Green Tea (*Camellia Sinensis*) Extract and Its Possible Role in the Prevention of Cancer

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Abstract

The American Cancer Society estimates that in the 1980s more than 4.5 million Americans died of cancer. In addition, there were nearly nine million new cases and about 12 million people were under medical care for cancer. With cancer being the second most common cause of death in the United States population, the possibility that readily-available natural substances may be beneficial in the prevention of cancer warrants closer examination. A growing body of research has demonstrated green tea polyphenols to be powerful antioxidants with anticarcinogenic properties. These polyphenolic compounds, specifically the catechins epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), and epicatechin-3-gallate (ECG), which account for 30-40 percent of the extractable solids of green tea leaves, are believed to mediate many of the cancer chemopreventive effects. Mechanisms of action may include antioxidant and free-radical scavenging activity, and stimulation of detoxification systems through selective induction or modification of phase I and phase II metabolic enzymes. In addition, green tea may inhibit biochemical markers of tumor initiation and promotion, including the rate of cell replication and thus inhibition of the growth and development of neoplasms. Current studies are hopeful, as they show an inverse association between green tea consumption and cancer risk, supporting a possible chemopreventive effect of green tea. Based on the knowledge that green tea is inexpensive, non-toxic, and is a popular beverage consumed worldwide, clinical trials should be conducted to evaluate the *in-vivo* effectiveness of green tea polyphenols on the inhibition and chemopreventive treatment of cancer.

Altern Med Rev 1999;4(5):360-370

Introduction

Camellia Sinensis, a member of the Theaceae family, is an evergreen shrub or tree that can grow to a height of 30 feet, but is usually clipped to a height of 2-5 feet in cultivation. The tree or shrub is heavily branched with dark-green, hairy, oblong-ovate leaves cultivated and preferentially picked as young shoots. Older leaves are considered to be of inferior quality.

Although both green and black teas are derived from *Camellia sinensis*, it is the production process which differentiates the two types of tea. Initially, after the young leaves are picked, they are allowed to wilt and then rolled. The leaves are allowed to ferment, converting the

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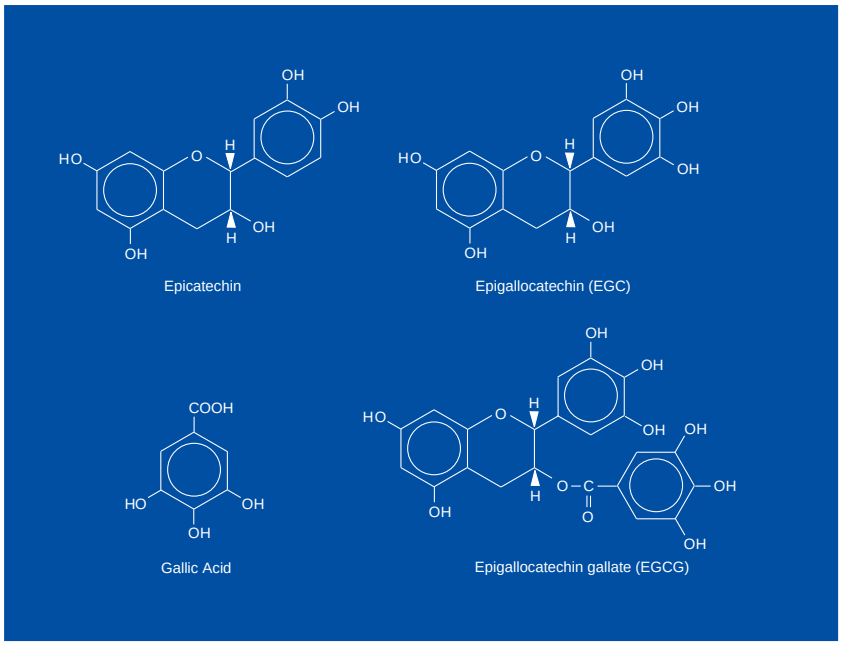
Figure 1. Green Tea Polyphenols.



polyphenols to phlobaphenes and forming aromatic compounds. Fermentation occurs as leaf enzymes, including polyphenol oxidase, react with tannins and catechins.[1] With green tea production, the young leaves are not allowed to oxidize. Instead, they are steamed, which inactivates the enzymes (i.e. polyphenol oxidase), thus preserving the polyphenols.

