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Tea Antioxidants in Cancer Chemoprevention

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Abstract In recent years, the concept of cancer chemoprevention has matured greatly. Significant reversal or suppression of premalignancy in several sites by chemopreventive agents appears achievable. This article summarizes experimental data on chemopreventive effects of tea polyphenols in different tumor bioassay systems. Tea (*Camellia sinensis*) is cultivated in about 30 countries, and is the most widely consumed beverage in the world. Three main commercial tea varieties—green, black, and oolong—are usually consumed, but most experimental studies demonstrating the antimutagenic and anticarcinogenic effects of tea have been conducted with water extract of green tea, or a polyphenolic fraction isolated from green tea (GTP). The majority of these studies have been conducted in a mouse skin tumor model system where tea is fed either as water extract through drinking water, or as purified GTP. GTP has been shown to exhibit antimutagenic activity in vitro, and inhibit carcinogen- as well as UV-induced skin carcinogenesis in vivo. Tea consumption has also been shown to afford protection against chemical carcinogen-induced stomach, lung, esophagus, duodenum, pancreas, liver, breast, and colon carcinogenesis in specific bioassay models. Several epicatechin derivatives (polyphenols) present in green tea have been shown to possess anticarcinogenic activity; the most active is (−)-epigallocatechin-3-gallate, which is also the major constituent of GTP. The mechanisms of tea's broad cancer chemopreventive effects are not completely understood. Several theories have been put forward, including inhibition of UV- and tumor promoter-induced ornithine decarboxylase, cyclo-oxygenase, and lipoxygenase activities, antioxidant and free radical scavenging activity; enhancement of antioxidant (glutathione peroxidase, catalase, and quinone reductase) and phase II (glutathione-*S*-transferase) enzyme activities; inhibition of lipid peroxidation, and anti-inflammatory activity. These properties of tea polyphenols make them effective chemopreventive agents against the initiation, promotion, and progression stages of multistage carcinogenesis. J. Cell. Biochem. Suppl. 27:59–67.

Key words: antioxidants; black tea; chemoprevention; epigallocatechin-3-gallate; green tea; tea polyphenols

There is abundant evidence that oxygen species, e.g., singlet oxygen, peroxy radicals, superoxide anion, and hydroxyl radical are involved in initiation, promotion, and progression stages of multistage carcinogenesis. For example, relevant to initiation, oxygen radicals can oxidize DNA bases and produce mutagenic lesions [1]. Radicals also cause DNA strand breaks and chromosome deletions and rearrangements. Further, activated oxygen species most likely play an important role in tumor promotion and progression [1]. For these reasons, the search for antioxidants as cancer chemopreventive *agents* is a continued saga.

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Various epidemiological, experimental, and metabolic studies show that nutrition plays an important causative role in the initiation, promotion, and progression stages of several types of human cancers [2,3]. In addition to substances that pose cancer risk, the human diet also contains vegetables, fruits, and beverages, which not only provide essential vitamins and minerals, but include important chemopreventive agents capable of protecting against some forms of human cancer [2–4]. Many cancer chemopreventive agents possess antioxidant potential [4]. Such chemopreventive agents are known as anticarcinogens, and ideally they should be non-toxic [2–4]. Among the more extensively studied chemopreventive agents are the polyphenols, including tea polyphenols.

TEA POLYPHENOLS

Tea (*Camellia sinensis*) is grown in about 30 countries. Next to water, it is the most widely

consumed beverage in the world [5]. Three main commercial tea varieties are available: green, black, and oolong. Green tea is consumed primarily in Asia and parts of North Africa. Oolong tea is favored in Taiwan and parts of China. The rest of the world primarily drinks black tea. The chemistry of the polyphenols in tea has been previously described [5,6]. The structures of complex catechins, the main antioxidant polyphenols, in green and black tea, are shown in Figure 1. Normally the composition of tea leaf varies with the climate, season, horticultural practices, variety of the plant, and age of the leaf. The main polyphenol present in green tea is (−)-epigallocatechin-3-gallate (EGCG, Fig. 1), and accounts for about 60–70% of the total catechin [5]. Defined polyphenols in black tea are theaflavine gallate (Fig. 1) and digallate. Green tea manufacturing involves chopping and rolling the leaves, steaming or heating the rolled leaves to inactivate the polyphenol oxidase enzyme, and drying, producing the product known as green tea. In black tea production, the chopped and rolled tea leaves are allowed to wither for about 6 hours; during this period, the polyphenols are enzymatically oxidized. Oolong tea is considered an intermediate stage of enzymic oxidation of black tea.

