Reading the Tea Leaves: Anticarcinogenic Properties of (-)-Epigallocatechin-3-Gallate

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Green tea is an extremely popular beverage worldwide. Derivatives of green tea, particularly (-)-epigallocatechin-3-gallate (EGCG), have been proposed to have anticarcinogenic properties based on preclinical, observational, and clinical trial data. To summarize, clarify, and extend current knowledge, we conducted a comprehensive search of the PubMed database and other secondary data sources, as appropriate, regarding the chemopreventive potential of EGCG. Apparently, EGCG functions as an antioxidant, preventing oxidative damage in healthy cells, but also as an antiangiogenic agent, preventing tumors from developing a blood supply needed to grow larger. Furthermore, EGCG may stimulate apoptosis in cancerous cells by negatively regulating the cell cycle to prevent continued division. Finally, EGCG exhibits antibacterial activity, which may be implicated in the prevention of gastric cancer. Although in vitro research of the anticarcinogenic properties of EGCG seems promising, many diverse and unknown factors may influence its in vivo activity in animal and human models. Some epidemiological studies suggest that green tea compounds could protect against cancer, but existing data are inconsistent, and limitations in study design hinder full interpretation and generalizability of the published observational findings. Several clinical trials with green tea derivatives are ongoing, and further research should help to clarify the clinical potential of EGCG for chemoprevention and/or chemotherapy applications.

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CI = confidence interval; EGCG = (-)-epigallocatechin-3-gallate; FAS = fatty acid synthase; IL = interleukin; OR = odds ratio; PCP = pentachlorophenol; PRC = People's Republic of China; RR = relative risk; VEGF = vascular endothelial growth factor

Tea beverages have been brewed from the *Camellia sinensis* plant for nearly 5000 years.[1] Alterations in the *C sinensis* manufacturing process result in black, green, and oolong tea, which account for approximately 75%, 23%, and 2% of the global production, respectively.[2] In the production of black tea, the plant leaves are picked and then allowed to wither indoors, ferment, and oxidize. For green tea, the plant leaves are steamed and parched after picking to prevent oxidation of the catechins present in the leaf.[3] Oolong tea is produced by "semifermenting" the green leaves, resulting in a tea that is chemically a mixture of green and black teas.[3] Even though each of these nonherbal teas is derived from *C sinensis*, qualitative and quantitative chemical differences result from the different processing techniques.[4] For example, black tea contains more complex antioxidants called theaflavins and thearubigins, while steamed and parched green tea contains more of the chemically simpler antioxidants called catechins.[3]

Green tea extracts have been used in traditional Chinese medicine for centuries to treat and prevent chronic disease,[5] but conventional medicine practitioners have only recently begun to explore the health-promoting benefits of green tea derivatives.[6] In this review, we focus on the potential anticarcinogenic effects of (-)-epigallocatechin-3-gallate (EGCG), which is the most abundant polyphenolic compound found in green tea (making up more than 40% of the total polyphenolic mixture).[7] Because EGCG acts against cancer through a variety of mechanisms, its potential for use in human cancer prevention and treatment seems very promising. This potential is reflected by the growing number of in vivo and in vitro research studies on this topic. However, to date, relatively few large-scale epidemiological studies in western populations and randomized, controlled intervention trials have been conducted.

We performed a series of PubMed database searches using the following key words, alone or in combination: *cancer*, *cancer prevention*, *chemoprevention*, *tea*, *green tea*, *epigallocatechin-3-gallate*, *case-control*, *cohort*, *prospective study*, and *clinical trial*. More than 400 citations were initially identified, and data were subsequently extracted from those articles that, in the authors' best judgment, were deemed most relevant to the topic of interest. Secondary data sources were also queried, as appropriate, including references cited in the primary articles and additional manuscripts, reviews, and Web-based materials known to the authors because of their expertise in the field.

BIOLOGIC MECHANISMS

Although the specific molecular targets and intracellular pathways modulated by EGCG remain incompletely defined, this compound appears to afford protection against cancer through multiple biologic mechanisms (Figure 1), as discussed in the following sections.

