ANTIOXIDANTS & REDOX SIGNALING
Volume 6, Number 3, 2004

Forum Review

Antioxidants of the Beverage Tea in Promotion of Human Health

IMTIAZ A. SIDDIQUI, FARRUKH AFAQ, VAQAR M. ADHAMI, NIHAL AHMAD, and HASAN MUKHTAR

ABSTRACT

Tea that contains many antioxidants is a pleasant and safe drink that is enjoyed by people across the globe. Tea leaves are manufactured as black, green, or oolong. Black tea represents ~78% of total consumed tea in the world, whereas green tea accounts for ~20% of tea consumed. The concept of "use of tea for promotion of human health and prevention and cure of diseases" has become a subject of intense research in the last decade. Diseases for which tea drinkers appear to have lower risk are simple infections, like bacterial and viral, to chronic debilitating diseases, including cancer, coronary heart disease, stroke, and osteoporosis. Initial work on green tea suggested that it possesses human health-promoting effects. In recent years, the research efforts have been expanded to black tea as well. Research conducted in recent years reveals that both black and green tea have very similar beneficial attributes in lowering the risk of many human diseases, including several types of cancer and heart diseases. For cancer prevention, evidence is so overwhelming that the Chemoprevention Branch of the National Cancer Institute has initiated a plan for developing tea compounds as cancer-chemopreventive agents in human trials. Thus, modern medical research is confirming the ancient wisdom that therapy of many diseases may reside in an inexpensive beverage in a "teapot." *Antioxid. Redox Signal.* 6, 571–582.

INTRODUCTION

PHENOLIC COMPOUNDS comprise one of the largest and most ubiquitous groups of plant metabolites. Plants synthesize them to protect against photosynthetic stress, reactive oxygen species (ROS), wounds, and herbivores. Based on food intake, these phenolic compounds form an important and major part of the human diet. The polyphenols present in the botanicals (fruits, vegetables, herbs, etc.) appear to be responsible for many of the protective effects against a variety of diseases (7, 12, 33, 57, 81). Consistent epidemiological data point to a reduced morbidity and mortality from various ailments in people consuming plant-derived substances. Many studies have shown the efficacy of naturally occurring botanical substances against an innumerable list of ailments (33, 44, 57, 81).

Early interest in polyphenols was related to their antinutritional effects *i.e.,* decreasing absorption and digestibility of food because of their ability to bind protein and minerals. Current interests in the plant polyphenols arise from the observations that these have antiinflammatory, anticarcinogenic, and antioxidative properties. Polyphenols are the potent antioxidants in foods and model systems, and they have been linked with the hypothesis that their redox activities may give them with specific health benefits. The present text reviews the available information on studies showing how tea and/or the polyphenolic antioxidants present therein play a role in the promotion of human health.

Department of Dermatology, University of Wisconsin, Madison, WI.

TEA ORIGIN AND ITS HEALTH-PROMOTING EFFECTS

Tea derived from the leaves of the plant *Camellia sinensis* of the family *Theaceae* has been consumed in Southeast Asia for thousands of years. Tradition says that emperor Shen Nung of China discovered tea for the first time in 2737 B.C. In ancient China, tea was lauded for various beneficial health-promoting effects, *e.g.,* as medicinal remedies for headaches, body aches, depression, immune enhancement, digestion, and detoxification, as an energizer, as an antioxidant, and to prolong life. From China, around 800 A.D., drinking of tea migrated to Japan from where it was introduced all over the world by traders and travelers. The Kamakura era (1191–1333) saw monk Eisai stressing the beneficial effect of tea in his book *Maintaining Health by Drinking Tea* in 1211, in which he emphasized, "Tea is a miraculous medicine for the maintenance of health." In present times, consumption of tea has been adopted and assimilated by many cultures around the world.

Approximately 2.5 million metric tons of dried tea is produced annually. Green tea, which amounts to 20% of total tea consumption, is primarily consumed in some Asian countries, such as Japan, China, Korea, and India, and a few countries in North Africa and the Middle East. Black tea is consumed in some Asian countries and Western nations and accounts for 78% of total tea consumed (44). Oolong tea is consumed in Southeastern China and Taiwan and totals a mere 2% of the consumption (44). There are also many products sold in the market as herbal tea, which are not derived from the plant *Camellia sinensis.* They are extracts of a variety of herbs, rather than the tea plant.

