Green Tea in Chemoprevention of Cancer

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The concept of prevention of cancer using naturally occurring substances that could be included in the diet consumed by the human population is gaining increasing attention. Tea, next to water, is the most popularly consumed beverage in the world and it is grown in about 30 countries. Abundant data, amassed from several laboratories around the world in the last ten years, provided convincing evidence that polyphenolic antioxidants present in tea afford protection against cancer risk in many animal-tumor bioassay systems. The epidemiological studies, though inconclusive, have also suggested that the consumption of tea is associated with a lowered risk of cancer. Much of this work has been done on green tea; less is known about black tea. Green tea contains many polyphenolic antioxidants, and (–)-epigallocatechin-3-gallate (EGCG) is the key polyphenolic antioxidant believed to be responsible for most of the cancer chemopreventive properties of green tea. This review will discuss these effects and the molecular mechanisms associated with the biological response to green-tea polyphenols.

Key Words: green-tea polyphenols; epigallocatechin-3-gallate (EGCG); cancer; chemoprevention.

Chemoprevention has emerged as a practical approach to reducing cancer incidence and therefore the mortality and morbidity associated with it. At present, at least 30 different groups of agents are known, from laboratory studies, to have cancer chemopreventive properties. Some of these agents are also showing promise in epidemiological studies (Challa *et al*., 1997; Chung *et al*., 1998; Dragsted *et al*., 1993; Kelloff *et al*., 1996; Pezzuto, 1997). One such group of agents is known as "polyphenols." Tea, next to water, is the most popular beverage consumed by humans, and it contains polyphenolic constituents known as "catechins" (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996). The anti-carcinogenic and anti-mutagenic activity of polyphenolic agents present in green tea were first reported almost a decade ago (Khan *et al*., 1988, Wang *et al*., 1989a,b). Green tea is derived from *Camellia sinensis,* an evergreen shrub of the *Theaceae* family. Tea, for many generations, has been considered to possess health-promoting potential in some parts of the world (Weisburger *et al*., 1997). Epidemiological studies, though inconclusive, suggest that the consumption of green tea is associated with a lower risk of cancer. The majority of studies assessing the usefulness of tea

in prevention of cancer have been conducted with green tea, whereas in a few studies, the chemopreventive potential of black tea has also been assessed (Katiyar and Mukhtar, 1996; Ahmad *et al.*, 1998). Based on studies in cell culture, laboratory animals, and epidemiological observations, clinical trials of green tea consumption and cancer risk have been initiated. The major polyphenolic antioxidants that are thought to be responsible for the cancer chemopreventive potential of green tea include (–)-epicatechin (EC), (–)-epigallocatechin (EGC), (–)-epicatechin-3-gallate (ECG), and (–)-epigallocatechin-3-gallate (EGCG). Among these, EGCG is believed to be the most protective agent (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996).

History of Tea Consumption

The plant *Camellia sinensis* was originally discovered and grown in Southeast Asia thousands of years ago, and according to the Chinese mythology, the emperor Shen Nung discovered tea for the first time in 2737 BC (Harbowy and Balentine, 1997). Since then, the popularity of this beverage has increased to a point where, at present is, next only to water, the most popular beverage around the world. The per capita worldwide consumption is approximately 120 ml brewed tea per day (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996). Tea is currently grown and cultivated in at least 30 countries around the world (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996). Many types of tea preparations, originating from the same plant source (*Camellia sinensis*) but having different processing methods, are consumed today. The three most popular major tea types include black tea (78%, mainly consumed in Western and some Asian countries), green tea (20%, mainly consumed in Asia, and a few countries in North Africa and the Middle East), and oolong tea (2%, consumed in some parts of China and Taiwan) (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996).

Tea and Cancer Chemoprevention

A number of studies in laboratory animals in various target-organ bioassay protocols, conducted in many laboratories around the world, have provided convincing evidence that the polyphenolic antioxidants present in tea are capable of affording protection against cancer initiation and its subsequent development (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996). Data from various epidemiological studies conducted in dif-

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ferent populations, though inconclusive, were considered to be of sufficient merit to embark on clinical trials evaluating the association of green tea consumption with cancer risk (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996; Kohlmeier *et al*., 1997).