TEA ANTIOXIDANTS AS CHEMOPREVENTIVE AGENTS: EXPERIMENTAL STUDIES

Protection Against Carcinogenesis of the Skin

In recent years, a wide range of studies using several tumor bioassay protocols have demonstrated that topical application or oral feeding of a polyphenolic fraction isolated from green tea (GTP), a water extract of green tea (WEGT), a water extract of black tea (WEBT), and individual epicatechin derivatives present in green tea, show anticarcinogenic effects in the mouse skin model (Table I).

Studies were conducted in the two-stage skin carcinogenesis mouse model to assess the anticarcinogenic potential of tea polyphenols against tumor initiation, promotion, and progression stages of carcinogenesis. Topical application of GTP to 3-methylcholanthrene- or 7,12-dimethylbenz(*a*)anthracene (DMBA)-initiated SENCAR, CD-1 and BALB/C mouse skin results in significant protection against skin tumorigenesis [7–9]. Similarly, oral feeding of GTP, and topical application of EGCG prior to DMBA initiation followed by promotion with 12-O-tetradecanoylphorbol-13-acetate (TPA), resulted in significant protection against skin tumor initiation in SENCAR mouse skin [10]. Topical application of varying doses of GTP to DMBA-initiated and TPA-promoted SENCAR or CD-1 mouse skin resulted in significant protection against skin tumor promotion in a dose-dependent manner [9,11]. The protection by GTP was observed in terms of lower tumor body burden, number of tumors per animal, tumor volume per mouse, and average tumor size [9,11]. Topical application of GTP or EGCG has been shown to inhibit tumor promotion mediated by TPA, teleocidin and okadaic acid in mouse skin [9,11–13]. Katiyar et al. [14,15] have shown that topical application of GTP prior to tumor promoters in DMBA-initiated mouse skin results in protection against both stage I and stage II

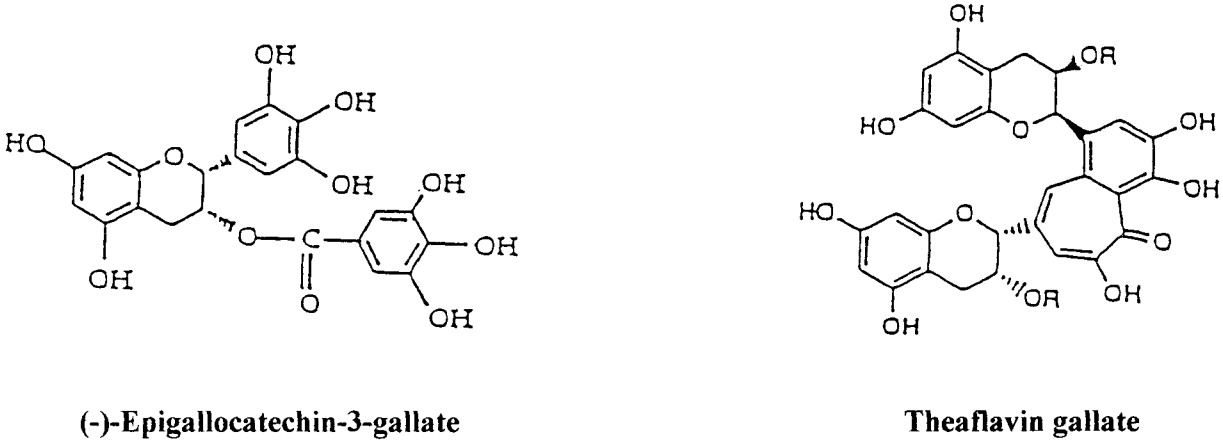

Fig. 1. Chemical structures of major tea polyphenols. Epigallocatechin-3-gallate found in green tea, and theaflavin gallate in black tea. The phenolic groups are responsible for antioxidant potential. R = galloyl group.

