Tea polyphenols: prevention of cancer and optimizing health

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ABSTRACT The tea plant *Camellia sinensis* is cultivated in >30 countries. Epidemiologic observations and laboratory studies have indicated that polyphenolic compounds present in tea may reduce the risk of a variety of illnesses, including cancer and coronary heart disease. Most studies involved green tea, however; only a few evaluated black tea. Results from studies in rats, mice, and hamsters showed that tea consumption protects against lung, forestomach, esophagus, duodenum, pancreas, liver, breast, colon, and skin cancers induced by chemical carcinogens. Other studies showed the preventive effect of green tea consumption against atherosclerosis and coronary heart disease, high blood cholesterol concentrations, and high blood pressure. Because the epidemiologic studies and research findings in laboratory animals have shown the chemopreventive potential of tea polyphenols in cancer, the usefulness of tea polyphenols for humans should be evaluated in clinical trials. One such phase 1 clinical trial is currently under way at the MD Anderson Cancer Center in collaboration with Memorial Sloan-Kettering Cancer Center. This study will examine the safety and possible efficacy of consuming the equivalent of ≥10 cups (≥2.4 L) of green tea per day. The usefulness of tea polyphenols may be extended by combining them with other consumer products such as food items and vitamin supplements. This “designer-item” approach may be useful for human populations, but it requires further study.

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INTRODUCTION Significant progress has been made in understanding diseases that cause alarming mortality and morbidity in humans: their processes, possible prevention, and therapies. Cancer and coronary heart disease are the most important of these disorders. Because of research efforts over the past 30 y, it is now well appreciated that although the causes of the major diseases are diverse and countless, changes in dietary habits and lifestyles may reduce their risk in many cases. Research has indicated that many common foods have nonnutritive components, commonly known as chemopreventive agents, that may provide protection against a variety of illnesses, including cancer and coronary heart disease. One such class of agents is antioxidants. The predominant mechanism of protective action of antioxidants appears to be the destruction of free radicals.

The water extract of the dry leaves of the plant *Camellia sinensis*, an evergreen shrub of the Theaceae family, is a popular beverage commonly known as tea. A drink that contains many compounds, including a mixture of polyphenols, tea has been consumed by some human populations for many generations and, in some parts of the world, has been considered to have health-promoting potential (1). Extensive laboratory research and the epidemiologic findings of the past 20 y have shown that polyphenolic compounds present in tea may reduce the risk of a variety of illnesses.

CONSUMPTION, COMPOSITION, AND CHEMISTRY OF TEA

The tea plant *C. sinensis* is native to Southeast Asia but is currently cultivated in >30 countries around the world. Tea is consumed worldwide, although in greatly different amounts; it is generally accepted that, next to water, tea is the most consumed beverage in the world, with per capita consumption of ≈120 mL/d (2). Of the total amount of tea produced and consumed in the world, 78% is black, 20% is green, and <2% is oolong tea. Black tea is consumed primarily in Western countries and in some Asian countries, whereas green tea is consumed primarily in China, Japan, India, and a few countries in North Africa and the Middle East. Oolong tea production and consumption are confined to southeastern China and Taiwan (2).

Green, black, and oolong teas undergo different manufacturing processes. To produce green tea, freshly harvested leaves are rapidly steamed or pan-fried to inactivate enzymes, thereby preventing fermentation and producing a dry, stable product. Epicatechins are the main compounds in green tea, accounting for its characteristic color and flavor. For the production of black and oolong teas, the fresh leaves are allowed to wither until their moisture content is reduced to ≈55% of the original leaf weight, which results in the concentration of polyphenols in the leaves. The withered leaves are then rolled and crushed, initiating fermentation of the polyphenols. During these processes, the catechins are converted to theaflavins and thearubigins. Oolong tea is prepared by firing the leaves shortly after rolling to terminate the oxidation and dry the leaves.