Oral consumption or topical applications of green tea and/or its polyphenolic constituents have been show to afford protection against chemical carcinogen- as well as ultraviolet radiation- induced skin carcinogenesis in the mouse model (Mukhtar *et al*, 1994). In many other animal studies, the polyphenolic fraction-isolated green tea, the water extract of green tea, or individual polyphenolic antioxidants present in green tea have also been shown to afford protection against chemically induced carcinogenesis in lung, liver, esophagus, forestomach, duodenum, pancreas, colon, and breast (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996). Based on recent studies, it is now believed that much of the cancer chemopreventive properties of green tea are mediated by (–)-epigallo-catechin-3-gallate (EGCG) (Ahmad *et al*., 1998; Katiyar and Mukhtar 1996). It is appreciated that other polyphenolic agents present in green tea also contribute to its cancer chemopreventive efficacy. However, it is not clear whether all the polyphenolic compounds of green tea work through a similar biochemical pathway or by different mechanisms.

An ideal chemopreventive agent for human use should have little or no toxicity, high efficacy in multiple sites, capability of oral consumption, a known mechanism of action, low cost, and human acceptance. A single cup of brewed green tea contains up to 400 mg of polyphenolic antioxidants, of which 200 mg is EGCG. It is also interesting to observe that at present, many available consumer products such as drinks, ice creams, healthcare products, and cosmetics are supplemented with green tea extracts.

Bioavailability of Tea Polyphenols

The bioavailability of the active polyphenolic constituents, after tea consumption by laboratory animals and humans, is poorly defined. Yang *et al* (1998) conducted a study in 18 individuals who were given different amounts of green tea, and plasma concentrations and urinary excretion of tea catechins were measured as a function of time. After consuming 1.5, 3.0, or 4.5 g of decaffeinated green tea (in 500 ml of water), the maximum plasma concentrations (C_{max}) of EGCG, EGC, and EC were found to be 326 ng/ml, 550 ng/ml, and 190 ng/ml respectively, as observed at 1.4–2.4 h after ingestion of the tea preparation. When the dose was increased from 1.5 to 3.0 g, the C_{max} values were found to increase by 2.7–3.4-fold, but further increasing the dose to 4.5 g did not increase the C_{max} values significantly, suggesting a saturation phenomenon. At all the concentrations employed, the half-life of EGCG was found to be longer than the half-life of EGC or EC. EGC and EC, but not EGCG were excreted in urine, and it was demonstrated that 90% of the total urinary EGC and EC were excreted within 8 h.

When the tea dosage was increased, the amount of EGC and EC excretion also increased, but a clear dose-response relationship was not observed. This study provided basic pharmacokinetic parameters of green tea polyphenols in humans, which may be used to estimate the levels of these compounds after drinking green tea.

Recently, Saganuma *et al* (1998) studied the distribution of radiolabeled [^{3}H]EGCG in mouse organs following oral administration. Radioactivity was found in many organs, including those where inhibition of carcinogenesis by EGCG or green tea extract has already been shown. These results suggested that frequent consumption of green tea enables the body to maintain a high level of tea polyphenols. These studies may be useful in designing future strategies aiming towards the development of green tea as a practical chemopreventive agent.

Mechanism(s) of Biological Effects of Green Tea

Initial Mechanistic Studies

A proper understanding of mechanisms of the biological effects imparted by green tea is essential, as it may be helpful in designing and improving the strategies for cancer chemoprevention. The initial mechanistic attempts in this direction were largely focused on assessing the effect of green tea polyphenols on the following:

- prevention against mutagenicity and genotoxicity of chemicals
- reduction in biochemical markers of tumor initiation
- reduction in biochemical markers of tumor promotion
- regulation of detoxification enzymes
- trapping of activated metabolites of carcinogens
- regulation of antioxidant and free-radical scavenging activity (Katiyar and Mukhtar, 1996).

Molecular Mechanisms

A summary of the research work conducted to decipher the molecular mechanisms involved with the biological responses of green tea polyphenols is given below.

Green tea polyphenols activate the mitogen-activated protein kinase (MAPK) pathway. The protective effects of green tea polyphenols have been attributed to the inhibition of enzymes such as the cytochromes P450, which are involved in the bio-activation of carcinogens (Yu *et al*., 1997). Some other *in vivo* studies have also demonstrated the involvement of Phase II detoxification enzymes during the biological response to green tea. Because the 5′ flanking regions of Phase II genes contain an antioxidant-responsive element (ARE) which is believed to mediate the induction of Phase II enzymes by many drugs, the involvement of the MAPK pathway was studied as a mechanism of biological response to green tea polyphenols. This study demonstrated that the activation of the MAPK pathway might be due to a potential signaling pathway involved in the regulation of ARE-mediated phase II enzyme

