanin-like compounds (Kondo et al. 1999), as well as seven-member B-ring anhydride dimers and ring-fission compounds (Valcic et al. 1999, 2000).

Another mechanism for the effective antioxidative activity is through metal ion chelation by the vicinal dihydroxyl and trihydroxyl structures, which prevents the generation of free radicals. Green tea can inhibit the oxidation of lipoproteins induced by Cu^{2+} in vitro (Hodgdon et al. 1999; Hashimoto et al. 2000). Pretreatment of macrophages or endothelial cells with green tea polyphenols reduced cellmediated low-density lipoprotein oxidation (Yoshida et al. 1999). The effects of tea and tea polyphenols on biomarkers of oxidative stress, such as DNA oxidative damage, have been demonstrated in animals after receiving carcinogenic or other types of oxidative stress; this topic will be discussed subsequently.

Administration of EGCG to rats was shown to reduce age-related increases in oxidative stress (Senthil Kumaran et al. 2008). For example, treatment of 24-month-old rats with EGCG at 100 mg/kg, i.g. decreased the levels of lipid peroxidation and protein carbonylation in the liver. The hepatic levels of antioxidants (e.g., reduced glutathione) as well as antioxidant enzymes (e.g., superoxide dismutase) were increased by the EGCG treatment. Similar effects were also observed in skeletal muscle. A second study by the same research group found that treatment of 24-month-old rats for 30 days with EGCG at 2 mg/kg, i.g. daily reduced the levels of protein carbonyls and malonyldialdehyde, and increased levels of ascorbic acid, α-tocopherol, and glutathione (reduced form) in the brain (Srividhya et al. 2008). In both of these studies, no effects were observed in young rats, suggesting that EGCG offers no protective effect in the absence of age-related increases in oxidative stress. The reasons for this age-related biological difference need to be investigated.

In humans, only transient and modest increases in total plasma antioxidant activity after tea ingestion were observed in some, but not other, experiments (Higdon and Frei 2003). Apparently, the bioavailability of tea polyphenols limits the biological activity in vivo.

Supplementation of healthy human volunteers with catechins (500 mg/day) for 4 weeks resulted in an 18% decrease in plasma oxidized low density lipoprotein (LDL) compared to the control (Inami et al. 2007). Similarly, supplementation of hemodialysis patients with 455 mg/day green tea catechins for 3 months decreased plasma hydrogen peroxide, *C*-reactive protein and several pro-inflammatory cytokines compared to placebo-treated controls (Hsu et al. 2007). Tea catechins also blunted dialysis-induced increases in several inflammatory markers including plasma levels of Fas ligand and interleukin (IL)-6 soluble receptor.

Similar to many other antioxidants, EGCG and other tea polyphenols may also act as pro-oxidants. Under cell culture conditions, EGCG is not stable, with a half-life of 0.5–2 h depending on the cultural medium (Hong et al. 2002; Hou et al. 2005). The half-life can be extended several fold by the addition of superoxide dismutase (SOD), suggesting a role for superoxide radicals in the oxidation and polymerization of EGCG. A proposed mechanism of EGCG auto-oxidation has been published previously (Hou et al. 2005). EGCG and other catechins can be oxidized to form phenolic radicals, superoxide radicals, and hydrogen peroxide. These species may trigger a variety of biochemical reactions and biological responses. For example, the radical species may contribute to the inactivation of epidermal growth factor receptor (EGFR) and telomerase, while hydrogen peroxide may contribute to cell apoptosis (Yang et al. 2007). It is not clear whether these pro-oxidation of EGCG-generated reactions occur in vivo, which usually has low oxygen partial pressure than systems in vitro. The oxygen partial pressure in a cell culture system (152 mmHg) is much higher than that in the blood or tissues (<40 mmHg) (Sherwood 2004).

The relative importance of the antioxidative and pro-oxidative activities in vivo remains to be determined. It is known that EGCG and other catechins can directly scavenge ROS and chelate free transition metals, thereby reducing oxidative stress. Tea polyphenols could also generate ROS, but the levels are relatively insignificant in the presence of existing oxidative stress. In the absence of pre-existing oxidative stress, the tea polyphenols could generate ROS that stimulate upregulation of the endogenous antioxidant systems by mechanisms through the Nrf2 signaling pathway. High concentrations of ROS generated could lead to toxicity. Some of the related studies will be discussed subsequently.