TABLE I. Summary of Studies Demonstrating Chemopreventive Effect of Tea Against Skin Tumorigenesis in Mouse

Tumorigenesis protocol	Mouse strain	Carcinogen	Promotor	Treatment	Mode of treatment[a]	Ref.
Initiation	SENCAR	DMBA	TPA	GTP	t, dw	[8]
	SKH-1	UVB	TPA	WEGT	dw	[18]
	CD-1	B[*a*]P,DMBA	TPA	GTP	t	[9]
Promotion	SENCAR	DMBA	TOPA	GTP	t	[11]
	CD-1	DMBA	TPA	GTP	t	[9]
	CD-1	DMBA	Teleocinidin, Okadaic acid	EGCG, GTP WEGT/WEBT	t	[12,13] [18,19]
	SKH-1	DMBA	TPA, UVB	GTP	dw	[14]
Stage I/II	SENCAR	DMBA	TPA/Mezerein		t	
Initiation + promotion	BALB/C	UVB	UVB	EGCG	t	[20]
	BALB/C	3-MC	—	GTP	t	[8]
	SKH-1	UVB	UVB	GTP	t, dw	[17]
Progression	SENCAR	BPO[b], 4-NQO[b]	—	GTP	t	[15]
	SKH-1	DMBA	UVB	WEGT/T DWWEBT	dw	[19]
Chemotherapeutic	CD-1	DMBA	TPA	GTP/WEBT/EGCG	dw/ip	
	CD-1	UVB	TPA	GTP/WEGT/EGCG	dw	[16]

[a]Varying doses; t, topical; dw, drinking water; ip, intraperitoneal.
[b]Used as malignant enhancer.

TABLE II. Summary of Chemopreventive Effect of Oral Feeding of WEGT, GTP, and EGCG in Drinking Water Against Chemical Carcinogen-Induced Tumorigenesis in Different Tumor Models

Tumor model	Carcinogen administered	Treatment	Reference
Lung/forestomach	DEN, B[*a*]P	GTP/WEGT	[21,22]
Lung	NNK	WEGT, EGCG, WEGT[a]	[23–25]
Duodenum	ENNG	EGCG	[27]
Esophagus	NMBA	WEGT	[26]
Colon	AOM	GTP	[30]
Mammary gland	DMBA	GTP	[36]
Small intestine	Multiple[b]	GTP	[29]
Liver	Aflatoxin B1, DEN/NNK	GTL*	[32–34]
Pancreas	NBA[c]	WEGT	[37]

[a]Decaffeinated.
[b]In multi-organ carcinogenesis model, DEN, NNK, 1,2-dimethylhydrazine, *N*-butyl-*N*-(hydroxybutyl)nitrosamine, *N*-methylnitrosamine, and 2,2′-dihydroxy-di-*n*-propylnitrosamine were used as carcinogens.
[c]*N*-nitroso-bis(2-oxopropyl)amine.
*GTL, green tea leaves.

tumor promotion, and also demonstrated that topical application of GTP inhibits the benzoyl peroxide- and 4-nitroquinoline-*N*-oxide-enhanced malignant progression of non-malignant lesions. Wang et al. [16] showed that consumption of WEGT or GTP, in addition to decreasing tumor formation and multiplicity, also markedly reduced tumor size. They also demonstrated that WEGT, or GTP or EGCG given intraperitoneally, inhibited tumor growth and caused partial regression of established skin papillomas [16]. Chronic oral feeding of GTP in drinking water or its topical application before UVB radiation exposure afforded protection against photo carcinogenesis in SKH-1 hairless mice [17,18]. Wang et al. [19] showed that oral consumption of water extract of either black tea, green tea, or decaffeinated tea by SKH-1 hairless mice prior and/or during UVB exposure reduces the risk of photo carcinogenesis. Recently, Gensler et al. [20] have shown that the induction of skin tumors by UV radiation was significantly reduced by topical, but not by oral, administration of purified EGCG. Collectively, these data obtained from multistage mouse skin models suggest that green and black tea components, particularly polyphenols present therein, possess significant chemopreventive effects against each stage of skin carcinogenesis; these polyphenols may be useful

against skin exposure to chemical carcinogens and tumor promoters as well as solar radiation.