With growing age, a major issue of health importance becomes how to remain disease-free. Thus, an understanding of what to eat and drink and what to avoid is of paramount importance for maintaining a healthy lifestyle. Evidence suggests that tea has some potential of reducing the incidence of major diseases, especially when combined with a healthy lifestyle that includes plenty of exercise and minimizes mental stress. It also means consuming a diet that possesses health-promoting effects. The use of plant products for medical benefits has played an important role in nearly every culture on earth. Importantly, many plant products are good sources of antioxidants, a group of chemicals that have been shown to play an important role in maintaining human health and improving the quality of life for thousands of years (6).

Epidemiological as well as laboratory investigations have indicated that the consumption of tea is associated with a lower incidence of certain diseases (33, 44, 57). In recent years, many studies have attempted to unravel the possible health-promoting and therapeutic benefits of green tea (33, 44, 57). Potentially, green tea might provide humanity with a safe and healthful beverage. Recent research is showing that many of the beneficial effects of tea are mediated by a group of chemicals known as polyphenols (Fig. 1) (44, 57). Tea polyphenols (Fig. 1) are potent antioxidant substances that have the ability to counteract the harmful oxidant radicals, which are regarded to play the causative role in many chronic diseases, including heart diseases and cancer.

Tea, which contains L-theanine, a precursor of the nonpeptide antigen ethylamine, primed peripheral blood γδ T cells to mediate a memory response on reexposure to ethylamine and to secrete interferon-γ in response to bacteria. This unique combination of innate immune response and immunologic memory shows that γδ T cells can function as a bridge between innate and acquired immunity.

CHEMICAL CONSTITUENTS OF TEA

Typically, 2.5 g of tea leaves brewed for 3 min in 250 ml of hot water usually contains 620–880 mg of water-extractable solids (8). Tea polyphenols such as catechins, quercetin, myricetin, and kaempferol account for 30–42% of dry weight of solids in the brew (8). The major antioxidant catechins present in green tea are (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECG), (−)-epicatechin (EC), (+)-gallocatechin, and (+)-catechin (Fig. 1). EGCG accounts for 50–80% of the catechins and is believed to be responsible for most of the beneficial effects in biological model system (57). EGCG is an extremely strong antioxidant that has been shown to possess stronger antioxidant ability than vitamin E and vitamin C, which are well known physiological antioxidants. In addition, tea contains phenolic acids, mainly caffeic, quinic, and gallic acids (57). Theanine is an amino acid found only in tea leaves that imparts a pleasantly sweet taste to tea (57). Theanine is degraded to glutamic acid and has been shown to have relaxation effects in humans. Tea leaves are unique as they are a rich source of catechins, caffeine, and theanine. These constituents impart flavor and taste to tea beverages. The different types of teas differ with respect to how they are produced. Green tea production involves steaming fresh leaves at elevated temperatures followed by a series of drying and rolling steps so that the chemical composition essentially remains similar to that of the fresh leaves. Black tea production involves withering of plucked leaves followed by extended fermentation. Thus, depending upon the extent of fermentation, the chemical composition of most black teas is slightly different. Solar withering of tea leaves followed by partial fermentation produces oolong tea.

Green tea also contains caffeine, theophylline, and theobromine, the principal alkaloids, and gallic acids and theanine, the phenolic acids. A brewed cup of green tea contains up to 200 mg of EGCG. Black tea, in addition to the catechins, also contains thearubigins (15–20%), theaflavins (2–6%), and caffeine (44, 57). Caffeine is a natural component of all teas. Although a serving of tea usually contains less than half the caffeine of coffee, actual caffeine levels are dependent on specific blends and strength of brew. In general, green tea contains 3–6% and black tea contains 2–4% of dry weight caffeine. Oolong tea contains monomeric catechins, theaflavins, and thearubigins (44, 57).

BIOCHEMICAL PROPERTIES OF TEA

Tea is consumed worldwide for different reasons ranging from improving blood flow, combating cancer and cardiovas-