Bioavailability and biotransformation of tea polyphenols

Biotransformation of tea polyphenols

We and others have extensively studied the biotransformation of green tea polyphenols (Kohri et al. 2001; Li et al. 2001; Hu et al. 2003; Lambert and Yang 2003; Auger et al. 2008). Tea catechins are subject to methylation, glucuronidation, sulfation, and ring-fission metabolism. EGCG is readily methylated by catechol-*O*-methyltransferase (COMT) to form 4″-*O*-methyl-(-)-EGCG and 4′,4″-*O*-dimethyl-(-)-EGCG (Lu et al. 2003b). Studies of EGCG glucuronidation reveal that EGCG-4″-*O*-glucuronide is the major metabolite formed in humans, mice, and rats (Lu et al. 2003a). Human UGT1A1, 1A8, and 1A9 have high glucuronidation activity toward EGCG, with the intestinal-specific UGT1A8 being the most efficient. Our studies also suggest that mice are more similar to humans in terms of enzymatic ability to glucuronidate tea catechins than are rats (Lambert et al. 2005a). EGCG and other catechins are also sulfated by sulfotransferase in human, mouse, and rat liver cytosol (Lu 2002). Our recent results from data-dependent tandem mass spectrometric analysis of mouse urine samples, after i.p. or i.g. administration of EGCG, have shown that methylated EGCG (or glucuronidated or sulfated EGCG) can be further glucuronidated and/or sulfated (or methylated) to form related mixed EGCG metabolites (Sang et al. 2008).

At toxic doses, EGCG can form two cysteine adducts in vivo, EGCG-2″-cysteine and EGCG-2′-cysteine (Sang et al. 2005). These metabolites can be detected in the urine following

administration of EGCG at 200–400 mg/kg, i.p. or 1,500 mg/kg, i.g. We hypothesize that these metabolites form as the result of oxidation of EGCG to a quinone or semi-quinone that then reacts with the sulfhydryl group of cysteine. It is possible that similar metabolites will be formed by reaction with glutathione and *N*-acetylcysteine, but these metabolites remain to be discovered.

In addition to phase II metabolites, our laboratory has identified several ring fission products of tea catechins in human urine and plasma after oral ingestion of decaffeinated green tea (Li et al. 2000). The compounds, 5-(3′, 4′, 5′-trihydroxyphenyl)-γ-valerolactone (M4), 5-(3′, 4′-dihydroxyphenyl)-γ-valerolactone (M6), and 5-(3′, 5′-dihydroxyphenyl)-γ-valerolactone (M6′), are believed to be derived from microbial metabolism in the colon. Indeed, anaerobic fermentation of EGC, EC, and ECG with human fecal microflora has been shown to result in the production of M4, M6, and M6′ (Meselhy et al. 1997).

Active efflux has been shown to limit the bioavailability and cellular accumulation of many compounds. The multidrug resistance-associated proteins (MRP) may play a role in limiting the bioavailability of tea catechins. We have reported that indomethacin (MRP inhibitor) increases the intracellular accumulation of EGCG; EGCG, 4″-*O*-methyl-EGCG, and 4′, 4″-di-*O*-methyl-EGCG in Madin-Darby canine kidney (MDCKII) cells overexpressing MRP-1 (Hong et al. 2003). Similarly, treatment of MRP-2 overexpressing MDCKII cells with MK-571 (an MRP-2 inhibitor) increases the intracellular levels of EGCG, 4″-*O*-methyl-EGCG, and 4′, 4″-di-*O*-methyl-EGCG, respectively. The combined effects of MRP-1 and MRP-2 on the bioavailability of the tea polyphenols remain to be determined in vivo. MRP-2, with its localization on the apical membrane of the small intestine, likely acts to limit EGCG bioavailability by actively exporting EGCG in the enterocyte back into the intestinal lumen. In contrast, MRP-1 is located on the basolateral membrane of enterocytes, hepatocytes, and other tissues. Substrates of this pump are effluxed from the interior of the cells into the blood stream or interstitial space. The role of MRP-1 would be expected to increase the bioavailability of EGCG in vivo. The influence of MRP-1 and MRP-2 on the bioavailability of EGCG in vivo is likely to depend on the tissue distribution of each efflux protein.

Pharmacokinetics of tea polyphenols

Pharmacokinetic studies of the tea catechins have been conducted in rats, mice, and humans (reviewed in Yang et al. 2008). Following i.g. administration of decaffeinated green tea (200 mg/kg) to rats, plasma levels of EGCG, EGC, and EC (conjugated and nonconjugated forms) were fit to a two-compartment model with elimination half-lives of 165, 66, and 67 min, respectively (Chen et al. 1997). The absolute bioavailability of EGCG, EGC, and EC after i.g. administration of decaffeinated green tea was 0.1, 14, and 31%, respectively. The bioavailability of EGCG in mice following oral administration of EGCG was higher (Yang et al. 2008). Whereas greater than 50% of plasma EGCG was present as the glucuronide, EGCG was present mainly as the free form in the tissues (Lambert et al. 2003). Administration of 50–2,000 mg/kg, i.g. EGCG to mice resulted in a linear increase in the plasma, liver, and prostate. In contrast, the levels of EGCG in the small intestine and colon plateaued at 500 mg/kg, i.g (Lambert et al. 2006). These results suggest that small intestinal and colonic tissues become saturated with EGCG, resulting in a plateau of the levels in these tissues.