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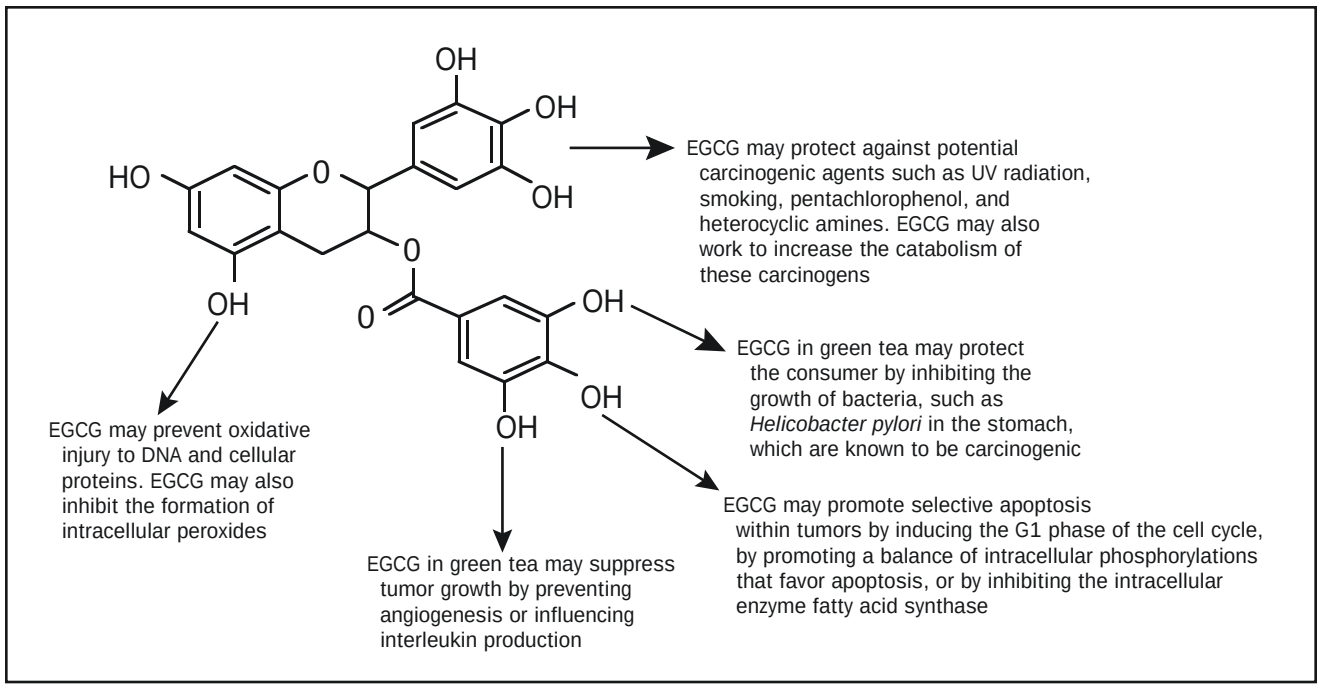

FIGURE 1. Structure of (-)-epigallocatechin-3-gallate (EGCG) and its proposed anticarcinogenic properties.

ANTIOXIDATION

One of the most frequently studied mechanisms of EGCG is its role as an antioxidant. Cancer development may be associated with oxidative damage to DNA, lipids, and proteins. Oxidative damage to cells may be caused by a number of factors, including UV light, carcinogens, and free radicals.[8] Oxidative damage to DNA is an important source of gene mutations that modify gene expression and cellular regulation.[8] Oxidative damage in cells can be assessed indirectly by measuring the byproducts of oxidative damage, such as oxidized derivatives of phosphatidylcholine in lipid damage and 8-hydroxyguanosine in DNA damage.[3,8] EGCG has been found to reduce significantly the plasma levels of biomarkers for oxidative damage to both lipids and DNA.[8] The effect of EGCG on oxidative protein damage also has been studied, and results are mixed. In rats, EGCG was found to suppress oxidative modification of muscle proteins; however, a controlled study in humans showed no effect of EGCG on biomarkers for oxidative protein damage.[3]