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Normal oolong tea is considered to be about half as fermented as black tea. The fermentation process results in oxidation of simple polyphenols to more complex condensed polyphenols to give black and oolong teas their characteristic colors and flavors.

The composition of the tea leaves depends on a variety of factors, including climate, season, horticultural practices, and the type and age of the plant. The chemical composition of green tea is similar to that of the leaf. Green tea contains polyphenolic compounds, which include flavanols, flavandiols, flavonoids, and phenolic acids and account for 30% of the dry weight of green tea leaves. Most of the polyphenols in green tea are flavanols, commonly known as catechins; the major catechins in green tea are (−)-epicatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin, and (−)-epigallocatechin-3-gallate (EGCG). In black teas, the major polyphenols are theaflavin and thearubigin. The structures of the major polyphenolic compounds present in green and black tea are shown in Figure 1.

TEA POLYPHENOLS AND THE RISK OF CANCER

Abundant experimental and epidemiologic evidence accumulated mainly in the past decade from several centers worldwide provides a convincing argument that polyphenolic antioxidants present in green and black tea can reduce cancer risk in a variety of animal tumor bioassay systems (2–4). Most of the studies showing the preventive effects of tea were conducted with green tea; only a few studies assessed the usefulness of black tea (2). These studies showed that the consumption of tea and its polyphenolic constituents affords protection against chemical carcinogen– or ultraviolet radiation–induced skin cancer in the mouse model. Tea consumption also affords protection against cancers induced by chemical carcinogens that involve the lung, foreastomach, esophagus, duodenum, pancreas, liver, breast, colon, and skin in mice, rats, and hamsters. We reviewed this area of research (2), and the bioavailability of the polyphenols from tea has been established by others (5). The relevance of the extensive laboratory information for human health can be assessed only through epidemiologic observations, however, especially in a population with high cancer risk.

Much of the cancer-preventive effects of green tea are mediated by EGCG, the major polyphenolic constituent of green tea (2). One cup (240 mL) of brewed green tea contains up to 200 mg EGCG. Many consumer products, including shampoos, creams, drinks, cosmetics, lollipops, and ice creams, have been supplemented with green tea extracts and are available in grocery stores and pharmacies.

The use of biochemical modulators in cancer chemotherapy has been studied extensively (6). The adverse effects of modulating drugs can be life threatening, and their use increases the patient’s medication burden as well. Thus, the substances used in diet and beverages should be studied for their potential as biochemical modulators that could increase the efficacy of therapy. In this regard, Sadzuka et al (6) showed that the oral administration of green tea enhanced the tumor-inhibitory effects of doxorubicin on Ehrlich ascites carcinomas implanted in CDF1 and BDF1 mice. The study showed that green tea treatment increases the concentration of doxorubicin in tumor but not in normal tissue. If these observations can be verified in human populations, they may have relevance to cancer chemotherapy.

TEA POLYPHENOLS AND THE RISK OF CORONARY HEART DISEASE

Coronary heart disease is most prevalent in the Western world, probably as a result of the lifestyle in this part of the world, which includes a diet high in saturated fats and low physical activity, and the large proportion of the population who smoke cigarettes and have high blood pressure. A variety of epidemiologic
studies showed the preventive effect of green tea consumption against atherosclerosis and coronary heart disease (see references 1 and 7 and the references therein). Tea consumption has also been shown to reduce the risk of high blood cholesterol concentrations and high blood pressure (8). In addition, studies in experimental animals showed the preventive effect of green tea against atherosclerosis (9).

EFFECTS OF TEA POLYPHENOLS AGAINST OTHER DISEASES
Many studies have shown that the consumption of tea or its polyphenols can afford protection against diseases other than cancer and coronary heart disease. A few of these studies are as follows: Weisburger (10) showed that tea is protective against stroke; Fujita (11) and Kao and P’eng (12) reported that tea consumption lowers the risk of osteoporosis; Imai and Nakachi (13) reported protection against liver disease; Horiba et al (14), Terrada et al (15), and Young et al (16) reported that tea consumption provides protection against bacterial infection; and Nakayama et al (17) and Tao (18) found that tea provides protection against viral infection.