gene expression (Yu *et al*., 1997). It was also demonstrated that green tea polyphenol treatment of human hepatoma (HepG2) cells transfected with a plasmid construct containing ARE and a minimal glutathione S-transferase Ya promoter linked to the chloramphenicol acetyltransferase (CAT) reporter gene causes an induction of CAT activity. This result suggests that green tea polyphenols stimulate the transcription of Phase II detoxifying enzymes through ARE. Green tea polyphenol treatment also resulted in a significant activation of MAPK, extracellular, signal-regulated kinase 2 (ERK2), as well as c-*Jun* N-terminal kinase 1 (JNK1) and an increase in the mRNA levels of early response genes c-*jun* and c-*fos*.

EGCG inhibits urokinase activity. Recently, it was proposed that the anti-cancer activity of EGCG is associated with the inhibition of urokinase, which is one of the most frequently expressed enzymes in human cancers (Jankun *et al*., 1997). Through the use of computer-based molecular modeling, it was demonstrated that EGCG binds to urokinase, blocking the histidine 57 and serine 195 of urokinase catalytic triad and extending towards arginine 35 from a positively charged loop of urokinase. These calculations were verified by assessing the inhibition of urokinase activity by the spectrophotometric amidolytic assay. However, the practicability of this study with achievable dose levels was later challenged by Yang (1997).

Green tea induces apoptotic cell death and arrest of the cell cycle. Because the life span of both normal and cancer cells within a living system is significantly affected by the rate of apoptosis (Fesus *et al*., 1995), chemopreventive agents that could modulate apoptosis might affect the steady-state cell population. On one hand, several cancer chemopreventive agents induce apoptosis, but on the other hand, the tumor-promoting agents are found to inhibit apoptosis (Boolbol *et al*., 1996; Mills *et al*., 1995; Wright *et al*., 1994). Therefore, it can be assumed that the chemopreventive agents with proven effects in animal tumor bioassay systems and/or human epidemiology, and the ability to induce apoptosis of cancer cells, may have wider implications for the management of cancer. At present, only a limited number of chemopreventive agents are known to cause apoptosis (Jee *et al*., 1998; Jiang *et al*., 1996). In our laboratory, we showed that EGCG induces apoptosis and cell cycle arrest in human epidermoid carcinoma (A431) cells (Ahmad *et al*., 1997). Importantly, this apoptotic response was specific for cancer cells, since EGCG treatment also resulted in the induction of apoptosis in human carcinoma keratinocytes HaCaT, human prostate carcinoma cells DU145, and mouse lymphoma cells LY-R, but not for normal human epidermal keratinocytes.

Another study (Chen *et al*., 1998) compared the effect of EGCG on the growth of SV40 virally transformed human fibroblasts (WI38VA) with that of normal WI38 cells. In this study, EGCG was found to inhibit the growth of the transformed WI38VA cells, but not of their normal counterparts. This study further demonstrated a similar differential growth inhibitory effect of EGCG between human colorectal cancer (Caco-2) cells, breast cancer (Hs578T) cells, and their respective normal counterparts. EGCG treatment also induced apoptosis, and enhanced serum-induced expression of c-*fos* and c-*myc* genes in transformed WI38VA cells, but not in the normal WI38 cells. This study suggested that the differential modulation of certain genes such as c-*fos* and c-*myc*, could be responsible for these differential responses of EGCG.

In another study (Fujiki *et al*., 1998), it was demonstrated that EGCG and other tea polyphenols inhibit growth of human lung cancer (PC-9) cells with a G2/M phase arrest of the cell cycle. This study demonstrated that [^{3}H]EGCG, administered by po intubation into the mouse stomach, results in small amounts of ^{3}H-activity in many organs such as skin, stomach, duodenum, colon, liver, lung, and pancreas, where EGCG and green tea extract have been shown to have anticarcinogenic effects. In this study, the involvement of the tumor necrosis factor (TNF)-α pathway was suggested as a mechanism of EGCG-mediated biological responses.