The antioxidants found in green tea and other plants have been suggested to work against oxidative damage in several ways. EGCG and other antioxidants neutralize free radicals in the body, scavenging harmful reactive nitrogen and oxygen species before they cause oxidative damage to cell components.[3] Because these antioxidants have a high affinity for some metal ions,[9] they can act as metal chelators, inactivating redox-active transition metal ions that would otherwise catalyze free radical formation.[3] Antioxidants may also block attachment of foreign agents such as bacteria and carcinogens to cells.[10] Furthermore, EGCG may prevent cellular oxidative damage by inhibiting lipoxygenase, cyclooxygenase, and xanthine oxidase enzymes, all potentially capable of causing oxidative damage in some tissues by their peroxidase activity.[3]

Although credited with protecting DNA through these mechanisms, catechins in general and EGCG in particular may induce DNA damage in the presence of Cu(II) and Fe(III) complexes, most likely via the generation of the hydroxyl radical from hydrogen peroxide.[11] EGCG has been observed in vitro to promote DNA damage in the human esophageal squamous cell carcinoma cell lines KYSE 510 and 150[12] and the leukemia cell line HL-60.[11,13] In healthy human lymphocytes examined in vitro, low concentrations of EGCG were found to protect DNA from strand breakage and high concentrations to promote strand breakage.[14] Although paradoxical, these observations will serve as the basis of future research that may lead to a greater understanding of the true nature of the protective effects of EGCG.

ANTIANGIOGENESIS

Biochemical differences between cancerous and healthy cells have been identified, allowing clinicians to use these differences to target cancerous cells without adversely af-

fecting normal tissue.[15] In posing less risk to normal tissue, this biochemical strategy offers a clear advantage over traditional cancer treatments such as radiation and chemotherapy or surgery. Radiation and chemotherapy can kill healthy and cancerous cells,[16] are not always effective at eradicating the tumor, and are often associated with serious adverse effects.[9] Surgery cannot be performed on micrometastases because potentially critical normal tissues would inevitably be removed along with the tumor.[9]

One exciting area of cancer treatment that uses the biochemical differences between healthy and cancerous cells is a strategy for preventing blood vessel formation in cancer cells. Angiogenesis, the process by which new blood vessels are formed, is critical to the growth of solid tumors.[10] Among other compounds, EGCG is being investigated for its potential to hinder angiogenesis. During the initial phase of growth, a tumor can gain nutrients and oxygen by diffusion alone. However, to grow larger than about 0.5 mm in diameter,[17] the tumor must create a supply of blood vessels to "feed" the growing tumor cells with oxygen and nutrients. Angiogenesis occurs through a complex series of biochemical steps that are controlled by molecules that can either "turn on" or "turn off" the process of new blood vessel formation and tissue growth. Cancerous cells can "hijack" the process by generating an imbalance of angiogenesis activators and inhibitors,[10] causing endothelial cell recruitment and proliferation.[9] Antiangiogenic agents such as EGCG may be used against tumors at different stages of growth. They not only inhibit further vascularization of existing tumors, but can turn off the "angiogenic switch"—the biochemical events that begin the process of angiogenesis—at an early stage when cells are in a state of dysplasia, thus preventing them from progressing toward invasive cancer.[9]

Because endothelial cells are common to all solid tumors, cancer therapies that target these cells are promising. In addition, because endothelial cells rarely undergo mutagenesis, they are unlikely to develop the multidrug resistance mechanisms that would render therapy ineffective.[9] Antiangiogenic compounds allow selective targeting of cancerous cells, because angiogenesis is only required in healthy individuals for wound healing, for growth of the endometrium, and in pregnancy.[17]