Protection Against Carcinogenesis in Internal Organs

In addition to preventive effects against skin carcinogenesis, several studies have assessed whether tea polyphenols are protective against carcinogenesis induced in internal organs (Table II). Oral consumption of WEGT (2.5%, w/v) or GTP (0.2%, w/v) by female A/J mice as the sole source of drinking water significantly reduced the induction of diethylnitrosamine (DEN, 20 mg/kg body weight)- and benzo[*a*]pyrene (B[*a*]P, 2 mg/animal)-induced forestomach and lung tumorigenesis [21]. This protective effect by WEGT or GTP was observed at all stages of carcinogenesis, i.e., initiation, promotion, and in complete carcinogenesis protocols, in terms of total number of tumors per mouse in forestomach or lung [21]. In further studies, we also demonstrated that the administration of GTP (5 mg/animal) by gavage, 30 minutes prior to challenge with carcinogen, afforded significant protection against both DEN- and B[*a*]P-induced forestomach and lung tumorigenesis in A/J mice [22]. Wang et al. [23] showed that oral feeding of WEGT or WEBT (0.6–1.2%, w/v) to A/J mice prior to or after challenge with DEN- or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) resulted in significant protection in terms of lung tumor incidence and multiplicity. Xu et al. [24] showed the protective effect of EGCG against NNK-induced lung tumorigenesis in A/J mice. Shi et al. [25] found that when decaffeinated green or black tea extracts were given to A/J mice as the sole source of drinking water, a significant reduction in NNK-induced lung tumor multiplicity was observed.

Chen [26] reported that oral administration of 2% tea infusion as the sole source of drinking water to rats resulted in inhibition of esophageal tumorigenesis induced by *N*-nitroso-methylbenzylamine (NMBA). Fujita et al. [27] and Fujiki et al. [28] provided information about the chemopreventive effect of EGCG against *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine (ENNG)-induced duodenum tumorigenicity in C57BL/6 mice. Oral feeding of EGCG (0.005%) in the drinking water resulted in significant protection against ENNG-caused tumor promotion in duodenum in terms of tumor incidence and number of tumors per mouse. Hirose et al. [29] demonstrated that the diet, supplemented with 1% GTP given during or after the carcinogen exposure period, inhibited adenoma and adenocarcinoma formation in the small intestine of F344 rats in the multiorgan carcinogenesis model. In a rat colon carcinogenesis model, Yamane et al. [30] demonstrated the inhibition of azoxymethane-induced colon carcinogenesis by oral feeding of GTP (0.01 or 0.1%, w/v) in drinking water in Fisher rats, while Narisawa and Fukaura [31] found that even a very low dose of GTP in drinking water can prevent *N*-methyl-*N*-nitroso urea (MNU)-induced colon carcinogenesis in F344 rats. Chen et al. [32] provided evidence that 5% green tea leaf in the diet resulted in significant inhibition of aflatoxin B_1-induced hepatocarcinogenesis. Li [33] has shown that 2.5% green tea leaf in the diet given to rats produced significant protection against DEN-induced hepatocarcinogenesis. Decaffeinated black tea extract given by oral gavage to male Swiss mice was found to reduce tobacco-induced liver tumors [34]. Recently, Matsumoto et al. [35] reported an inhibitory effect of tea catechins, black tea extract, and oolong tea extract on the development of hepatocarcinogenesis in rat.

Hirose et al. [36] reported the inhibitory effect of 1% green tea catechins on mammary gland carcinogenesis in female Sprague-Dawley rats pretreated with DMBA. In these experiments, the average size of the palpable mammary tumors was significantly smaller in the green tea catechins-fed group in comparison to the non-catechin-fed group of animals. Harada et al. [37] showed that dietary supplementation with GTP can inhibit *N*-nitroso-bis(2-oxopropyl)amine-induced pancreatic tumorigenesis in Syrian golden hamsters. These experimental studies amply demonstrate that polyphenolic antioxidants present in tea are capable of affording protection in various animal tumor bioassay systems, and suggest that emphasis should be placed on clinical trials exploring the usefulness of tea polyphenols as a chemopreventive agent in humans.