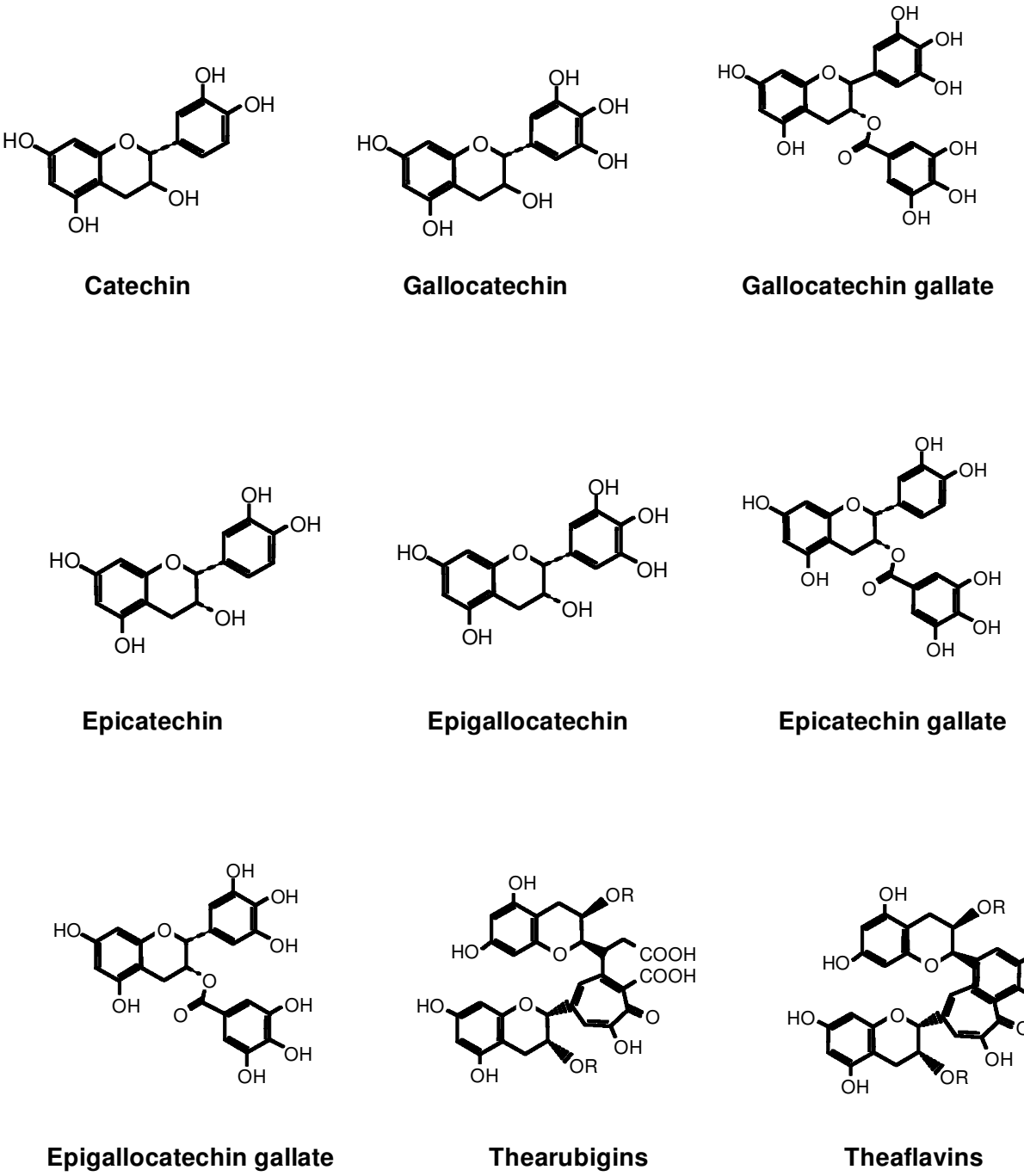

FIG. 1. Chemical structures of major green and black tea polyphenols. The phenolic groups provide antioxidant potential. R = galloyl group.

cular disease, eliminating various toxins, and improving resistance to various diseases. Supportive scientific evidence for these claims, surfacing in recent times, has led to an increase in consumption of green tea. Much emphasis is being placed on events at the cellular level due to its strong antioxidant activity. Several studies have suggested that the polyphenols, present in green tea, possess high antioxidant activities, which, in turn, protect cells against the adverse effects of damaging ROS that are constantly produced in the body. ROS, such as superoxide radical, hydroxyl radical, singlet oxygen, hydrogen peroxide, peroxynitrite, and alkoxyradicals, damage lipids, protein, and nucleic acids, and cellular components, such as ion channels, membranes, and chromatin, lead to cellular injury and cellular dysfunctions. These ROS are known to contribute to the etiology of many chronic health problems, including cardiovascular diseases, inflammatory diseases, diabetes, obesity, and cancer (44, 57). Wei *et al.* (80) have shown that the polyphenolic constituents of tea