Chemical Composition of Green Tea

The chemical composition of green tea is similar to that of the young shoots initially cultivated. It contains many polyphenolic compounds, which account for 30-40 percent of the extractable solids of dried green tea leaves, with most of the polyphenols being flavanols more commonly known as catechins.[2,3] The primary catechins in green tea are epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG).[2] Other polyphenols include flavanols and their glycosides and depsides, such as cholorogenic acid, coumaroylquinic acid, and one unique to tea, theogallin (3-galloylquinic acid).[4] Also present are quinic acids, carotenoids, trigalloylglucose, lignin, protein, chlorophyll, minerals (depending on the soil content, aluminum and manganese are particularly prominent), caffeine, and very small amounts of other methylxanthines such as theophylline, theobromine, and theanine. Depending on the amount of oxidation and condensation of catechins, green tea may also contain constituents commonly found in black tea, such as theaflavin, theaflavic acids, volatile compounds, and thearubigens.[3,4]

Pharmacokinetics of Green Tea

The pharmacokinetics of tea polyphenols following an oral dose has been moderately studied in human subjects. Evidence exists to support the fact that ingested polyphenols and their metabolites provide a localized tissue action, in addition to indirect gastrointestinal effects, due to demonstration of polyphenol concentrations in blood, urine, saliva, and feces following oral ingestion of green tea infusion or catechin extracts.[5-7]

In a 56-day study with 10 healthy adult subjects, researchers demonstrated the effects of green and black tea consumption on urinary and fecal excretion, and whole blood and blood serum concentrations, of polyphenols. Green tea consumption resulted in the greatest fecal and urinary excretions, highest retention, and highest whole blood concentrations of polyphenols compared with black tea, decaffeinated black tea, and no tea treatment. The results of this study demonstrate green tea polyphenols are at least partly absorbable.[6]

To better understand the bioavailability of tea catechins, Yang et al[5] gave 18 individuals different amounts of green tea and measured the time-dependent plasma concentrations and urinary excretion of tea catechins. After taking

1.5, 3.0, and 4.5 grams of decaffeinated green tea solids dissolved in 500 ml of water, the maximum plasma concentration values (Cmax) were observed at 1.4-2.4 hours after ingestion. Cmax results were 326 ng/ml for EGCG, 550 ng/ml for EGC, and 190 ng/ml for EC. When the dosage was increased from 1.5 to 3.0 g, the Cmax values increased 2.7-3.4 fold, but increasing the dose to 4.5 g did not change the Cmax values significantly, indicating a saturation phenomenon. The half-life of EGCG was approximately 5-5.5 hours, almost twice that of EGC or EC (2.5-3.4 h). EGC and EC, but not EGCG, were excreted in the urine, with over 90 percent of the total urinary EGG an EC excreted within eight hours. Although the amount of EGC and EC excretion seemed to increase when the tea dosage was increased, a clear dose-response relationship was not observed.[5] It was also demonstrated and concluded that catechins from green and black tea are rapidly absorbed and the addition of milk does not impair bioavailability of tea catechins.[8]

In another study, an infusion of green tea containing approximately 400 mg of catechins was given to healthy volunteers, and plasma and urine samples were collected. EGCG and ECG were detected in plasma samples, reaching maximum concentration at 2 hours. Urine samples collected at 6-48 hours contained detectable amounts of catechin metabolites totaling 60 mg.[9] In a similar study, further light was shed on the ability to maintain serum levels of catechins following repeated tea consumption. Van Het Hof et al examined plasma and lipoprotein levels of tea catechins in 18 healthy adults, in an incomplete balanced cross-over design. The subjects consumed one cup every two hours for a total of eight cups per day for three days, with blood samples being drawn in the morning and evening of each day. Plasma total catechin concentration was determined in all blood samples and distribution of catechins among lipoproteins was evaluated at the end of the study. It was found that repeated tea consumption during the day rapidly increased plasma total catechin levels, whereas they declined overnight when no tea was consumed. Blood levels rapidly declined, with an elimination half-life (t1/2) of 4.8 hours. Green tea catechins were found mainly in the protein-rich fraction of plasma (60%) and in high-density lipoproteins (23%).[8,10]