Several studies of the systemic bioavailability of orally administered green tea and catechins in human volunteers have been conducted. We showed that oral administration of 20 mg green tea solids/kg body weight resulted in C_{max} in the plasma for EGC, EC, and EGCG of 223, 124, and 77.9 ng/mL, respectively (Lee et al. 2002). Plasma EC and EGC were present mainly in the glucuronidated and sulfated form whereas 77% of the EGCG was in the free form. EGC was also methylated (to 4′-*O*-methyl-EGC) in humans. EGCG was also methylated: the maximum plasma concentration of 4′,4″-di-*O*-methyl-EGCG was 20% of that of EGCG but

the cumulative excretion of 4′,4″-di-*O*-methyl-EGCG in the urine was 10-fold higher (140 μg) than that of EGCG (16 μg) over 24 h (Meng et al. 2002). In addition to methylated and conjugated metabolites, the ring-fission metabolites, M4, M6, and M6′, were detected in urine at 8, 4, and 8 μM, respectively, following ingestion of 200 mg EGCG (Li et al. 2000; Meng et al. 2002). Chow et al. reported that following 4 weeks of green tea polyphenol treatment of human volunteers with a dosing schedule of 800 mg once daily, there was an increase in the area under the plasma EGCG concentration-time curve from 95.6 to 145.6 min/μg min (Chow et al. 2003). No significant changes, however, were observed in the pharmacokinetics of EGCG after repeated green tea polyphenol treatment at a regimen of 400 mg twice daily. Similarly, there was no significant change in the area under the curve for EGC or EC.

Effects of tea polyphenols on carcinogen metabolism and DNA damage

Effects on carcinogen metabolism

Tea polyphenols have been shown to inhibit the expression of carcinogen activating enzymes such as cytochromes P450 (CYP) and increase the levels of enzymes which detoxify carcinogens. For example, Krishnan et al. showed that pretreatment of Swiss mice with 1% black tea polyphenols blunted the increase in expression of CYP1A1 and 1A2 induced in the liver and lung by a single oral dose of benzo[a]pyrene (B[a]P) (Krishnan et al. 2005). This is likely due to interference at the aromatic hydrocarbon receptor level. Intragastric treatment of rats with theaflavins (20 mg/kg) for 4 weeks reduced CYP1A1 activity in the intestine but not in the liver (Catterall et al. 2003). This discrepancy may be due to the limited systemic bioavailability of theaflavins. Long-term treatment of rats with green or black tea resulted in increased expression of hepatic 1A2 (Sohn et al. 1994; Xu et al. 1996). Studies from our laboratory suggested that induction of 1A2 activity is due to the caffeine present in the tea preparation (Chen et al. 1996).

Studies in animal models have also demonstrated that tea treatment can induce Phase II drug-metabolizing enzymes. Treatment of piglets with 0.2% green tea extract (45% EGCG) for 3 weeks increased the rate of formation of glutathione conjugated aflatoxin (AF)B_1 by small intestinal microsomes in ex vivo studies (Tulayakul et al. 2007). Treatment of female Wistar rats with 2% green tea extract for 4 weeks was shown to increase cytosolic glutathione-*S*-transferase (GST) activity in the liver (Maliakal et al. 2001). However, later studies in which Wistar rats were given tea polyphenols at 833 mg/kg, i.g. once daily for 6 months, showed no effect on hepatic GST activity (Liu et al. 2003). Pretreatment of rats with 2% green tea for 6 weeks prior to a single dose of 2-amino-3-methylimididazo[4,5-*f*]quinoline (IQ) was found to increase excretion of glucuronide and sulfate metabolites of IQ in the urine (Embola et al. 2001). Others, however, suggested that caffeine may be the major tea component responsible for this activity (McArdle et al. 1999). Oral gavage of EGCG (200 mg/kg) to C57bl/6 J mice was shown to upregulate gene expression of γ-glutam-yltransferase, glutamate cysteine ligase, and hemeoxygenase 1 (Shen et al. 2005). This effect appeared to be via the Nrf2-antioxidant response element pathway. This topic has recently been reviewed (Na and Surh 2008).