A variety of angiogenic growth factors "activate" the process of blood vessel formation.[18] Two such activators are angiogenin and vascular endothelial growth factor (VEGF), a protein associated with increased angiogenesis in human colon, breast, and other cancers.[7,18] EGCG has been shown to inhibit angiogenin-induced angiogenesis.[10] Proteases, enzymes that catalyze the breakdown of proteins and allow the tumor to invade surrounding tissues, are also associated with angiogenesis. EGCG has been found to inhibit the activity of 2 types of proteases, matrix metalloproteinases and urokinase-plasminogen activator, in vitro.[9] Both of these enzymes are responsible for degradation of the extracellular matrix and subsequent tumor invasion.[19]

EGCG may help suppress cancer growth by affecting interleukins. In the lymphatic fluids that drain from tumors, EGCG has been found to elevate levels of interleukin (IL) 12, a molecule that activates antiangiogenic events in both mouse cells and human blood cells in vitro.[9] In contrast, in human epithelial cells, EGCG suppresses production of IL-8, a molecule promoting angiogenesis.[20] Thus, EGCG may limit or suppress tumor growth and metastasis by influencing IL-12 and IL-8 functions.

Many of the anticarcinogenic effects of EGCG may be due to its influence on proteins, transcription factors, and gene expression. Development of the complementary DNA microarray has enabled researchers to monitor the effects of EGCG on many genes at once. EGCG may influence cell-signaling pathways and either up-regulate or "knock down" the transcription of angiogenesis activators.[7] EGCG suppresses angiogenesis by targeting extracellular-regulated kinase function and VEGF expression.[7] The metal-chelating ability of EGCG may interfere with the supply of metal ion cofactors to receptor kinases.[7] Also, EGCG has been shown to promote apoptosis in human chronic lymphocytic leukemia cells by selectively suppressing the critical phosphorylation of VEGF-R1 and -R2 receptors.[21]

Apoptosis and Cell Cycle Regulation

One of the defining characteristics of cancerous cells is their ability to elude apoptosis or programmed cell death. Apoptosis is regulated by a complex cascade of genetic events. One important regulatory protein in this process is tumor suppressor protein p53.[22] Considered the "guardian of the genome,"[23] p53 responds to a variety of cellular stressors by regulating cell cycle progression, checkpoint activation, apoptosis, and DNA damage repair.[10] For example, activated p53 arrests the cell cycle in response to DNA damage[23] and triggers apoptosis in response to alterations in cellular redox potential.[22] More than 50% of solid tumors do not express wild-type p53 protein because of either deletion or point mutation in the *p53* gene.[23] Tea polyphenols have been associated with increased p53 levels and increased apoptosis.[22]

Antioxidant molecules, including EGCG, can alter the redox potential of the cell, thereby activating p53 and promoting apoptosis.[22] In one in vitro study, cervical cancer cells exposed to 35 μM of EGCG were arrested at the G1 phase of the cell cycle, whereas those exposed to 100 μM of EGCG underwent apoptosis, suggesting that low concentrations of EGCG promote cell cycle arrest whereas high concentrations trigger apoptosis.[16] Using complemen-

tary DNA microarray technology, the same investigators determined that EGCG down-regulated 16 genes and up-regulated 4. Many of the protein products of these genes are known to play a role in cellular metabolism and cell cycle regulation.[16]

EGCG is thought to activate the p53 protein by inducing phosphorylation of critical serine residues.[23] Phosphorylation of these residues increases the half-life of this normally short-lived protein. Increased transcriptional activity of p53 can impact several target genes and their downstream protein products, shifting the balance between pro- and antiapoptotic factors and triggering G1 phase arrest and, ultimately, apoptosis.[23]

Additionally, EGCG may induce apoptosis by inhibiting the activity of fatty acid synthase (FAS), a metabolic enzyme involved in lipid synthesis.[24] Present at low levels in many human tissues, this enzyme is overexpressed in several types of human cancer cells,[25] including prostate, breast, ovary, endometrium, lung, and colon.[24] EGCG inhibits growth of both healthy cells (which exhibit a low level of FAS) and tumor cells (which exhibit a higher level of FAS).[24] However, EGCG induces apoptosis only in the tumor cells, perhaps through accumulation of toxic precursors such as malonyl-coenzyme A in the process of lipid synthesis.[24]