A final point of interest in the pharmacokinetics of green tea is another study by Yang et al,[7] in which human salivary tea catechin levels were investigated following oral consumption of a green tea infusion. After drinking green tea preparations equivalent to 2-3 cups of tea, peak saliva levels of EGC (11.7-43.9 mcg/ml), EGCG (4.8-22 mcg/ml), and EC (1.8-7.5 mcg/ml) were observed after several minutes in six human volunteers. These recorded levels were two orders of magnitude higher than those in the plasma, although the t1/2 of salivary catechins was only 10-20 minutes. Holding a tea solution in the mouth for a few minutes without swallowing produced even higher salivary catechin levels. Holding an EGCG solution in the mouth resulted in EGCG and EGC in the saliva, and subsequently, EGC in the urine, suggesting EGCG was converted to EGC in the oral cavity and that both catechins were absorbed through the oral mucosa. A catechin esterase which converts EGCG to EGC was found in the saliva; however, the activity of this enzyme was not inhibited by a common human esterase inhibitor. When the volunteers took a capsule of green tea solids there were no detectable salivary levels of catechins The results of the study suggest slow drinking of green tea is a very effective way to deliver high concentrations of catechins to the oral cavity and esophagus. The researchers emphasize the importance of these findings because of the possible application of green tea in the prevention of oral and esophageal cancers.

Mechanism of Action

High concentrations of polyphenols are typically found in plants such as fruits, tea, and vegetables. Due to their multiple structure-conditioned interactions with various biomolecules, they exhibit a variety of roles, including modulation of various enzyme systems, antioxidant, and chelating properties. Research is beginning to highlight the important role these natural substances play in the promotion and maintenance of health.

Despite the growing body of research demonstrating tea polyphenols to be powerful antioxidants with antiatherogenic and anticarcinogenic properties, understanding of the mechanisms involved in the biological effects of green tea is far from complete. Initial studies focused on: (1) antioxidant and free-radical scavenging activity which may play a role in lowering LDL-cholesterol, with a consequent decreased risk of cardiovascular disease; (2) stimulation of detoxification systems, specifically selective induction or modification of phase I and phase II metabolic enzymes which increase the formation and excretion of detoxified metabolites of carcinogens; (3) inhibition of biochemical markers of tumor initiation and promotion, including lowering the rate of cell replication and thus the growth and development of neoplasms; and (4) prevention of mutagenicity and genotoxicity.[11,12]

Yu et al suggested activation of the mitogen-activated protein kinase pathway (MAPK) by green tea polyphenols might be responsible for the regulation of the antioxidant responsive element (ARE). The ARE is believed to mediate the induction of phase II enzymes by many drugs and may be stimulated by green tea polyphenols in the transcription of phase II detoxifying enzymes.[13,14] Oral administration of 0.5 percent lyophilized green tea to female CD-1 mice for 18 days stimulated liver microsomal glucuronidation of estrone, estradiol, and 4-nitrophenol by 33-37 percent, 12-22 percent, and 172-191 percent, respectively.[15]

Another area which has been increasingly looked at is the role green tea catechins play in arresting abnormal cell growth or inducing apoptosis. Apoptosis, also known as programmed cell death, is a normal biological process vital to an organism's ability to maintain homeostasis. It has been demonstrated that EGCG induces apoptosis and cell cycle arrest in human epidermoid carcinoma cells A431, human carcinoma keratinocytes HaCaT, human prostate carcinoma cells DU145, and mouse lymphoma cells LY-R. Apoptosis or cell arrest was specific only to cancer cells and not to normal epidermal keratinocytes.[14,16] Research suggests green tea polyphenols also have an antiproliferative effect in vascular smooth muscle cells. EGC was found to inhibit, in a dose-dependent relationship, the induced proliferation response of rat aortic smooth muscle cells, human coronary artery smooth muscle cells, rabbit cultured aortic smooth muscle cells, and human CEM lymphocytes. The data suggest the antiproliferative effect of EGC may be mediated through inhibition of protein tyrosine kinase activity, reducing c-jun mRNA expression, and inhibiting JNK1 activation.[14,17]