TABLE 1. BENEFICIAL EFFECTS OF TEA CONSUMPTION

Disease	*Evidence in humans/animals*	*Possible targets/mechanisms*	*References*
Cardiovascular	Strong/moderate	Ability to inhibit the oxidation of LDL. Decrease the plasma phosphatidylcholine hydroperoxide level. Improve brachial artery dilation. Lower hypercholesterolemia to normal levels and reduce blood pressure.	18, 28, 48, 51, 68
Cancer	Population-dependent/ strong	Prevent the activation of procarcinogens. Protect against DNA scissions and mutations. Antioxidant actions. Block activated protein-1 and inhibit mitotic signal transducers. Reduce the occurrence of chromosomal aberrations. Inhibit the formation of 5-α-reductase. Inhibition of inducible NO synthase and generation of NO. Inhibition of urokinase. Induction of apoptosis and cell cycle arrest.	3, 13, 15, 31, 44, 56, 63, 75, 84
Diabetes	Suggestive/moderate	Inhibit the formation of sugars. Repress glucose production and phosphoenolpyruvate carboxykinase and glucose-6-phosphatase gene expression. Antihyperglycemic effects. Protect against cytokine-mediated damage of pancreatic β-cells.	29, 41, 77, 90
Obesity	Suggestive/moderate	Decline in food intake. Lower the blood levels of glucose and insulin. Increase the 24-h energy expenditure. Reduce high-fat diet-induced body weight gain.	17, 19, 43, 65
Osteoporosis	Some/none	Increase bone mineral density.	32
Arthritis	Suggestive/some	Reduction of inflammatory mediators, neutral endopeptidase activity, and IgG levels.	30
Neurological	Some/none	Inhibit tyrosinase. Inhibit COMT and prolylendopeptidase. APP secretion and protection against Aβ toxicity.	5, 54, 69
Bacterial	Suggestive/some	Modulation in composition of microflora. Inhibit the growth of clostridia and promote bifidobacteria colonization. Decrease in pH of feces. Generation of oxidants. Inhibiting collagenase activity.	23, 24, 59, 82

can act as scavengers of ROS and thereby prevent damage to cellular macromolecules. The scavenging activity of the specific catechin molecules is related to the number of *o*-dihydroxy and *o*-hydroxyketo groups, solubility, concentration, the accessibility of the active group to the oxidant, and the stability of the reaction product (57).

Some of the effects of tea polyphenols may also be due to the chelation of metal ions. Tea manifests chelating activity *in vivo* as indicated by the fact that tea consumption lowers absorption of dietary iron in controlled feeding studies and decreases body iron balance (57). Also, this chelating activity is important because it protects iron-loaded hepatocytes from lipid peroxidation by removing iron from these cells. The study has shown that EGCG may chelate the cations, which may contribute to its ability to inhibit angiotensin-converting enzyme. Polyphenols of tea chelate copper ions, and this mechanism has also been suggested to protect low-density lipoproteins (LDLs) against peroxidation. Because of its chelating properties, tea may additionally protect against toxicity due to heavy metals (57). Catechins may also affect signal transduction pathways, modulate many endocrine systems, and alter hormones and other physiological processes as a result of their binding these metals/ enzyme cofactors (42). The beneficial effects of tea consumption in health and the associated mechanisms by which it provides health benefits are summarized in Tables 1 and 2.

DISEASE CONTROL AND PREVENTION BY TEA

Tea and cancer

Cancer is believed not to be a single disease, but rather a conglomeration of several diseases. Most of the work on chemoprevention of cancer by tea has been conducted using green tea or its individual polyphenolic constituents, especially EGCG, which is a major constituent of green tea.

TABLE 2. CANCER CHEMOPREVENTIVE MECHANISMS OF TEA POLYPHENOLS

Mechanisms	*References*
Enhancement of detoxification enzymes	1, 49
Inhibition of cytochrome P450	78
Inhibition of mutagenicity	64, 79
Inhibition of genotoxicity	83
Inhibition of urokinase activity	39
Induction of apoptosis and cell cycle arrest	4
Activation of mitogen-activated protein kinases	46
Suppression of extracellular signals and cell proliferation	2, 55
Scavenging of free radicals	49
Inhibition of reactive oxygen species	45, 47, 49