In another study by Yang *et al* (1998), the growth inhibitory effects of green tea polyphenols were investigated using 4 human cancer cell lines. Growth inhibition was measured by ^{3}H-thymidine incorporation after 48 h of treatment. EGCG and EGC displayed strong growth inhibitory effects against lung-tumor cell lines H661 and H1299, with estimated IC$_{50}$ values of 22 μM, but were less effective against lung-cancer cell line H441 and colon-cancer cell line HT-29 with IC$_{50}$ values 2- to 3-fold higher. ECG was found to have lower activities whereas EC was even less effective. In this study, exposure of H661 cells to a dose of 30 μM EGCG, EGC, or theaflavins for 24 h resulted in a dose-dependent apoptosis. The incubation of H661 cells with EGCG also resulted in a dose-dependent formation of H$_2$O$_2$. Addition of H$_2$O$_2$ to H661 cells resulted in an apoptotic response similar to EGCG. EGCG-induced apoptosis in H661 cells was found to be completely inhibited by exogenously added catalase (50 units/ml). This inhibition suggests that tea polyphenol-mediated H$_2$O$_2$ production results in apoptosis of the cells, contributing to the growth inhibitory potential of tea polyphenols *in vitro*. In this study, the involvement of H$_2$O$_2$, as well as the effect of catalase, was an intriguing observation because the tea polyphenols are generally regarded as antioxidants. The explanation provided by the authors is that tea polyphenols also possess pro-oxidative activities (Yang *et al*., 1998).

EGCG inhibits cellular proliferation and tumor progression via epidermal growth factor receptor (EGFR) pathway. The activation of the epidermal growth factor receptor (EGFR) tyrosine kinase by its ligand is believed to initiate multiple cellular reponses associated with cell proliferation on one hand. The over-expression of EGFR is shown to produce neoplastic phenotype on the other hand. Based on these facts, a recent study by Liang *et al*. (1997) demonstrated that EGCG significantly inhibits both DNA synthesis and the protein ty-

rosine kinase activities of EGFR, platelet-derived growth-factor receptor (PDGFR), and fibroblast growth-factor receptor (FGFR), but not of pp60^{v-src}, protein kinase C (PKC), or protein kinase A (PKA), in A431 cells. EGCG was also found to inhibit the auto-phosphorylation of EGFR by EGF and to block the binding of EGF to its receptor. This study suggested that EGCG might inhibit tumor development by blocking the EGFR-pathway.

EGCG inhibits the induction of nitric oxide (NO)-synthase via a down-regulation in the transcription factor nuclear factor-κB (NFκB). Nitric oxide (NO) is a bioactive molecule that plays an important role in inflammation and carcinogenesis, and in a recent study, Lin and Lin (1997) assessed the effects of green tea polyphenols on the modulation of NO-synthase in thioglycollate-elicited and lipopolysaccharide (LPS)-activated peritoneal macrophages. Gallic acid (GA), EGC, and EGCG were found to inhibit the protein expression of inducible NO-synthase as well as the generation of NO. This study further demonstrated that EGCG inhibits the activation of the transcription factor NFκB, an event that is believed to be associated with the induction of inducible NO-synthase (iNOS). Taken together, these data suggested that EGCG may block the early event of NO-synthase induction via inhibiting the binding of transcription NFκB to the iNOS promoter, thereby, inhibiting the induction of iNOS transcription. The theory of involvement of NO in the biological response of EGCG was strengthened by another study by Chan et al. (1997), who demonstrated that EGCG causes an inhibition of lipopolysaccharide (LPS)- and interferon (IFN)-γ-activated iNOS mRNA expression in a cell-culture system. EGCG was also found to inhibit the enzyme activities of iNOS and neuronal NO-synthase (nNOS).

Peroxynitrite (OONO) is a highly toxic oxidizing and nitrating species that is produced *in vivo* via a reaction between superoxide radical (O^2-) and NO. In another study, Pannala *et al* (1997) demonstrated the ability of green tea polyphenols, *viz.*, catechin, epicatechin, ECG, EGC, and EGCG to (i) inhibit OONO-mediated tyrosine-nitration, and (ii) limit surface charge alteration of low density lipoprotein (LDL). In this study, all the compounds tested were found to be potent OONO scavengers, as they were effective in preventing the nitration of tyrosine. These polyphenols were also found to protect against OONO-mediated LDL modification.

EGCG inhibits tumor promoter-mediated activator protein-1 (AP-1) activation, and cell transformation. Because many studies have suggested recently that the activation of AP-1 plays an important role in tumor promotion, the down-regulation of this transcription factor is now thought to be a general therapeutic strategy against cancer (McCarty, 1998). In a recent study (Dong *et al.*, 1997) employing the JB6 mouse epidermal cell line, an extensively used in vitro model system for tumor promotion studies, Dong et al investigated anti-tumor promoting effects of EGCG and theaflavins. Both of these were found to inhibit EGF- or TPA- induced cell transformation, as well as AP-1-dependent transcriptional activity and DNA binding activity. This study further showed that the inhibition of AP-1 activation occurs via the inhibition of a c-Jun NH2-terminal kinase (JNK)-dependent pathway.