The effect of EGCG on growth factor receptors, specifically epidermal growth factor receptor (EGFR) has also been examined. EGFR's tyrosine kinase activation is believed to initiate multiple cellular responses associated with mitogenesis and cell proliferation. The overexpression of EGFR might produce a neoplastic phenotype. Liang et al found EGCG inhibited the autophosphorylation of EGFR by its ligand, EGF, and blocked the binding of EGF to its receptor. EGCG also significantly inhibited DNA synthesis and protein tyrosine kinase activities of EGFR. The results suggest EGCG might inhibit tumor development by blocking growth factor-associated signal transduction pathways.[14,18]

It has been suggested that green tea catechins may have a hypolipidemic effect, and their ingestion has been associated with

decreased serum triacylglycerols (TG) and cholesterol. Possible mechanisms of action include downregulation of liver fatty acid synthase (FAS), 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA-R)—a key enzyme in cholesterol synthesis—and intestinal acyl Co-A:cholesterol acyltransferase (ACAT), which is believed to play an important role in intestinal cholesteryl esterification before cholesterol is absorbed in the chylomicrons. It is also believed that antioxidant effects of these polyphenols help protect LDL-cholesterol from oxidative damage.[10,19,20]

The evidence supporting the mechanisms of action for green tea catechins' role in risk reduction for cardiovascular disease is equivocal at best.[10,19-21] Although literature suggests supplementation with green tea extract offers protection to low-density lipoproteins (LDL) against oxidation, Van Het Hof et al determined that after repeated oral consumption of green tea over three days, although present in LDL, the concentration of catechins was not sufficient to enhance the resistance of LDL to oxidation *ex vivo*.[10]

In another study, Ping et al shed new light on a different mechanism by which green tea catechins may have a hypolipidemic effect. The study examined the hypolipidemic activity of isolated green tea epicatechins and green tea water extract (GTWE) in hamsters. It was determined that isolated green tea epicatechins and GTWE have similar hypolipidemic activities, indicating the epicatechins are the major active components, or contribute at least in part to the hypolipidemic activity of green tea. This study is the first report to examine the influence of dietary green tea epicatechins on the profile of both fecal neutral and acidic sterols. The excretion of fecal neutral sterols (cholesterol and coprostanone) during days 0-20 and acidic sterols (deoxycholic acid, chenodeoxycholic acid, and cholic acid) during days 21-34 were significantly greater in green tea epicatechins-supplemented hamsters than in controls. The reduced absorption of dietary cholesterol during days 0-20 was directly associated with a lower serum cholesterol in the GTE-supplemented group. In addition, the greater synthesis and excretion of acidic sterols (the major end-products of cholesterol catabolism) in hamsters fed GTE during days 21-34 would also serve to lower the level of serum cholesterol. Although this study was in hamsters and not directly applicable to humans, the results warrant further research. The authors concluded the reduction in serum TG and cholesterol by dietary catechins is not associated with inhibition of liver FAS, HMG-CoA-R, and intestinal ACAT, due to the fact that very little change was seen in the activity of these enzymes. The hypolipidemic effect observed was most likely mediated by inhibition of dietary fat and cholesterol absorption, and decreased reabsorption of bile acids.[19]

Cancer: Clinical Applications of *Camellia Sinensis*

The American Cancer Society estimates that in the 1980s more than 4.5 milllion Americans died of cancer. In addition, there were nearly nine million new cases and about 12 million people under medical care for cancer. Although heart disease is the most common cause of death in the United States and accounts for 33.5 percent of all deaths, the second most common is cancer. While death rates from heart disease, stroke, and other diseases have been decreasing over the past generation, the percentage of deaths due to cancer rose from 16.8 percent in 1967 to 23.5 percent in 1990.[22] Thus, the growing body of literature suggesting a possible role for green tea extract in the chemoprevention of cancer is worth examining.