Studies in humans have not shown the modulation of CYP expression and activity by tea and tea polyphenols. For example, 4-week treatment of human volunteers with 800 mg Polyphenon E (65% EGCG) did not significantly alter the activity of CYP1A2, CYP2D6, or CYP2C9 based on the pharmacokinetics of selected probe compounds (Chow et al. 2006). Similarly, treatment of healthy volunteers with 844 mg decaffeinated green tea extract (59% EGCG) for 14 days did not significantly affect CYP3A4 or CYP2D6 activity (Donovan et al. 2004). These results raise questions about the human relevance of the observed CYP-modulating effect in animal studies. By contrast, there is evidence suggesting that green tea preparations can modulate human Phase II metabolism. Treatment of human volunteers for 4 weeks with 800 mg/day Polyphenon E increased GST-π activity in blood lymphocytes (Chow et al. 2007). This effect

was greatest in individuals with the lowest tertile baseline GST-π activity (80% increase compared to baseline). A recent intervention study in China showed that a 3-month treatment with 500 or 1,000 mg/day green tea polyphenols increased urinary excretion of the mercapturic acid conjugated of AFB_1 (AFB_1-NAC) by 10-fold and 8.4-fold, respectively compared to baseline (Tang et al. 2008). This result could be due to the induction of glutathione-*S*-transferases.

Prevention and repair of DNA damage

Tea and tea components have been shown to inhibit carcinogen-induced DNA damage in a number of cell line studies. For example, co-treatment of human leukocytes with EGCG (2 μM) and bleomycin (20 μg/mL) resulted in a 50% decrease in bleomycin-induced DNA damage compared to treatment with bleomycin alone (Glei and Pool-Zobel 2005). Green tea, black tea, and Oolong tea extract dose-dependently protected Chang liver cells from B[a]P-induced DNA damage (Yen et al. 2004). Pure EGC, EGCG, and theaflavins (10–50 μM) dose-dependently protected cells from B[a]P-induced DNA damage. At higher concentrations, however, EGC, EGCG, and theaflavins induced DNA damage by pro-oxidative mechanisms.

Studies in animal models have been consistent with the results in the cell line studies. Pretreatment of C57bl/6 Big Blue *lacI* transgenic mice with 2% green tea prior to a single dose of B[a]P resulted in a 54% decrease in characteristic GC to TA transversions in the liver compared to water-treated controls (Jiang et al. 2001). In contrast, green tea administration did not inhibit DNA adduct formation in the 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumorigenesis model in A/J mice even though tea did reduce tumorigenesis (Shi et al. 1994). In a similar model, Xu et al. showed that green tea can prevent the formation of 8-oxo-2-deoxyguanosine (Xu et al. 1992). These results suggest that the ability of tea to prevent DNA adduct formation and oxidative DNA damage contribute to its cancer preventive activity.

C3(1) SV40 T,t antigen transgenic multiple mammary adenocarcinoma (TAg) mice spontaneously develop mammary adenocarcinoma. Treatment of mice with a solution of 0.05% green tea catechins (60% EGCG) or black tea theaflavins as the sole source of drinking fluid for 18 weeks decreased malonyldialdehyde-DNA adduct formation in the tumors (Kaur et al. 2007). This event was related to decrease mammary tumor volume and increased survival compared to water-treated controls. In another series of studies, Lin et al. reported that pre-treatment of rats with 3% green tea extract as the sole source of drinking fluid for 10 days reduced 2-amino-3-methylimididazo[4,5-*f*]quinoline (PhIP)-DNA adduct formation (Lin et al. 2003). PhIP-DNA adducts were reduced by 50–63% in the colon, heart, lung, and liver by green tea treatment. An interesting recent study suggested that EGCG could prevent photocarcinogenesis via an IL-12 dependent DNA repair pathway (Meeran et al. 2006). Application of EGCG (1 mg/cm^2) to the backs of wildtype (C3H/HeN) mice inhibited UVB-induced photocarcinogenesis, but no inhibition was observed in IL-12$^{-/-}$ litter mates. The authors found that this phenomenon was related to decreased repair of pyrimidine dimers in the skin of IL-12$^{-/-}$mice compared to wild-type litter mates.

In a pilot study by Schwartz et al. heavy smokers and non-smokers were treated with green tea (400–500 mg green tea powder per cup) 5 times per day for 4 weeks (Schwartz et al. 2005). The authors found that the levels of B[a]P-deoxyguanosine (B[a]P-dG) adducts were higher in smokers than in non-smokers (two–fourfold elevation), and tea-treatment caused a 50% decrease in B[a]P-dG adducts by the end of the experiment. Tea treatment for 4 weeks also reduced the number of 8-OHdG positive cells in smokers to 50% of the pre-treatment levels. Other researchers have reported that supplementation with green tea or green tea preparations can reduce biomarkers of oxidative DNA damage. For example, Hakim et al. found in a randomized, controlled intervention study, that supplementation of heavy smokers (>10

cigarettes per day) with four cups of decaffeinated green tea (73.5 mg catechins per cup) per day for 4 months reduced urinary 8-OHdG levels by 31% compared to the control group (Hakim et al. 2003). A recent study in China found that green tea polyphenols modulated the formation of serum aflatoxin-albumin (AfA) adducts in a population at high-risk for liver cancer (Tang et al. 2008). Treatment of AfA-seropositive individuals with 500 or 1,000 mg green tea polyphenols for 3 months resulted in a dose- and time-dependent decrease in the serum levels of AfA as well as a dose-dependent decrease in urinary 8-OHdG levels compared to placebo (Tang et al. 2008).