Of great interest to researchers is the ability of EGCG to selectively promote apoptosis in cancerous but not healthy cells. Chen et al[15] compared the effect of EGCG in virally transformed W138 human fibroblasts (W138VA) and normal W138 cells as well as in breast and colorectal cancer cells and their normal counterparts. EGCG treatment induced apoptosis in 50% of transformed cells but in only 1% of their normal counterparts.[15] Breast and colorectal cancer cells were nearly absent from cultures treated with EGCG, whereas EGCG had no effect on cell density of healthy cells in culture.[15] Chen et al determined that EGCG did not affect expression of the apoptosis-promoting genes *c-myc* or *c-fos* in healthy cells but up-regulated the expression of these genes in the transformed cells. Others have provided evidence that EGCG induces apoptosis specifically in abnormal or cancerous cells.[15,16,23]

Antimicrobial Activity

Infection with the organism *Helicobacter pylori* is thought to be a risk factor for developing gastric carcinoma. When cocultured with human gastric carcinoma cell lines, *H pylori* enhances expression of messenger RNAs encoding IL-8, VEGF, angiogenin, urokinase-plasminogen activator, and metalloproteinase.[26] As indicated earlier, all these compounds are implicated in cancer formation. Green tea has been found to exhibit antibacterial activity against *H pylori* in animal models[27] and in vitro, especially when used with other antibiotic agents.[28]

Exposure Modification

Perhaps one of the most promising areas of green tea research relates to the compound's protective effect against skin cancer caused by UV irradiation.[29] Application of green tea polyphenols to skin before exposure to UV-A or UV-B light was shown to prevent DNA damage, as measured by cyclobutane pyrimidine dimer levels, in both mouse models and human clinical trials.[30-32] Furthermore, both topical treatment and oral ingestion of green tea polyphenols were shown to prevent UV-B radiation–induced immune suppression in mice.[32] Oral ingestion of green tea polyphenols has also been found to reduce UV-A radiation–induced oxidative DNA damage in mice.[31]

Several studies have suggested that EGCG may also help protect against other environmental factors. Chung et al[22] showed that EGCG administration reduced DNA damage and increased apoptosis in the oral cells of smokers. Another group found that green tea consumption significantly reduced the frequency of sister chromatid exchange, a mutagenicity marker, in the DNA of both smokers and nonsmokers.[8] Umemura et al[33] explored the relationship between green tea and reduction of harmful effects of the environmental pollutant pentachlorophenol (PCP). This study revealed that mice exposed to PCP and green tea were less likely to develop hepatocellular and cholangiocellular tumors, and if such tumors did develop, progression of the tumor was less likely. The hepatic benefits of green tea have been attributed to a reduction of PCP-induced oxidative stress.[33] Also posing an environmental threat in the liver are heterocyclic amines, carcinogenic compounds formed during the cooking of meat and fish. Furthermore, EGCG may decrease the mutagenic effects of these harmful chemicals, perhaps by accelerating their breakdown.[34]

EPIDEMIOLOGICAL DATA

According to a recent national telephone survey, only 15% of US adults drink green tea on a typical day.[35] Not surprisingly then, most studies examining an association between green tea and lowered cancer risk have been conducted abroad, primarily in Asia and to a lesser extent in Europe. These studies, classified by general design, are discussed in the following sections.

Retrospective Studies

Several case-control studies have investigated the potential protective effects of green tea against aerodigestive malignancies in Shanghai, People's Republic of China (PRC). Gao et al[36] initially reported that drinking green tea was associated with reduced esophageal cancer risk, although the estimated odds ratio (OR) was only statistically signifi-

cant for women (OR, 0.50; 95% confidence interval [CI], 0.30-0.83). Using slightly different methodologies, subsequent reports from this same geographic region described statistically significant inverse associations for gastric, lung, pancreas, rectal, and gallbladder cancers, with risk reductions ranging from 23%-47%.[37-41] Three additional retrospective studies conducted elsewhere in China reported the potentially protective effects of green tea against breast, ovarian, and prostate cancers.[42-44] Conversely, a relatively small study from Xuan Wei County, PRC, found no association between green tea consumption and a lowered risk of lung cancer. Among Japanese subjects, increased green tea intake has been associated with decreased risks of gastric and colorectal cancers,[45,46] as well as an increased risk of genitourinary tract cancer.[47,48] However, the latter observation was made by 2 studies that based risk estimates on comparisons to hospital-based, rather than population-based, controls.