Green tea catechins act as antioxidants and inhibit the growth of cancer in experimental animal models. This raises the possibility that consumption of green tea or its catechins may lower cancer risk in humans. Several epidemiological studies conducted so far have verified this suggestion. EGCG inhibits the action of enzymes to prevent the activation of procarcinogens, resulting in their inactivation and finally excretion (58). As shown by McArdle *et al.* (60), consumption of both green tea and black tea aqueous extracts influences the excretion of mutagens and promutagens in the urine of animals. In animal studies, the polyphenolic fraction isolated from green tea, the water extract of green tea, or individual polyphenolic antioxidants present in green tea have been shown to afford protection against chemically induced carcinogenesis in lung, liver, esophagus, pancreas, forestomach, duodenum, colon, and breast (3, 44, 57, 63). From some recent studies conducted, it is now believed that much of the cancer chemopreventive properties of green tea are mediated by EGCG, but other polyphenolic constituents may also possess similar effects (3, 44, 63). However, it is yet to be decided whether the different polyphenolic constituents of green tea work through similar or different mechanisms. The outcome of investigator-initiated studies could possibly suggest some convincing results in this regard.

The outcome of several epidemiological studies has suggested that tea and its associated compounds prevent certain types of cancers (57). This is understandable as cancer is a complex disease with multiple etiologies, even for one body site. Therefore, it seems to be a false hope that any single nutritional or synthetic agent can prevent or treat all types of cancer. However, based on a large volume of cell culture, animal studies, and human observational studies, there is a hope that tea consumption can retard cancer development at selected sites in some populations. The challenge is to find these populations that could reap the benefit.

Yamada and Tomita (84) and Yoshioka *et al.* (85) showed that EGCG exhibits substantial protection against DNA scissions, mutations, and nonenzymatic interception of superoxide anions in Ames test and superoxide tests. Black, green, and oolong teas were found to decrease significantly the reverse mutation induced by different mutagens in cell culture assays, suggesting that the antimutagenic action of these teas is closely associated with their antioxidant action (75, 84). EGCG and theaflavin-3,3′-digallate (the major polyphenol in black tea) block activated protein-1 (AP-1), a signal transducer that may play a critical role in the development of skin cancer, and can inhibit the mitotic signal transducers responsible for cell proliferation (15). A study showed that green tea polyphenols reduce the occurrence of chromosomal aberrations during mutagen exposure (83).

Green tea users have an ~50% reduction in risk for both esophageal cancer (21) and stomach cancer (87). Inhabitants of tea-producing districts in Japan have a lower mortality due to stomach cancer, possibly due to the regular consumption of green tea (70). In addition to regular drinking of tea, the Japanese population consumes green tea in all types of products, including candy, gums, bread, and many other edible products. Green tea was found to be linked to a reduced risk of oral cancer in northern Italians and a Chinese population, esophageal cancer in Chinese women, gastric cancer in Swedish adolescents, pancreatic cancer in residents of a retirement community in the U.S.A., and colon cancer among retired male self-defense officials in Japan (50, 57, 73). Cohort studies suggest a protective effect of green tea for colon, urinary bladder, stomach, pancreatic, and esophageal cancer (11). In a Japanese population survey, an overall protection together with a slowdown of the increase of cancer incidence with age was reported (37). The effects were found to be more pronounced when the consumption of tea was >10 cups per day. According to a study, consumption of seven or more cups of green tea per day significantly decreased the risk of stomach cancer (by 31%) compared with no green tea consumption (38). Regular drinkers of tea experienced a 12% and 53% lower incidence of cancer among males and females, respectively, compared with non-tea drinkers (40). When the intake of tea exceeded 200 g/month (dry weight of tea prior to brewing), the risk reduction remained unchanged among women, whereas the incidence of pancreatic cancer was further decreased by 43% in men (40). Another case-control study from Poland reported a significant reduction in risk of pancreatic cancer with increasing lifetime consumption of tea (89). An increased consumption of green tea was closely associated with a decreased number of axillary lymph node metastases among premenopausal patients with stage I and II breast cancer and overall decreased recurrence of stage I and II breast cancer (17% for individuals drinking more than five cups and 24% for those drinking less than four cups) (66).

Studies from *in vitro* systems have shown that catechin gallates (EGCG, ECG, etc.) selectively inhibit 5-α-reductase. This enzyme is known to be responsible for the conversion of testosterone to its diverse form 5-α-dihydrotestosterone (56), which, at high levels, has been implicated in the etiology of prostate cancer and male pattern baldness. We recently suggested that regular consumption of green tea might prolong life expectancy and quality of life in prostate cancer patients (25). Consistent with this, our recent studies have shown that green tea polyphenols inhibit the growth and progression of prostate cancer in transgenic adenocarcinoma of mouse prostate (TRAMP) model that mimics human disease (27). Prostate cancer is an ideal cancer type for prevention by green tea because the disease is typically diagnosed in older men and thus even a modest delay in disease development could produce a substantial benefit (27).