Several human cohort and case-controlled studies, as well as many animal studies, suggest green tea polyphenols possess significant chemopreventive properties and

have demonstrated inhibitory effects against tumor formation and growth. These polyphenols, especially EGCG, the major polyphenolic constituent of green tea, are believed to mediate much of the cancer chemopreventative effects.[23,24]

Population studies have demonstrated green tea consumption may be one of the reasons why the occurrence of cancer is lower in Japan. In a cohort study of a Japanese population, researchers surveyed 8,522 individuals over 40 years of age on their living habits, including daily consumption of green tea. During the nine years of follow-up (71,248.5 person years), 384 cases of cancer (in all sites) were identified. Results found a negative association between green tea consumption and cancer incidence, especially among females drinking more than 10 cups per day. The age-standardized average annual incidence rate was significantly lower among females who consumed large amounts of green tea. Relative risk (RR) of cancer incidence was also lower among both females (RR = 0.57, 95% CI = 0.33-0.98) and males (RR = 0.68, 95% CI = 0.39-1.21) in groups with the highest consumption, although the preventive effects did not achieve statistical significance among males, even when stratified by smoking and adjusted for alcohol and dietary variables.[24]

Although the effect of green tea polyphenols has been studied in different populations by many investigators, no clear-cut conclusions can be drawn between green tea consumption and cancer incidence at specific organ sites in human subjects. Despite inconclusive results, current studies are hopeful in suggesting a possible chemopreventive effect of green tea in cancer of the breast, prostate, and gastrointestinal tract—including cancers of the esophagus, stomach, pancreas, and colon. Preliminary studies also indicate a possible chemoprotective role of green tea catechins in smokers.

Breast Cancer

The association between consumption of green tea prior to clinical cancer onset and various clinical parameters was assessed among 472 patients with stage I, II, and III breast cancer. Increased consumption of green tea was closely associated with a decreased number of axillary lymph node metastases, especially among premenopausal patients with stage I and stage II breast cancers. In a seven-year follow-up study of these patients, increased consumption of green tea correlated with a decreased recurrence of stage I and II breast cancer ($P<0.05$ for crude disease-free survival); the recurrence rate was 16.7 percent among those consuming five or more cups, and 24.3 percent for four or less cups per day, and the relative risk of occurrence was 0.564 (95% CI, 0.350-0.911) after adjustment for other lifestyle factors. However, no improvement in prognosis was observed in stage III breast cancer.[25] An experiment using the estrogen-dependent MCF-7 cell line showed the mechanism of action to be inhibition of estrogen binding with its receptors. It was found that EGCG and other compounds in green tea block the interaction of tumor promoters, hormones, and growth factors with their receptors: a kind of sealing-off effect.[26]

Prostate Cancer

Cancer of the prostate is the most common malignancy in men in the United States and, depending on the source, is the second or third leading cause of cancer-related deaths among U.S. males[38]. According to one estimate, one of every 11 American men will eventually develop prostate cancer, although some will remain asymptomatic until death.[27] Because it is not typically diagnosed until after age 50, even a modest delay in neoplastic development achieved through pharmacological or nutritional intervention could result in a substantial reduction in the incidence of clinically detectable disease.

Many laboratory experiments conducted in cell culture systems and in animal models have shown the usefulness of green tea, more specifically the catechins, against prostate cancer. In a recent study looking at the induction of apoptosis in prostate cancer cell lines by EGCG, researchers found EGCG inhibited growth of prostate cancer cell lines LNCaP, PC-3, and DU145. The inhibition by EGCG was found to occur via apoptotic cell death, as demonstrated by changes in nuclear morphology and DNA fragmentation.[27,28] Epidemiological observations also suggest individuals who consume green tea on a regular basis have a lower risk of prostate cancer-related death. One observation worth noting is that China, whose population consumes green tea on a regular basis, has the lowest incidence of prostate cancer in the world.[27]