With respect to US residents, Wu et al[49] conducted a case-control study of Asian-American women living in Los Angeles County and found a negative dose-response relationship between green tea consumption and breast cancer risk, with adjusted OR (95% CI) estimates of 0.71 (0.51-0.99) and 0.53 (0.35-0.78) for those who consumed 85.7 mL or less and those who consumed greater than 85.7 mL per day, respectively, compared with those who did not drink green tea. Follow-up molecular testing suggested that the putative chemoprevention benefits derived from green tea might be related to a low catechol-O-methyltransferase activity in this subject group and slower metabolism of the polyphenolic compounds derived from green tea.[50]

Prospective Studies

Relative to the generally favorable observations reported from case-control studies, associations between green tea consumption and cancer risk have been less consistent in large prospective cohort studies. Among Japanese subjects, Nakachi et al[51] observed lower total cancer incidence rates among subjects who consumed more than 10 cups of green tea per day compared with subjects who consumed fewer than 3 cups per day (relative risk [RR], 0.58; 95% CI, 0.34-0.99) in a population-based study from Saitama Prefecture. Similarly, Inoue et al[52] found that consumption of more than 3 cups of green tea per day before breast cancer diagnosis was associated with a decreased risk of recurrent disease (RR, 0.69; 95% CI, 0.47-1.00) in a hospital-based cohort study.[52] In the Japan Public Health Center Study,[53] incidence rates of distal gastric cancer were significantly lower among women who drank more than 5 cups vs less than 1 cup of green tea per day (RR, 0.51; 95% CI, 0.30-0.86). Other large prospective cohort studies from Japan have also failed to show that green tea offers any protective effects against gastric,[54,55] breast,[56] or colorectal cancer.[57] In addition, the Ohsaki National Health Insurance Cohort Study found no association between green tea consumption and total cancer mortality[58] or incident prostate cancer.[59]

A nested case-control study of Chinese women living in Singapore found no association between green tea consumption and breast cancer risk.[60] In a relatively small prospective study of patients with ovarian cancer from Hangzhou, PRC, green tea intake was associated with prolonged survival time.[61] Furthermore, Sun et al[62] reported that, in a subset of participants in the Shanghai Cohort Study, urinary epigallocatechin levels were lower in those with gastric cancer than in controls, suggesting that green tea–associated cancer risk estimates may differ depending on whether intake is self-reported or objectively measured. To our knowledge, no prospective studies of green tea consumption and cancer risk have been reported to date from European or American subject populations.

Meta-analyses

Quantitative summaries of existing epidemiological data have been performed to further characterize associations between green tea intake and colorectal[63] and breast cancer[64,65] risks. On the basis of the combined results of 4 case-control and 4 cohort studies, Sun et al[63] estimated that subjects with the highest levels of green tea consumption had an 18% reduction in colorectal cancer risk (summary OR, 0.82; 95% CI, 0.69-0.98). However, significant heterogeneity was detected across studies (P=.03), with the potential benefits of green tea restricted to observations from case-control studies. This same investigative team also analyzed combined data from 1 case-control and 3 cohort studies referent to green tea intake and breast cancer risk,[64] deriving a summary risk estimate of 0.78 (95% CI, 0.61-0.98) without evidence of significant heterogeneity across studies (P=.11). Of note, an earlier meta-analysis of green tea consumption and breast cancer risk by Seely et al[65] reported somewhat different, nonstatistically significant summary risk estimates of 0.44 (95% CI, 0.14-1.31) and 0.89 (95% CI, 0.71-1.10) from 2 case-control and 3 cohort studies, respectively, using slightly different study eligibility criteria.