ANTIINFLAMMATORY EFFECTS OF TEA
In several studies from our laboratory and elsewhere, the polyphenolic fraction from green tea was shown to protect against inflammation caused by certain chemicals, such as 12-O-tetradecanoylphorbol-13-acetate, a principal irritant in croton oil (2, 19, 20), or by ultraviolet radiation B (290–320 nm) (21). Green tea has also been shown to be effective against the immunosuppression caused by ultraviolet radiation B (2, 22). In addition, green tea polyphenols have shown protection against cytokines induced by tumors (23).

MECHANISMS OF BIOLOGICAL EFFECTS OF TEA
Because tea consumption has been shown to have protective effects against a variety of diseases, defining the mechanisms of the biological effects of tea is important. In addition, elucidation of mechanisms may provide additional opportunities to intervene at other targets. Initial mechanistic studies (reviewed in reference 2) regarding the cancer chemopreventive effects of green tea or its polyphenols largely focused on 1) protection against mutagenicity and genotoxicity, 2) inhibition of biochemical markers of tumor initiation, 3) inhibition of biochemical markers of tumor promotion, 4) effects on detoxification enzymes, 5) trapping of activated metabolites of carcinogens, and 6) antioxidant and free radical scavenging activity. Novel mechanistic work to define the anticarcinogenic effects of polyphenolic extracts from green tea and its constituents has been pursued; recent advances in this area are described in the following sections.

Green tea activates mitogen-activated protein kinases
The activation of mitogen-activated protein kinases by green tea polyphenols was shown to be a potential signaling pathway in the regulation of phase II enzyme gene expression mediated by an antioxidant-responsive element (24). In this study, green tea polyphenols induced chloramphenicol acetyltransferase (CAT) activity in human hepatoma HepG2 cells transfected with a plasmid construct containing an antioxidant-responsive ele-

ment and a minimal glutathione S-transferase Ya promoter linked to the CAT reporter gene. This result indicates that green tea polyphenols stimulate the transcription of phase II detoxifying enzymes through the antioxidant-responsive element. In addition, green tea polyphenol treatment of HepG2 cells resulted in a significant activation of extracellular signal–regulated kinase 2 and c-Jun N-terminal kinase 1, which are members of the mitogen-activated protein kinase family. Green tea polyphenol treatment also increased messenger RNA amounts of the immediate-early genes c-Jun and c-fos.

EGCG inhibits urokinase activity
A widely publicized study showed that the anticancer activity of EGCG in green tea might be due to inhibition of the enzyme urokinase (u-plasminogen activator), one of the most frequently expressed enzymes in human cancers (25). With the use of molecular modeling, the authors showed that EGCG binds to urokinase, blocking His 57 and Ser 195 of the urokinase catalytic triad and extending toward Arg 35 from a positively charged loop of urokinase. This computer-based calculation was verified by quantifying the inhibition of urokinase activity with a spectrophotometric amidolytic assay. The validity of this finding has been challenged, however (26).

Green tea induces apoptosis and cell cycle arrest
In recent years, apoptosis has become a challenging area of biomedical research. The life spans of both normal and cancer cells within living systems are thought to be significantly affected by the rate of apoptosis, a programmed type of cell death that differs from necrotic cell death and is regarded as a normal process of cell elimination (27). It follows that the chemopreventive agents that can modulate apoptosis and thereby affect the steady state cell population may be useful in the management and therapy of cancer. Many cancer-chemopreventive agents induce apoptosis; and, conversely, several tumor promoters inhibit apoptosis (28–30). It is reasonable, therefore, to assume that chemopreventive agents that have proven effects in animal tumor bioassay systems or human epidemiologic studies on the one hand and that induce apoptosis of cancer cells on the other hand may have wider implications for the management of cancer. Only a few chemopreventive agents are known to cause apoptosis, however (31). We found that EGCG induced apoptosis and cell cycle arrest in human epidermoid carcinoma cells A431 (32). Importantly, we also found that the apoptotic response of EGCG was specific to cancer cells, because the induction of apoptosis was also observed in human carcinoma keratinocytes HaCaT, human prostate carcinoma cells DU145, and mouse lymphoma cells L5R but not in normal human epidermal keratinocytes.