Inhibition of carcinogenesis

Cancer prevention by tea and tea components has been studied in many different animal models of carcinogenesis (reviewed in Yang et al. 2002,2007;Lambert et al. 2005b;Ju et al. 2007). Tea and tea constituents have been shown to inhibit the development of cancer in animal models of oral, esophageal, forestomach, stomach, intestinal, colon, skin, liver, bladder, prostate, and breast cancer. Whereas most studies have focused on the activity of the tea polyphenols, several studies have reported the importance of caffeine in the prevention of skin and lung (reviewed in Lambert et al. 2005b).

Several recent studies highlight the inhibitory activity of tea polyphenol preparations in animal models of tumorigenesis, and begin to provide some mechanistic data related to the inhibitory effect. For example, our laboratory has extensively studied the anti-tumorigenic activities of tea polyphenols in the *APC*$^{min/+}$ mouse model of intestinal tumorigenesis. EGCG solution, as the sole source of drinking fluid, dose-dependently (0.02–0.32% w/v) inhibited small intestinal tumorigenesis in this model (Ju et al. 2005). Inhibition of tumor multiplicity was associated with increased expression of E-cadherin and decreased levels of nuclear β-catenin, c-Myc, phospho-Akt, and phospho-extracellular regulated kinase (Erk) 1/2. We also compared the effectiveness of EGCG as a pure compound with a defined catechin mixture, Polyphenon E (PPE), containing 65% EGCG (Hao et al. 2007). Total tumor multiplicity was decreased by both dietary PPE (0.12%) or the corresponding amount of dietary EGCG (0.08%). Although PPE appeared to be more effective than EGCG at reducing total tumor multiplicity, the difference was not statistically significant. The cancer preventive activity of tea and tea polyphenol preparation has also been demonstrated in other models for colon carcinogenesis (reviewed in Ju et al. 2007). Further studies are required to more fully elucidate whether PPE or other green tea catechin preparations are more effective at inhibiting tumorigenesis than EGCG.

Whereas the colon cancer prevention activity of tea and tea polyphenol preparations has been consistently demonstrated in mouse models, results in the rat model have not been consistent (reviewed in Ju et al. 2007). We have recently examined the effect of PPE on the development of colon aberrant crypt foci (ACF) and cancer in azoxymethane (AOM)-treated rats. Treatment of rats with PPE (0.12, 0.24% in the diet) for 8 weeks, following injection with AOM, dose-dependently decreased the total number of ACF per rat by 16.3 and 36.9%, respectively. The inhibitory activity was associated with decreased levels of nuclear β-catenin and cyclin D_1, and increased retinoid X receptor α staining in the ACF with high-grade dysplasia (Xiao et al. 2008). After treatment with 0.24% PPE for 34 weeks, the incidence of adenocarcinoma decreased from 57 to 23%, and the multiplicity of adenocarcinoma and adenoma was decreased by 80 and 45%, respectively (unpublished). Carter et al. examined the effect of EGCG when given during the post-initiation phase, on PhIP-induced ACF in the rat (Carter et al. 2007). Treatment with EGCG for 15 weeks reduced PhIP-induced ACF by 71% compared to water-treated controls. This decrease in ACF was associated with a 40% decrease in bromodeoxyuridine labeling in the crypt, suggesting that EGCG is inhibiting aberrant cell proliferation. The underlying mechanisms remain unclear.

Administration of green tea, black tea, EGCG, or theaflavins during initiation or promotion stage was shown to inhibit NNK-induced lung tumorigenesis in rats, mice, or hamsters (Wang et al. 1992; Xu et al. 1992; Yang et al. 1997; Chung et al. 1998; Mimoto et al. 2000; Zhang et al. 2000; Liao et al. 2004; Schuller et al. 2004; Lu et al. 2006). Treatment with green or black tea for 60 weeks also inhibited the spontaneous formation of lung tumors in A/J mice (Landau et al. 1998). In our recent study, the oral administration of 0.5% PPE or 0.044% caffeine in the drinking fluid for 32 weeks was found to inhibit the progression of lung adenomas to adenocarcinomas in A/J mice that had been treated with a single dose of NNK 20 weeks earlier (Lu et al. 2006). PPE and caffeine treatment inhibited cell proliferation in adenocarcinomas, enhanced apoptosis in adenocarcinomas and adenomas, and decreased levels of c-Jun and phospho-Erk1/2. In the normal lung tissues, neither agent had a significant effect on cell proliferation or apoptosis. Oral administration of green tea infusion reduced the number of lung colonies of mouse Lewis lung carcinoma cells in a metastasis system (Yang et al. 2005). These results suggest that tea preparations may be preventive agents for all stages of lung carcinogenesis.