A proper understanding of the mechanisms of the biological effects of tea is essential for designing better strategies for cancer management. The protective effects of tea polyphenols have been attributed to the inhibition of enzymes such as cytochrome P_{450}, which are involved in the bioactivation of some carcinogens. Sachinidis *et al.* (71) showed that EGC reduces the phosphorylation of many proteins with different molecular weights at the tyrosine site, indicating that EGC may inhibit the protein tyrosine kinase activity or stimulate the protein phosphatase activity. Nitric oxide (NO) is a bioactive molecule that plays an important role in inflammation and carcinogenesis (52). Gallic acid, EGC, and EGCG were found to inhibit the protein expression of inducible NO synthase, as well as the generation of NO (13). Because many studies have suggested that the activation of AP-1 plays an important role in tumor promotion, McCarty (61) suggested

the down-regulation of this transcription factor as a general therapeutic strategy against cancer.

A much publicized study has proposed that the anticancer activity of EGCG may be associated with the inhibition of urokinase, which is one of the most frequently expressed enzymes in human cancers (39). Because the life span of both normal and cancer cells within a living system are determined by the rate of apoptosis (programmed cell death), chemopreventive agents that can induce apoptosis may affect the steady-state cell population. On the one hand, several cancer chemopreventive agents have been shown to induce apoptosis, whereas, on the other hand, the tumor-promoting agents inhibit apoptosis (10, 62). Therefore, it can be inferred that chemopreventive agents with proven effects in animal tumor bioassay systems and/or human epidemiology, and an ability to induce apoptosis of cancer cells, may have wider potential for the management of cancer. Studies from our laboratory have shown that EGCG induces apoptosis and cell cycle arrest in some cancer cell types (4). Importantly, this apoptotic response was specific for cancer cells as EGCG treatment did not result in the induction of apoptosis in normal human epidermal keratinocytes. Disruption of the cell cycle is believed to be the hallmark of a cancer cell (31). Studies from our laboratory have shown that EGCG treatment of human carcinoma cells resulted in inhibition of cell growth, cell cycle arrest, and induction of apoptosis (26). These studies were later verified in a variety of other cell systems in many laboratories worldwide.

Tea and cardiovascular diseases

Cardiovascular diseases, responsible for the greatest fatality count, are known as the biggest human killers in the world. Tea has been studied extensively for its effect on cardiovascular health. The impetus sparking this scientific inquiry was the result of many epidemiological studies that have suggested inverse association of tea with cardiovascular diseases. It was shown that one of the mechanisms for the possible protective effect of tea against cardiovascular diseases may be its ability to inhibit the oxidation of LDL, which is known to be involved in the development of atherosclerosis (51). Further, green tea consumption is shown to be associated with decreased serum concentrations of total cholesterol and with an affiliated decrease in the proportion of LDL. Other possible mechanisms for the action of tea include attenuating the inflammatory process in atherosclerosis, reducing thrombosis, promoting normal endothelial functions, and blocking the expression of cellular adhesion molecules. Green tea has been studied extensively in the prevention of cardiovascular diseases. Green tea extract containing catechins has been shown to decrease the plasma phosphatidylcholine hydroperoxide level, a marker of oxidized lipoprotein, suggesting that tea catechins are powerful antioxidants and, therefore, may decrease the risk of heart diseases (68). Imai and Nakachi (36) in a cross-sectional study revealed that people consuming >10 cups of green tea per day had lower levels of serum cholesterol, LDL, very-low-density lipoproteins, and triglycerides, an increase in level of high-density lipoprotein, and a reduction in atherogenic index. Recent studies indicate that the black tea consumption in patients with coronary heart disease did not affect *ex vivo* platelet aggregation, but short- and long-term tea consumption improved brachial artery dilation in patients with cardiovascular disease (18).

Studies have suggested that consumption of green tea is associated with protection against atherosclerosis (86). A reduced risk of death from coronary heart disease and stroke was found with tea consumption (51). In a long-term study of a Dutch cohort, tea consumption was associated with a lower risk of death from coronary heart disease and lower incidence of stroke. In a follow-up study in Rotterdam, an inverse association of tea intake with the severity of aortic atherosclerosis was observed (22). The Boston Area Health Study found that subjects who drank one or more cups of black tea per day had approximately half the risk of a heart attack compared with those who did not drink tea (74). The risk for developing stroke was 73% lower in the group with the highest intake of flavonoids (>28.6 mg/day) than in the group with the lowest intake (<18.3 mg/day) (48). A recent study has suggested that there is no inverse association between green tea intake and coronary artery diseases; however, an intake of $\geq$1 cup/day significantly decreases myocardial infarcation (34).