Esophagus, Stomach, Pancreas, and Colon Cancer

Although studies in laboratory animals suggest inhibitory effects of green tea on the induction of esophageal cancer, only a few epidemiological studies have evaluated green tea as a potential inhibitor of human esophageal cancer. In a study at the Shanghai Cancer Institute, People's Republic of China, Gao et al looked at the relationship between green tea consumption and risk of esophageal cancer. Medical records of patients aged 30-74 who were diagnosed with esophageal cancer were identified and patient interviews conducted using a structured, standardized questionnaire to obtain information on demographic characteristics, residential history, height, weight, diet, smoking, alcohol and tea drinking, medical history, family history of cancer, occupation, physical activity, and reproductive history. Of the 902 patients interviewed, 734 (81.4%) had their disease pathologically confirmed. There were 1522 control subjects interviewed, including 240 alternates. All analyses of tea effects were conducted separately among men and women, and all were adjusted for age. A protective effect of green tea drinking on esophageal cancer was observed among women (odds ratio {OR} = 0.50; 95% CI = 0.30-0.830), and this risk decreased (P for trend ≤ 0.01) as tea consumption increased. Among men, the ORs were also below 1.00, although not statistically significant. ORs for green tea intake were estimated among non-smokers and non-drinkers. In these individuals, a statistically significant decrease was observed in both men (OR = 0.43; 95% CI = 0.22-0.86; P for trend = 0.05) and women (OR = 0.40; 95% CI = 0.20-0.77; P for trend <0.001).[29]

Data also indicates drinking large amounts of green tea may be a viable recommendation to help protect humans from stomach cancer. Studies have shown that exposure of human stomach cancer KATO III cells to green tea catechin extract and EGCG resulted in growth inhibition and induction of apoptosis. The fragmentation of DNA to oligonucleosomal-sized fragments, characteristic of apoptosis, was determined to be concentration and time-dependent.[30] A population-based case-control study in China indicates green tea may disrupt gastric carcinogenesis at both the intermediate and late stages. A total of 711 cases of diagnosed primary stomach cancer and 711 matched controls were analyzed. After adjusting for age, gender, place of residence, education, birthplace, alcohol consumption, and cigarette smoking, the OR comparing drinkers of green tea with nondrinkers was 0.71 (CI 95% = 0.54-0.93). The adjusted OR decreased with an increased number of new batches of green tea consumed each day (P value trend = 0.006). With the largest series of stomach cancer cases analyzed to date, this study not only found a positive correlation between green tea consumption and a lower risk of stomach cancer, the effect also was independent of the age when habitual green tea drinking began.[31]

Another large population-based case-control study conducted in Shanghai, China, examined the hypothesis, based on numerous animal studies and several epidemiologic investigations, that green tea consumption may reduce the risk of cancers of the colon, rectum, and pancreas. Newly-diagnosed cancer cases (931 colon, 884 rectum, and 451 pancreas) during 1990-1993 among residents 3-74 years of age were investigated. Controls (n=1552) were selected among Shanghai residents and matched to cases by gender and age. Mulitvariate ORs and 95 percent CI of each cancer type correlated with green tea consumption after adjustment for age, income, education, and cigarette smoking. An inverse association with each cancer was observed with increasing amount of green tea consumption, with the strongest trends for rectal and pancreatic cancers. For men, compared with non-regular tea drinkers, ORs among those in the highest tea consumption category (≥ 300 g/month) were 0.82 for colon cancer, 0.72 for rectal cancer, and 0.63 for pancreatic cancer, with p values for trend being 0.38, 0.04, and 0.04, respectively. For women, the respective ORs for the highest consumption category (≥ 200 g/month) were 0.67, 0.57, and 0.53, with the respective p values for trend being 0.07, 0.001, and 0.008.[32]

Other Cancers

There is some evidence to suggest green tea polyphenols (GTP) have a chemopreventive effect in smokers and the incidence of lung cancer. The chemopreventive effects of green tea and coffee among cigarette smokers were examined in 52 clinically healthy male subjects between ages 20-51. Subjects were divided into four groups: non-smokers (group 1), smokers (II), smokers consuming green tea (III), and smokers/coffee drinkers (IV). The mean years of smoking (>10 cigarettes/day) of groups II, III, IV, ranged from 13.4 - 14.7 years. The volunteers' daily intake of green tea and coffee (groups III and IV) was three cups per day over six months. The frequencies of sister-chromatid exchange (SCE) in mitogen-stimulated peripheral lymphocytes from each experimental group were determined and statistically analyzed. SCE rates were significantly elevated in smokers (9.46 +/- 0.46) vs. non-smokers (7.03 +/- 0.33); however, the frequency of SCE in smokers who consumed green tea was comparable to non-smokers (7.94 +/- 0.31), suggesting GTP may have an anitmutagenic effect against smoke-induced mutations in humans by blocking the cigarette-induced increase in SCE frequency.[33] It has also been shown that cultured human lung cells (A 549) pretreated with GTP for two hours and then exposed to a cigarette smoke solution or H_2O_2 for 30 minutes had a reduced incidence of DNA strand breaks.[36] Pretreatment with GTP also reduced the overall toxicity of H_2O_2 as determined by cell growth after exposure. These results suggest GTP might inhibit DNA damage and other mutations in cells exposed to oxidants.