TEA ANTIOXIDANTS AS CHEMOPREVENTIVE AGENTS: MECHANISTIC STUDIES

Tea and its polyphenolic constituents have been shown to inhibit carcinogenesis by several mechanisms. The underlying mechanisms of carcinogenesis have a number of distinct elements, which may operate selectively in spe-

cific instances or may have a very broad impact through several overall actions. Early steps in carcinogenesis (initiation) involve the action of genotoxic carcinogens on the genetic material of the cell, yielding specific DNA adducts, which give rise to mutations in protooncogenes or in tumor suppressor genes [38,39]. During carcinogen activity, oxidation mechanisms can operate due to the production of active oxygen species, leading to the formation of 8-hydroxy-deoxyguanosine in DNA and 8-hydroxyguanosine in RNA. Xu et al. [24] demonstrated that NNK-induced lung tumorigenesis has been reduced by 50% in mice given green tea extract in drinking water. It was also observed that the level of 8-hydroxy-deoxyguanosine paralleled the tumor incidence data and was lower in mice drinking green tea [24]. Tea antagonizes the action of NNK by reducing metabolism-generating active oxygen species. Tea polyphenols and a number of other plant antioxidants were antagonistic to the formation of 8-hydroxy-deoxyguanosine, or increased repair of this lesion, or they decreased oxidative damage to endothelial cells [reviewed in 38].

Tea Antioxidants Inhibit Mutagenicity and Genotoxicity

GTP and WEGT were found to significantly inhibit the mutagenicity induced by B[*a*]P, aflatoxin B_1, 2-aminofluorene, and methanol extract of coal tar pitch in bacterial or mammalian cell test systems [40]. Jain et al. [41] showed that tea extracts inhibited *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)-induced mutagenicity in vitro as well as in the intragastric tract [NBA] of rats. Oral feeding of green tea or black tea extracts to rats was shown to inhibit chromosomal aberrations in rat bone marrow cells if the extracts were given 24 hours prior to aflatoxin B_1 treatment [42]. Recently, Kuroda [43] reported the antimutagenic effects of green tea catechins on induction of 6-thioguanine-resistant mutations induced by 4-nitroquinoline 1-oxide in cultured Chinese hamster V79 cells. This study suggests that the antimutagenic effects of catechins may act intracellularly as a bio-antimutagenic blocking agent or suppressive agent.

Frying or grilling meat forms a new class of genotoxic carcinogens, heterocyclic amines (HCAs), thought to be associated with such cancers as the breast, colon, or pancreas in meat-eating populations [44]. Weisburger et al. 1994 (44) studied the effect of black and green tea, and of the tea polyphenol theaflavine gallate (black tea) and EGCG (green tea), on the formation of typical HCAs, 2-amino-3,8-dimethylimidazo [4,5-f]quinoxaline, and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, using the model in vitro systems of Jagerstad. This study revealed that green tea, black tea, and the associated tea polyphenols decrease the formation or expression of genotoxicity of such HCAs in the model system, suggesting that tea polyphenols may be another approach to lower the formation of HCAs and their associated cancer risk [44].

Tea Antioxidants Inhibit Biochemical Markers of Tumor Initiation: Cytochrome P-450-Dependent Metabolism

Cytochrome P-450 (P-450) is the major enzyme system responsible for the metabolism of procarcinogens to their DNA-binding metabolites. This binding to DNA is considered essential for tumor initiation [45,46]. We studied the interaction of GTP and its constituent polyphenols, (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and EGCG with P-450 and associated mono-oxygenase activities [47]. The addition of EC, EGC, ECG, EGCG, and GTP to microsomes prepared from rat liver resulted in a dose-dependent inhibition of P-450-dependent arylhydrocarbon hydroxylase, 7-ethoxycoumarin-O-deethylase, and 7-ethoxyresorufin-O-deethylase activities [47]. This study also showed that epidermal arylhydrocarbon hydroxylase activity and epidermal enzyme-mediated binding of B[*a*]P and DMBA to DNA was inhibited by these polyphenols [47]. Sohn et al. [48] found significant increase in P-450 1A1, 1A2, and 2B1 activities in liver of rats drinking green tea or black tea; no change in P450, 2E1, and 3A4 activities occurred. Of the phase II enzymes, UDP-glucuronyltransferase increased, but glutathione-*S*-transferase did not [48]. Shi et al. [25] have shown that EGCG inhibited the catalytic activities of several P450 enzymes and was more potent against P450 1A and 2B1 than 2E1. Bu-Abbas et al. [49] used aqueous extracts of tea (2.5%, w/v) as the sole source of drinking water to rats for 4 weeks and determined hepatic cytochrome P450 activity by using chemical probes with selectivity for particular isoforms. Feeding of green tea gave rise to an increase in the levels of CYP1A2 and CYP4A1.