Because of the low blood and tissue levels of tea polyphenols achievable through oral administration, their effectiveness in cancer prevention is limited. An approach that has been explored is to use polyphenols in combination with other agents. For example, we recently demonstrated the synergistic inhibitory action of a combination of PPE and atorvastatin against NNK-induced lung carcinogenesis in A/J mice (Lu et al. 2008). The synergistic action of this combination against human lung H1299 and H460 cells was also demonstrated. In both the cell lines and mouse model, down-regulation of the anti-apoptotic protein Mcl-1 and induction of apoptosis were shown to be associated with the synergistic inhibitory action (Lu et al. 2008).

Mechanisms for the anti-cancer activities of tea polyphenols

In addition to the ability of tea polyphenols to inhibit the level of activated carcinogens, oxidative stress-induced cellular damage, carcinogen-DNA adduct formation, and possibly the initiation of carcinogenesis, the inhibition of post-initiation events has also been studied extensively. Most of the studies on the anti-cancer activities have focused on the effects of EGCG on signal transduction pathways in cell lines, and numerous mechanisms for the action of tea polyphenols have been proposed (reviewed in Hou et al. 2004; Lambert et al. 2005b; Khan et al. 2006; Yang et al. 2007). These include inhibition of MAP kinases and the PI3K/AKT pathway, inhibition of NFκB- and AP-1-mediated transcription, inhibition of growth factor-mediated signaling, inhibition of aberrant arachidonic acid metabolism, and other activities. The end result of these effects may be the inhibition of tumor cell growth, induction of apoptosis, or the inhibition of angiogenesis. Some of these activities have been demonstrated to be associated with the inhibition of carcinogenesis in animal models. In most cases, however, the concentrations of EGCG required to observe these biological effects in vitro exceed the concentrations achievable in plasma and tissues by 10–100-fold, and questions remain as to the relevance of these in vitro observations to the mechanisms of the cancer-preventive activities in vivo (reviewed in Hou et al. 2004; Yang et al. 2007).

In general, if an effect can be observed in vitro at concentrations lower or similar to those observed in vivo, then the event may occur in vivo. For example, EGCG was reported to bind to the 67-kDa laminin receptor with a K_d of 0.04 μM, to vimentin with a K_d of 3.3 nM, and interact with Bcl-2 with a K_i of 0.33 μM (Leone et al. 2003; Ermakova et al. 2005). In all these studies, there were experiments demonstrating the biological relevance of the effects in their specific experimental systems, but it required much higher concentrations of EGCG to cause growth inhibition and induce apoptosis. The general applicability of these mechanisms for cancer prevention remains to be investigated. The differences between the effective

concentrations determined with pure enzymes and those in cell lines or tissues are probably due to the non-specific binding of EGCG to many proteins and the limited amount of EGCG that can enter the cells. When a small amount of pure enzyme is used in an enzymatic assay, inhibition may be observed with nanomolar concentrations of EGCG, but it may take much higher concentrations of EGCG to inhibit the activity in cell lines or tissues. This point is illustrated in the inhibition of 20 s proteasome chymotryptic activities by EGCG; i.e., the IC_{50} observed in a cell-free system was 0.1–0.2 μM, but it was 1–40 μM in tumor cell lines (Nam et al. 2001). Based on the above considerations, our understanding of the mechanisms of the cancer preventive action of EGCG, and perhaps other phenolic compounds, are as follows: (1) different mechanisms are likely to be involved in different experimental systems; (2) the possible involvement of multiple targets in one system and their possible synergistic actions remain to be studied; (3) some of the proposed mechanisms based on studies in cancer cell lines may not be relevant to cancer prevention because of the high concentration of agents used; (4) many of the observed effects are probably secondary events or downstream events and it is important to identify the direct targets of EGCG action; and (5) mechanisms of cancer prevention need to be demonstrated in relevant models or human tissues.

Possible cancer prevention by tea in humans

Many case-control studies have shown that individuals who frequently consume tea had lower cancer risk; for example, lower risk of gastric and esophageal cancer was observed among green tea consumers in Japan and China (reviewed by Ju et al. 2007). Gao et al. reported that green tea consumption was associated with a reduced risk of esophageal cancer (Gao et al. 1994). From the Shanghai Cancer Registry, 1,016 eligible cases of esophageal cancer were matched with controls, and patient interviews were conducted. After adjustment for known confounders, a protective effect was observed in nonsmokers, mostly women. For women consuming ≥ 15 g of dry green tea leaves per month (one cup of tea typically contains 2 g tea leaves), the odds ratio (OR) was 0.34. Among men (mostly smokers), the OR was 0.80, but not statistically significant. In a more recent study, we and our collaborators investigated the association between pre-diagnostic urinary tea polyphenols, and the risk of developing gastric and esophageal cancers. Using a nested case-control design, we compared 190 cases of gastric cancer and 46 cases of esophageal cancer with 772 control subjects from the Shanghai Cohort. Urinary EGC positivity showed a statistically significant inverse association with gastric cancer (OR = 0.52) after adjustment for confounders. The protective effect was primarily seen among subjects with below population median levels of serum carotenoids. Similar tea polyphenol-cancer risk associations were observed for combined risk of gastric cancer and esophageal cancer (Sun et al. 2002). In the same cohort, a similar result was also observed between urinary levels of tea catechins (and their metabolites) and colon cancer risk (Yuan et al. 2007).