Since EGCG has been demonstrated to be growth inhibitory in a number of tumor cell lines, Chen et al investigated whether the effect is cancer specific in a study comparing the effect of EGCG on the growth of SV40 virally-transformed WI38 human fibroblasts (WI38VA) with that of normal WI38 cells. EGCG at 40mM completely inhibited the growth of WI38VA cells, but had little effect on the growth of normal cells. EGCG at a concentration of 40-200mM induced a significant amount of apoptosis in WI38VA cultures, but not in WI38 cultures, as determined by terminal deoxynucleotidyl transferase assay. After prolonged exposure (8 hours) to EGCG at 200mM, more than 50 percent of WI38VA cells in a confluent culture became apoptotic, while only one percent of WI38 cells displayed apoptotic labeling under the same condition.

Similar growth inhibition was observed between a human colorectal cancer cell line (Caco-2), a breast cancer cell line (Hs578T), and their respective counterparts.[35] It must be noted that many of these polyphenol concentrations are not necessarily achievable in plasma or tissue *in vivo*.

Research also points to other possible roles for green tea extract as a chemopreventive or inhibitory agent in the treatment of skin cancer,[36,37] bladder tumors,[38] ovarian sarcomas,[39] leukemia,[40] liver cancer,[41] and oral leukoplakia.[42]

Dosage and Toxicity

Based on current literature there does not appear to be any significant side-effects or toxicity associated with green tea consumption. However, overconsumption of caffeine-containing substances may cause intoxication but not clinical dependence. Effects include insomnia, restlessness, flushing, diuresis, twitches, nervousness, rambling thoughts and speech, tachycardia, and psychomotor agitation, with symptoms lasting six to 16 hours. In general, the stimulatory effect from green tea is considerably less than that of coffee. On average, a cup of green tea contains less than 50 mg of caffeine, whereas coffee may contain up to 150 mg per cup.

Although antiproliferative effects and inhibition of tumorigenesis at both the initiation and promotion stages have been demonstrated in human cancer cell lines by GTP, the concentrations used in many of the experiments are frequently higher than achievable in tissues *in vivo*.[43] Depending on the source, the average infusion of green tea varies in its phenolic content, ranging from 50-400 mg of polyphenols per cup.[9,44] Recent human epidemiological studies suggest a total daily intake of approximately 10 cups of green tea per day has a chemopreventive effect. Based on this information, a recommended dose of 500 mg GTP three or four times a day may be necessary to achieve the desired effect.

Conclusion

Green tea has been consumed in China to promote health and longevity since 3,000 B.C. In recent years, much attention has been focused on green tea and more specifically, its polyphenolic content. Although exact mechanisms have not been clearly elucidated, a variety of experimental animal studies have demonstrated antimutagenic, anticarcinogenic, antioxidant, and antipromotional effects of green tea polyphenols. Retrospective epidemiological studies have shown an inverse association between green tea consumption and cancer risk. The limitation of human epidemiological studies conducted so far is that they are primarily case-control studies, which rely heavily on interviews and patient responses to questionnaires.

Because the relationship between green tea consumption and human cancer incidence is an important concern, comprehensive, in-depth studies need to be conducted in order to further elucidate mechanisms of action and to verify clinically the chemopreventive qualities of green tea constituents. Also, based on the fact that green tea is a popular beverage consumed worldwide, inexpensive, and non-toxic, it seems appropriate to recommend additional clinical trials be conducted to evaluate the *in-vivo* effectiveness of green tea polyphenols in the inhibition and chemopreventive treatment of cancer. Finally, careful consideration should be given in future research to the fact that the biological activity of plant polyphenols act synergistically in complex ways with other constituents of the plant. These unknown and poorly understood interactions might play a significant role in the anticarcinogenic efficacy of the polyphenol constituents. As learned from many pharmaceutical agents available today, isolated extracts of one primary active constituent are generally not without side-effects.

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