EGC inhibits the activity of the protein tyrosine kinase, c-jun mRNA expression, and JNK1 activation. In a recent study, Lu *et al* (1998) investigated some possible mechanisms involved with the antiproliferative ability of EGC. Employing rat aortic smooth-muscle (A7r5) cells, it was demonstrated that the activity of the serum-stimulated membranous protein, tyrosine kinase (PTK), is inhibited by EGC. EGC was also found to reduce the phosphorylation of many proteins with different molecular weights, at the tyrosine site, indicating that EGC may inhibit activity of tyrosine kinase, or stimulate the activity of phosphatase. It was further demonstrated that EGC reduces the levels of c-*jun* mRNA, phosphorylated JNK1, and JNK1-kinase activity. These data suggest that the antiproliferative effect of EGC, at least in part, is mediated through the inhibition of tyrosine kinase activity, reducing c-*jun* mRNA expression and inhibiting JNK1 activation.

The involvement of PTK activity and protein phosphorylation was further explained by another study, where Kennedy *et al* (1998) evaluated the mechanism of the antiproliferative potential of green tea polyphenols in Ehrlich ascite tumor cells. In this study, EGC and EGCG treatments were found to result in a significant decrease in cell viability. EGC, but not EGCG, caused a stimulation of PTK activity. EGC treatment was also found to result in tyrosine phosphorylations of 42 and 45 kDa proteins, and in the activity of ornithine decarboxylase (ODC), an essential cellular enzyme in polyamine biosynthesis.

Skin Effects of Green Tea

Skin is the largest body organ and serves as a protective barrier against the deleterious effects of environmental insults, including those caused by ultraviolet (UV) radiation. Much of the deleterious effect of solar UV radiation is because of UVB (290–320 nm). Although the long-term abnormalities of UVB typically become evident in the population aged 50 years and beyond, epidemiological studies indicate that much of the critical sunlight exposure responsible for these adverse effects is received at a young age. Recent epidemiological observations suggest that individuals with a history of non-melanoma skin cancer have increased risk of melanoma and certain non-cutaneous cancers.

UVB induces skin cells to produce reactive oxygen species, eicosanoids, proteinases, and cytokines, and inhibition of these mediators is thought to reduce skin damage. Evidence for this comes from the demonstration that antioxidants such as ascorbic acid and alpha tocopherol produce photoprotective effects in some *in vitro* and *in vivo* studies (Elmets and Mukhtar, 1996; Mukhtar and Elmets, 1996).

Studies have suggested that green tea polyphenols may be

useful in affording protection against inflammatory responses and against skin-cancer risk. Topical application of green tea polyphenols to mouse skin inhibits 12–0-tetradecanoylphorbol-13-acetate and other skin tumor-promoter-caused induction of protein and mRNA expression of the pro-inflammatory cytokines interleukin (IL)-1 α and TNF-α. Skin application of green tea polyphenols inhibits UV-radiation-induced local and systemic suppression of contact hypersensitivity and edema responses in C3H/HeN mice. In many *in vitro* studies, green tea polyphenols or crude extracts of green tea have also shown preventive effects in systems considered essential in inflammatory and carcinogenic processes (Ahmad *et al.*, 1997; Katiyar and Mukhtar, 1996).

The relevance of the extensive *in vitro* and *in vivo* laboratory data on adverse effects caused by solar UVB in human skin is not clear. This information can be derived either based on epidemiological studies in a high-risk population, or based on using short-term assays with noninvasive techniques and acceptable protocols in human volunteers. Recently, we assessed the protective effect on skin of the application of green tea polyphenols against UV-induced erythema in human volunteers. In this study, a polyphenolic fraction obtained from green tea was applied, in different strengths, on the untanned backs of normal volunteers. Thirty min later the sites were exposed to twice the minimal erythemogenic dose (MED) of UV radiation from a solar simulator. Sites pretreated with green tea polyphenols exhibited significantly less erythema when compared to vehicle-treated sites. The photoprotective effects of green tea polyphenols were dependent on the strength of the dose applied, with maximum protection observed from 200 μl of a 5% solution. In time course studies, the green tea polyphenol-mediated cutaneous photoprotective effect was evident, even when UV irradiation was delayed for many h. The protective effects lasted for at least 72 h, thus indicating a relatively long-term protection, particularly against chronic low-dose environmental insult. Skin application of green tea polyphenols to human volunteers also resulted in significant protection against 2 MED-induced enhancement of sunburn-cell formation and depletion of CD1 a$^+$ Langerhans cell density (Mukhtar *et al.*, 1996).