In a recent study conducted in Saudi adults, it was found that there is a positive dose-response effect between tea consumption and coronary heart diseases (28).

Tea and diabetes

Tea and its various preparations have been used extensively in China for the treatment of diabetes. One such preparation, Bai-Yu-Cha (BYC), made from the catechin-rich tender leaves of old tea trees grown in certain areas in China, is one such example. An aqueous extract of BYC (10 g/kg of body weight of mice), orally administered to mice, protects against experimentally induced damage of pancreatic islets, the major cause of diabetes, and oral administration of BYC at a dose of 1.5 g/kg also decreased the blood glucose concentration in normal rabbits (90). EC, EGC, gallocatechin, and caffeine individually do not have any antidiabetic activity. However, mixtures reconstructed from the isolated compounds, according to the relative levels of these four compounds in BYC, reproduce the protective action against diabetes induced by alloxan in mice. The blood-lowering effect of the prescription mixture is comparable to that of clinically used antidiabetic drugs (90).

It has been suggested that tea extracts might be useful as functional foods for diabetic patients, and the catechins in tea inhibit the formation of sugars that cause diabetic complications, such as cataracts, retinopathy, neuropathy, and nephropathy (41). Waltner-Law *et al.* (77) showed that EGCG represses glucose production and phosphoenolpyruvate carboxykinase and glucose-6-phosphatase gene expression by modulation of the redox state of the cell, suggesting that EGCG may have a beneficial effect for the treatment of diabetes. In a recent study, it was shown that EGCG protects against cytokine-mediated damage of pancreatic β-cells (29). Based on the findings, the author suggested that EGCG might be a possible agent for the prevention of diabetes mellitus progression.

Tea and obesity

Long-term use of green tea has been considered to be beneficial for keeping a healthy body weight. Kao *et al.* (43) have shown that EGCG given to rats by intraperitoneal injec-

tion at a dosage of 50–90 mg/kg of body weight daily could reduce body weight by ~20–30% within 2–7 days; however, other structurally related catechins, such as EC, EGC, and ECG, are not effective at the same dose. The reduction of body weight appears to be due to EGCG-induced decline in food intake, although the loss of appetite might involve neuropeptide(s) in tea. The effective dose of EGCG is, at first, 30–50 mg/kg of body weight; however, rats gradually acclimatize, and within 1 week higher doses of EGCG (100 mg/kg) are needed to reduce or prevent weight gain and the weight loss is reversible when EGCG administration is stopped (43). The EGCG effect on food intake is apparently not dependent on an intact leptin receptor. Lean (leptin receptor-positive) and obese (leptin receptor-deficient) male and female rats treated with EGCG lose weight and have lower blood levels of glucose, insulin, and serum levels of sex hormones, leptin, and insulin growth factor-I. EGCG may interact specifically with a component of the leptin receptor-independent appetite control pathway and reduce food intake.

Bell and Goodrick (9) observed that green tea increases the 24-h energy expenditure, suggesting a role in weight reduction. Diminished catechol-*O*-methyltransferase (COMT) activity delays the metabolism of norepinephrine and epinephrine and may cause subsequent increases in sympathetic thermogenesis. This may explain why humans increase their 24-h energy expenditure after consuming EGCG-containing green tea extracts and why EGCG alone or synergistically with caffeine augments and prolongs sympathetic stimulation of thermogenesis in rat brown adipose tissues (19). Obesity has also often been associated with decreased sympathetic nervous system activity; hence, sympathomimetic agents have been proposed as a possible way to partially correct this situation. One of these agents, caffeine, is present in varied amounts in all teas. Caffeine increases energy expenditure and reduces energy intake under some circumstances and thus aids in weight loss (17). Murase *et al.* (65) have shown that tea catechin resulted in a significant reduction of high-fat diet-induced body weight gain in experimental mice.