Collectively, these studies show that the administration of tea extract or tea constituents to rodents results in inhibition and induction of various P450s, the resultant effect of which may affect cancer outcomes in a preventive manner.

Tea Antioxidants Inhibit Biochemical Markers of Tumor Promotion

Application of 12-0-tetradecanoylphoybol-13-acetate (TPA) on mouse skin results in induction of ornithine decarboxylase (ODC) activity followed by an increase in the levels of polyamines, epidermal hyperplasia, inflammation, and increase in the number of dark basal keratinocytes [11]. It has not been established which of these parameters or many others are obligatory or sufficient for the process of tumor promotion. The induction of inflammation in skin mediated by TPA is believed to be governed by cyclo-oxygenase and lipoxygenase catalyzed metabolites of arachidonic acid, specifically prostaglandins and hydroxyeicosatetraenoic acids respectively [50,51]. The importance of induction of epidermal ODC, cyclo-oxygenase, and lipoxygenase activities in skin tumor promotion is evident; several inhibitors of these enzymes inhibit the tumor promotion in murine skin [50,51, and references therein].

Topical application of GTP to mouse skin was found to inhibit TPA and several other structurally different mouse skin tumor promoter-mediated inductions of epidermal ODC activity in a dose-dependent manner [52]. Prior application of GTP on mouse skin treated with TPA resulted in significant inhibition of TPA-induced epidermal edema and hyperplasia [11,53]. As quantitated by the formation of prostaglandins and hydroxyeicosatetraenoic acid metabolites from cyclo-oxygenase- and lipoxygenase-catalyzed (respectively) metabolism of arachidonic acid, skin application of GTP to SENCAR mice was also found to result in significant inhibition of TPA-caused effects on these two enzymes [11]. Inhibition of all of these pathways alone or in combination may contribute to overall anti-tumor promoting effects of tea polyphenols.

Tea Antioxidants Enhance Detoxification Enzymes Activity

We showed that topical application or oral administration of GTP to SENCAR mice inhibited carcinogen-DNA adduct formation in epidermis after topical application of [^{3}H]B*a*P or [^{3}H]DMBA [8]. We also showed that chronic oral administration of 0.2% GTP in drinking water to mice for 4 weeks significantly enhanced glutathione peroxidase, catalase, NADPH-quinone oxidoreductase, and glutathione-*S*-transferase (GST) activities in small bowel, lung, and liver [54]. These enzymatic pathways play a role in detoxifying carcinogenic metabolite formation by P-450 and other enzymes; the ability of tea antioxidants to inhibit enzymatic pathways that are a key determinant for cancer initiation may have a chemopreventive effect against carcinogenesis [5,6,54]. Phase II enzyme GST not only catalyses the conjugation of both hydroquinones and epoxides of PAH with reduced glutathione for their excretion, but also shows low activity toward organic hydroperoxides for their detoxification from cells/tissue [55]. These findings suggest that tea may reduce carcinogenesis by raising the level of detoxifying enzymes.