Tea consumption has also been associated with the reduced risk of other types of cancer. For example, a population-based case-control study of women of Asian descent living in Los Angeles, found that green tea drinkers had a significantly reduced risk of breast cancer (OR = 0.71 and 0.53 for consumption of 0–85.7 mL and >85.7 mL of tea per day, respectively) (Wu et al. 2003b). Among women who carried at least one low-activity COMT allele (Wu et al. 2003a). The authors concluded that individuals with a low-activity COMT allele have a reduced risk of breast cancer because they metabolize tea polyphenols less efficiently and, therefore, had prolonged exposure to the active parent compound. The Japanese Public Health Center-based Prospective Study (JPHC) reported an association between green tea consumption and decreased risk of advanced prostate cancer (Kurahashi et al. 2008). In a cohort of 49,920 men, a dose-dependent decrease in the risk of advanced prostate cancer was observed (*P* for trend = 0.01). There was, however, no association between tea consumption and the risk of localized prostate cancer.

Not all epidemiological studies have observed an inverse relationship between tea consumption and cancer risk (reviewed in Ju et al. 2007). Several recent prospective studies in Japan found no association between green tea intake and decreased breast cancer risk (Hoshiyama et al. 2005). In the Ohsaki National Health Insurance Cohort Study in Japan, after an 11-year follow-up, although green tea consumption was associated with decreased mortality due to cardiovascular diseases, it had no association with cancer deaths (Kuriyama et al. 2006).

The inconsistent results of epidemiological studies of tea and cancer prevention could be due to a variety of reasons. Case-control studies are generally less powerful than prospective studies, because of confounding factors. For example, individuals with a stomach problem, which increases the risk for gastric cancer, may refrain from drinking green tea because of stomach irritation. Genetic factors in different populations may affect the results; for example, a greater protective effect of tea against breast cancer was observed in women with at least one low activity allele of COMT (Wu et al. 2003b). Nutritional factors could also play a role in affecting the results; for example, the protective effect against colon cancer was more clearly seen in subjects with lower serum levels of carotenoids (Sun et al. 2002). The quantity and quality of the tea consumed will definitely affect the outcome of epidemiological studies. Reliance on questions of “number of cups of tea consumed per day” represents a potential weakness in many epidemiological studies. In future studies, more precise quantitative and qualitative information of tea consumption should be a goal in the study design. Objective measurements of exposure biomarkers, such as urinary catechins and their metabolites (Yuan et al. 2007), could be very useful and should be explored further.

Even though the results of epidemiological studies have not yielded a clear conclusion between tea consumption and cancer risk, tea or tea polyphenol preparations could be used for the prevention of certain types of cancer, if such an activity could be demonstrated in well-designed intervention studies. A recent double-blind study by Bettuzzi et al. followed 200 individuals with high-grade prostate intraepithelial neoplasia (PIN) receiving either 600 mg of green tea catechins daily or placebo (100 individuals in each group) for 12 months. Only 3% of the patients in the catechin treatment group developed prostate cancer, whereas the rate of cancer development on the placebo group was 30% (Bettuzzi et al. 2006). No adverse effect was associated with the treatment. These results are very exciting, and the impact would be tremendous if the results could be reproduced in similar trials with larger numbers of subjects. Several human trials with tea polyphenol preparations for the prevention of cancer of the prostate, breast, colorectum, oral cavity and as well as leukemia are ongoing or being planned. It is hoped that these studies will yield clear conclusions.

Concluding remarks

The antioxidative and anti-carcinogenic activities of tea polyphenols have been clearly demonstrated in animal models. Nevertheless, the relative importance of the antioxidative mechanisms in comparison to other proposed mechanisms for cancer prevention remains unclear. In theory, tea polyphenols should be able to quench ROS generated during the metabolism of environmental carcinogenesis or during inflammation and carcinogenesis. Nevertheless, the effectiveness of this mechanism is limited by the low blood and tissue concentrations of polyphenols derived from oral administration or consumption of tea or tea polyphenols. The antioxidative activity may be prominent when high doses of tea are ingested to counteract the effect of high levels of exogenous or endogenous ROS. On this topic, the results in the literature have not been consistent, and more studies are needed. Even when the antioxidative activity can be measured by the commonly used biomarkers, it does not mean that this is the mechanism by which tea polyphenols block carcinogenesis; other anti-carcinogenesis mechanisms as described above may be just as or even more important. Inhibition of oxidative DNA damage by the consumption of tea polyphenols has been

demonstrated in heavy smokers. The possibility of using tea polyphenols to protect against cellular damage caused by environmental pollutants remains to be investigated.