EGCG suppresses extracellular signals and cell proliferation through epidermal growth factor receptor binding
Liang et al (33) showed that EGCG could significantly inhibit DNA synthesis in A431 cells. In addition, EGCG inhibited the protein tyrosine kinase activities of epidermal growth factor (EGF) receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor but not of pp60-src, protein kinase C, and protein kinase A. EGCG also inhibited the phosphorylation of EGF receptor by EGF and blocked the binding of EGF to its receptor. These findings suggest that EGCG might inhibit the process of tumor formation by blocking cellular signal transduction pathways.
EGCG blocks the induction of nitric oxide synthase by down-regulating transcription factor nuclear factor κB

Lin and Lin (34) assessed the effects of EGCG on nitric oxide production by murine peritoneal macrophages. Their results suggest that EGCG blocked early events of nitric oxide synthase induction by inhibiting the binding of transcription factor nuclear factor κB to the inducible nitric oxide synthase (iNOS) promoter, thereby inhibiting the induction of iNOS transcription.

EGCG and theaflavins inhibit tumor promoter-induced activator protein 1 activation and cell transformation

To examine antitumor promotion effects of EGCG and theaflavins in the molecular level, Dong et al (35) used a JB6 mouse epidermal cell line, a system that has been used extensively as an in vitro model for tumor promotion studies. EGCG and theaflavins inhibited EGF- or 12-O-tetradecanoyl-phorbol-13-acetate–induced cell transformation in a dose-dependent manner. EGCG and theaflavins also inhibited activator protein 1 (AP-1)-dependent transcriptional activity and DNA binding activity. Finally, this study showed that the inhibition of AP-1 activation occurs through the inhibition of a pathway dependent on c-Jun N-terminal kinase.

TEA AND CLINICAL TRIALS

Because epidemiologic studies and research findings in laboratory animals have shown the chemopreventive potential of tea polyphenols in cancer, the usefulness of these polyphenols for humans should be evaluated in clinical trials. The first such trial is being conducted by the MD Anderson Cancer Center in collaboration with the Memorial Sloan-Kettering Cancer Center; MD Anderson has obtained an Investigational New Drug application permit from the US Food and Drug Administration to begin phase 1 clinical trials. To examine the safety and possible efficacy of consuming the equivalent of ≥10 cups (≥2.4 L) of green tea/d, 30 cancer patients with advanced solid tumors will be given daily capsules of formulated powdered green tea for ≥6 mo (if the treatment appears beneficial).

CONCLUSION AND FUTURE DIRECTIONS

Dietary habits influence the risk of developing a variety of diseases, especially cancer and heart disease. The use of dietary substances is receiving increasing attention as a practical approach for reducing the risk of developing these diseases. Epidemiologic observations and laboratory studies have indicated that tea consumption may have beneficial effects in reducing certain types of cancer in some populations. Although a considerable body of information provides evidence supporting the preventive potential of tea against cancer, a proper understanding of the mechanisms by which tea polyphenols reduce the risk of diseases is necessary to devise strategies for better health. Black tea is the major form of tea consumed, but its chemistry, biological activities, and chemopreventive properties, especially of the polyphenols that are present, are not well defined.

Because information on the bioavailability of tea polyphenols after tea consumption is limited in humans, studies on absorption, distribution, and metabolism of green and black tea polyphenols in animals and humans are needed. After careful evaluation of the available data and additional studies, specific recommendations may be made for consumption of tea by humans. The usefulness of tea polyphenols may be extended by combining them with other consumer products, such as food items and vitamin supplements. This “designer-item” approach may be useful for the human population.

REFERENCES