In additional studies, we investigated (Katiyar *et al.*, 1999) whether or not the topical application of EGCG would protect against UVB-induced adverse effects in human skin. In this study, we assessed the effect of EGCG treatment on inhibition of UVB-induced infiltration of leukocytes (macrophage/neutrophils), a potential source of generation of ROS and prostaglandin (PG) metabolites, which play a critical role in skin-tumor promotion in multistage skin carcinogenesis. Human subjects were exposed to UVB radiation (at 4 MED doses) on sun-protected skin, and skin biopsies or keratomes were obtained 24 h or 48 h later. We found that topical application of EGCG (3 mg/2.5 cm^2) before UVB exposure to human skin significantly blocked UVB-induced infiltration of leukocytes and reduced myeloperoxidase activity. The infiltration of leukocytes is considered the major source of generation of ROS. In the same set of experiments, we found that the topical application of EGCG before UVB exposure decreased UVB-induced erythema. In additional experiments, we found that EGCG treatment before UVB exposure produced significantly lower PG metabolites, particularly PGE$_2$, in the epidermal microsomal fraction of the skin, as compared to non-pretreated skin. Histological examination of skin revealed that EGCG-pretreated and UVB-exposed human skin contained fewer dead cells in the epidermis when compared to non-pretreated, UVB-exposed skin. These data demonstrate that EGCG has the potential to block the UVB-induced infiltration of leukocytes and the subsequent generation of ROS in human skin. This may be responsible, at least in part, for the anti-inflammatory effects of green tea.

Based on the work described above, it is tempting to suggest that the use of GTP in cosmetic preparations may be a novel approach for preventing the adverse effects associated with UV radiation in humans. It is of interest that many low-priced cosmetics marketed by small companies, as well as expensive lines of cosmetics marketed by the name brand companies, are supplementing their products with green tea extracts.

Modulatory Effects of Green Tea for Cancer Chemotherapy

A recent study (Sadzuka *et al.*, 1998) has shown that green tea can also modulate the efficacy of cancer-chemotherapeutic drugs in such a way that it increases the drugs' efficacy. In this study, the oral administration of green tea enhanced the tumor-inhibitory effects of doxorubicin on Ehrlich ascite carcinomas implanted in CDF$_1$ and BDF$_1$ mice. Green tea treatment resulted in an increased availability of doxorubicin in tumor, but not in normal tissue. If verified in the human population, these observations may have relevance to cancer chemotherapy.

Conclusion and Future Directions

Since 1990, approximately ten million new cases of cancer were diagnosed and four million cancer-related deaths have occurred. It is believed that almost one third of the cancers are caused by dietary habits and the manipulation in diet is increasingly being recognized as a potential strategy against cancer (Katiyar and Mukhtar, 1996; Weisburger, 1996). The use of tea, especially green tea, as a cancer chemopreventive agent has only been appreciated in the last ten years. Green tea is a popularly consumed beverage, is relatively inexpensive and non-toxic, and has been shown to afford protection against many cancer types. The epidemiological as well as laboratory studies have shown an inverse association of green tea consumption with the development of certain cancer types. Although compelling evidence is now available that shows the preventive potential of green tea against cancer, a clear understanding of the mechanisms associated with its action is far from complete. A complete knowledge of the molecular mechanism(s) involved with the anti-carcinogenic efficacy of green

tea polyphenols may be useful in devising better chemopreventive strategies against cancer.

In view of the available data from laboratory and epidemiological studies, clinical trials are now warranted to evaluate the usefulness of green tea and the polyphenolic antioxidants present therein. Vastag (1998) realized that a cup of tea provides an antioxidant boost that may protect against several cancer types, and that these tea antioxidants are much more potent than vitamins C and E in their ability to scavenge potentially carcinogenic free radicals. It is important to emphasize here that Phase I Clinical Trials to evaluate the possible efficacy of formulated green tea, in patients with advanced solid tumors, are currently underway at M.D. Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center.

ACKNOWLEDGMENTS

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