Data Interpretation

Unfortunately, differences in the methods used to assess green tea consumption and adjust for potential confounding factors make it difficult to derive firm conclusions from existing epidemiological data. Moreover, as previously noted, most observational studies reported to date have been conducted in China and Japan, perhaps leaving unrecognized genetic, environmental, and cultural factors that

could influence the association between green tea consumption and cancer risk in non-Asian populations.

CLINICAL TRIALS

Limited data are currently available from green tea chemoprevention trials. Phase 1 trials of healthy volunteers have defined the basic biodistribution patterns, pharmacokinetic parameters, and preliminary safety profiles for short-term oral administration of various green tea preparations.[66-69] After oral administration, only a small proportion of the total EGCG (0.1% of the administered dose at the maximum achieved concentration) is absorbed into the gut.[70] Maximal plasma concentrations are achieved for EGCG in the form of tea solids by 1.4 to 2.4 hours[66] and for green tea by 1.3 to 1.6 hours[70] after oral administration. Orally administered EGCG is excreted primarily via the fecal route,[70] with only a minimal amount excreted in urine.[71] The consumption of green tea appears to be relatively safe. The novel study by Pisters et al[72] determined that even persons with solid tumors could safely consume up to 1 g of green tea solids, the equivalent of approximately 900 mL of green tea, 3 times daily. This observation supports the use of green tea for both cancer prevention and treatment.

Beneficial effects of green tea consumption can be observed relatively rapidly after even a single dose. Tissue prostaglandin E2, which may stimulate colorectal carcinogenesis, was reduced in normal subjects 4 hours after the ingestion of a single dose of green tea.[73] Among patients with established premalignant conditions, green tea derivatives have shown potential efficacy against cervical, prostate, and hepatic malignancies, without inducing major toxicities.[74-76] However, one relatively large phase 2 trial from China detected no appreciable effects from decaffeinated green tea on intermediate biomarkers of esophageal squamous carcinogenesis.[77] Multiple early-phase chemoprevention trials are currently ongoing (information available at www.clinicaltrials.gov; accessed January 5, 2007). Use of green tea extracts for adjuvant chemotherapy has been somewhat less impressive, with limited activity noted in a pair of studies of prostate cancer and a single lung cancer trial.[78-80]

EGCG offers several potential clinical advantages compared to other traditional cancer drugs. Many of the antiangiogenic agents currently under investigation in human cancer research trials are expensive to produce in pure form and must be administered either intravenously or subcutaneously on a long-term basis. In contrast, EGCG is globally available as tea, is inexpensive to isolate, and can be administered orally.[18] While traditional cancer drugs often destroy some healthy cells along with cancerous cells,[16] EGCG appears to target biochemical and genetic features unique to cancer cells.[15,16,23] Some of the anticarcinogenic agents currently in use have toxic adverse effects, but data from clinical trials reported to date suggest that EGCG has a very acceptable safety profile.[81,82] These benefits support further development of EGCG as a potentially useful anticarcinogenic agent.

CONCLUSION

EGCG is a complex molecule with many potential anticarcinogenic functions. It acts as an antioxidant, serving to neutralize free radicals in the body before they cause cell damage. EGCG blocks angiogenesis, the process by which new blood vessels are formed, thereby depriving tumors of the nutrients needed for growth. It also inhibits the cell cycle, preventing cancerous cells from dividing and selectively causing cancerous cells to undergo apoptosis. Finally, EGCG has antibacterial properties that can combat *H pylori*, an organism implicated in the formation of gastric cancer. Although research data obtained from in vitro studies are promising, results from animal models, observational studies, and human intervention trials remain somewhat mixed. Nonetheless, further evaluation of EGCG as a candidate compound for chemoprevention and/or chemotherapy appears warranted on the basis of the preponderance of currently available data. Additional studies are needed to determine how the active ingredients in green tea interact with environmental and genetic factors, as well as to identify the EGCG mechanisms effective against given cancer types, so that these mechanisms can be fine-tuned or supplemented to increase the desired effects. However, the potential of green tea as an anticarcinogenic agent is high because of its low cost, wide availability, and apparent low toxicity.

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