In spite of the strong evidence for the cancer preventive activity of tea polyphenols in animal models, such an activity has not been consistently observed in studies on humans. This may be due to the relatively low levels of tea consumption by humans and the confounding factors in epidemiological studies involving different populations. More definitive information on the cancer preventive or anti-carcinogenic activity of tea polyphenols will come from well-designed cohort studies as well as human intervention trials. Knowledge gained from the above reviewed studies on the biological properties and activities of tea polyphenols will help in the design of these studies.

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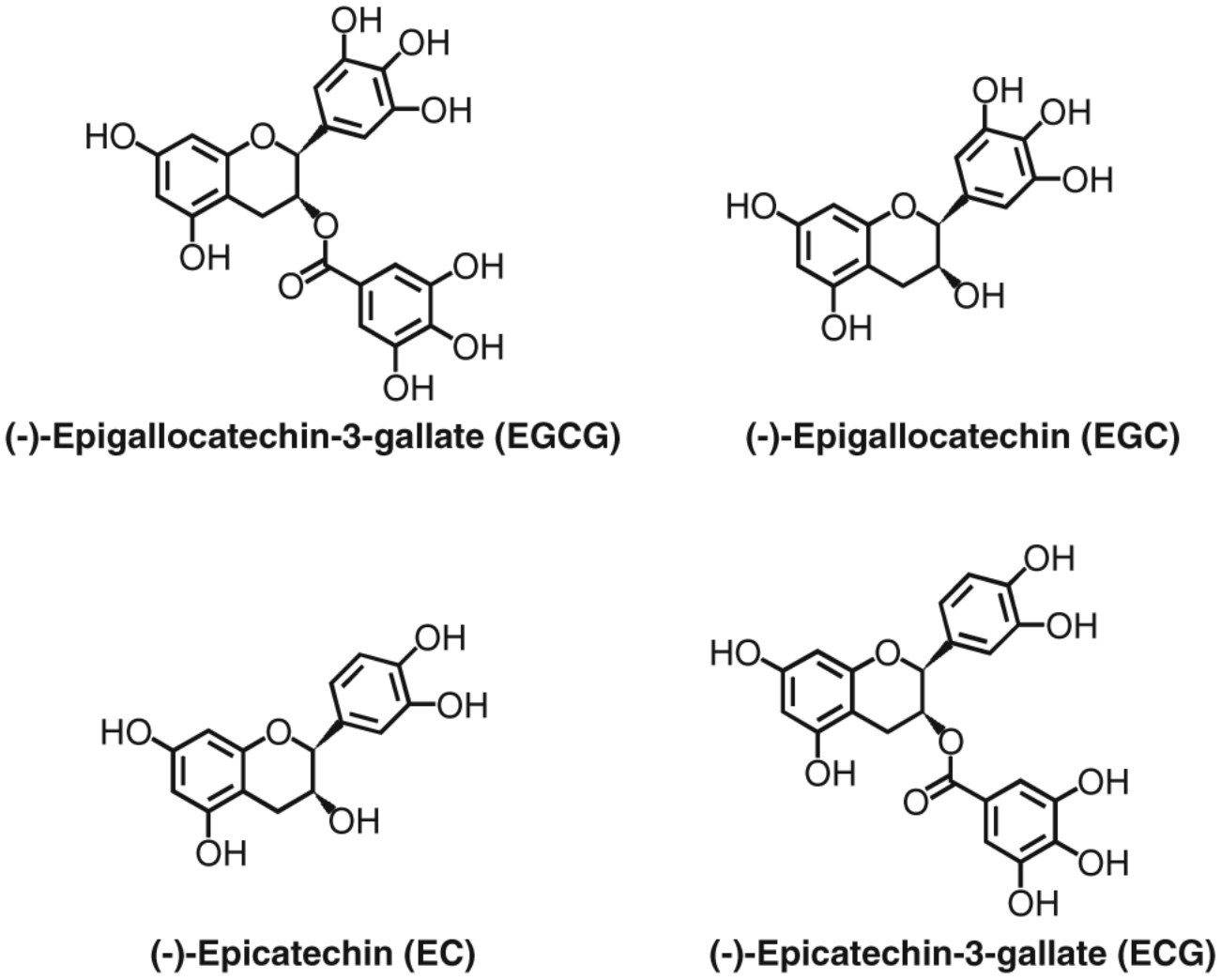

Fig. 1.
Structures of the major tea polyphenols