Tea Antioxidants and Free Radical Scavenging Activity

The generation of reactive oxygen species in biological systems, either by normal metabolic pathways or as a consequence of exposure to chemical carcinogens, contributes to the multistage process of carcinogenesis [50]. Several reports suggest that peroxides and superoxide anion ($^{\cdot}O_{2-}$) produce cytotoxicity/genotoxicity in the cellular systems [56]. The source of hydrogen peroxide (H_2O_2) in cells/tissues is mainly through superoxide dismutase-mediated dismutation of $^{x}O_{2-}$, which is generated in the cells/tissues by endogenous enzyme systems as well as by the nonenzymatic pathways [56]. In addition, the highly reactive hydroxy radical (^{x}OH) generated from H_2O_2 is known to damage DNA to produce pathological alterations [56]. Cancer chemoprevention studies have shown that the levels of antioxidant enzymes are elevated in various organs of the test animals following administration of chemopreventive agents [55]. Compared to that observed in non-GTP-fed control group of mice, the oral feeding of GTP in mouse drinking water significantly increased glutathione peroxidase, catalase, and quinone reductase (QR) activities in small bowel, liver, and lungs, and GST activity in small bowel and liver [54]. In another study, Katiyar et al [21] reported that feeding WEGT (2.5%) or GTP (0.2%) in drinking water with DEN or B[*a*]P to

female A/J mice significantly enhanced GST activity in liver and small bowel and QR activity in small bowel, lung, and stomach, compared to only DEN- or B[*a*]P-treated animals, perhaps contributing to the chemopreventive effects observed with tea polyphenols.

Extensive experimental data show that anticarcinogenic properties of tea are due to multifactorial antioxidative effects of epicatechin derivatives (ECDs, polyphenols) present therein. Katiyar et al. [57] found that EGCG, EGC, and ECG from green tea significantly inhibits Fe^{3+}/ADP-supported spontaneous lipid peroxidation in mouse epidermal microsomes. Each of these ECDs was also effective in inhibiting photoenhanced lipid peroxidation generated by incubating epidermal microsomes in the presence of photosensitizer, silicon phthalocyanine, and at 650 nm irradiation. At equimolar basis, EGCG, which is also the major constituent in GTP, showed maximum inhibitory effects compared to other ECDs. This study provides evidence for the antioxidative property of ECDs. Terao et al. [58] also showed the antioxidative property of EC and ECG by measuring the inhibition of lipid peroxidation in large unilamellar liposomes composed of egg yolk phosphatidylcholine. This study provided the evidence that EC and ECG serve as powerful antioxidants against lipid peroxidation when phospholipid bilayers are exposed to aqueous oxygen radicals [58]. Oral administration of green tea inhibited the formation of 8-hydroxydeoxyguanosine in mice [24], and topically treated GTP inhibited TPA-induced hydrogen peroxide formation [55]. Tea polyphenols may inhibit carcinogenesis through their antioxidative activities supported by finding that (+)-catechin inhibited NNK-induced DNA single-strand breaks in rat hepatocytes [6]. Recently, Miller et al. [59] reported the antioxidative properties of black tea polyphenols by investigating their abilities to scavenge free radicals in the aqueous and lipophilic phases. The results show that the hierarchy of reactivity of the compounds as antioxidants is: theaflavine digallate $>$ 3′-monogallate $=$ 3-monogallate $>$ theaflavine. The antioxidative property of these tea polyphenols also explains why tea polyphenols are strong scavengers against superoxide anion radicals and hydroxy radicals—two major reactive oxygen species that can damage DNA and other cellular molecules and can initiate lipid peroxidation reactions. Tea polyphenols can also react with peroxy radicals and thus terminate lipid peroxidation chain reactions. Reactive oxygen species play important roles in carcinogenesis by damaging DNA, altering gene expression, or affecting cell growth and differentiation [60].

SUMMARY

The goal of reducing cancer occurrence has put the role of dietary factors in cancer prevention under intensive investigation in many laboratories around the world. Evidence from epidemiological studies and experiments in laboratory animals suggest that food consumed by the general population contains certain ingredients that may reduce the incidence of cancer. These ingredients are collectively known as chemopreventive agents. The mode of action of most of these chemopreventive agents is still unknown, although many of them are antioxidants. This article suggests that tea polyphenols have significant potential as cancer chemopreventive agents against chemical carcinogen- or UV radiation-induced skin as well as carcinogenesis in internal body organs, such as stomach, lung, liver, pancreas, esophagus, duodenum, breast, and colon, when assessed in specific tumor bioassay models. On the basis of available information on anticarcinogenic potential of tea antioxidants, appropriate strategies could be framed for future clinical chemoprevention trials to translate animal data to human cancer risk.

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