Tea and longevity

Some evidence suggests that tea drinking may also promote longevity, which is expressed as low mortality rates, among Japanese females who are traditional practitioners of the tea ceremony (72). Cutler (16) has shown that the higher the concentration of the antioxidants in the bodies of animals, the longer they live. This suggests that active consumption of agents that are effective antioxidants may slow the aging process. Catechins in green tea are far stronger antioxidants than the well-known antioxidant vitamin E (~20 times stronger). Although there is no direct evidence that suggests a relationship between green tea consumption and aging, the fact that it contains powerful antioxidants is suggestive that it can help slow the process of aging. The Saitama Cancer Center in Japan conducted an 8-year follow-up survey concerning the effects of green tea on the prolongation of human life using 8,500 participants in Saitama Prefecture. Those who had more than three cups of green tea every day had an average life span of 66 years for males and 68 years for females. However, those who had >10 cups of green tea per day had an average life span of 70 years for males and 74 years for females. In this study, a decreased relative risk of death from cardiovascular disease was also found for people consuming >10 cups of green tea a day, and, importantly, green tea consumption also had life-prolonging effects on cumulative survival (20). Our study has shown that consumption of 0.1% green tea polyphenols by TRAMP mice prolongs their overall survival more than twofold (27). Confirmation of these findings in other disease models needs verification before a generalized statement can be made. Nakachi *et al.* (67) found an apparent delay of cancer onset/death and all causes of death associated with increased consumption of green tea, specifically in ages before 79 in a prospective cohort study of a Japanese population with 13-year follow-up data. This was consistent with analyses of age-specific cancer death rate and cumulative survival, indicating a significant slowing of the increase in cancer death and all causes of death with aging. These results suggested that daily consumption of green tea in sufficient amounts would help to prolong life by avoiding premature death.

Tea and osteoporosis

Low bone mineral density known as "osteoporosis" is the biggest cause of fractures among elderly women. The leading cause of this disease is hormone deficiencies due to which the bones and joints become thin and fragile. A study by Hegarty *et al.* (32) suggested that drinking one to six cups of tea daily might significantly reduce the risk of bone fracture by increasing bone mineral density. In this study, of the 1,256 women between the ages of 65 and 76 surveyed, 1,134 consumed at least one cup of tea every day. Bone mineral density at the base of the spine and at two hip regions was significantly higher in tea drinkers when the data were adjusted to account for age and body weight.

Tea, arthritis, and inflammation

In one of our studies in a mouse model of arthritis (30), we found that consumption of green tea polyphenols produces a significant reduction in arthritis incidence with a marked reduction of inflammatory mediators, neutral endopeptidase activity, IgG, and type II collagen-specific IgG levels in arthritic joints. Many published studies have suggested that green tea has anti-inflammatory properties, and new research is beginning to explain the reasoning behind these observations. Previous animal studies and other laboratory research had found that polyphenols in green tea are potent antiinflammatory agents, but the mechanism behind this action is not well understood.

Tea and neurological effects

According to No *et al.* (69), tea components (EGCG, ECG, *etc.*) competitively inhibit tyrosinase, the rate-limiting enzyme in the synthesis of melanin, L-dihydroxyphenylalanine, norepinephrine, and epinephrine. EGCG and EGC competitively inhibit COMT, which is one of the major enzymes in the metabolism of catecholamines, associated with Parkinson's disease (5). A high activity of prolylendopeptidase is found in patients with Alzheimer's disease and other neuropathological disorders, and some studies have shown that

this enzyme could be inhibited by EGCG. A recent study has shown that green tea extract and its main polyphenolic constituent EGCG possess potent neuroprotective activity in cell culture and a mouse model of Parkinson's disease (54). The central hypothesis guiding this study was that EGCG might play an important role in amyloid precursor protein (APP) secretion and protection against toxicity induced by β-amyloid (Aβ). The study showed that EGCG enhances the release of the nonamyloidogenic soluble form of APP (sAPPα) into the conditioned media of human SH-SY5Y neuroblastoma and rat pheochromocytoma PC12 cells. sAPPα release was blocked by the hydroxamic acid-based metalloprotease inhibitor Ro 31-9790, which indicated mediation via α-secretase activity. Inhibition of protein kinase C (PKC) with the inhibitor GF109203X, or by down-regulation of PKC, blocked the EGCG-induced sAPPα secretion, suggesting the involvement of PKC. EGCG was found to result in the induction of phosphorylation of PKC. EGCG was not only able to protect, but it could rescue PC12 cells against the Aβ toxicity in a dose-dependent manner. In addition, administration of EGCG (2 mg/kg) to mice for 7 or 14 days significantly decreased membrane-bound holoprotein APP levels, with a concomitant increase in sAPPα levels in the hippocampus. EGCG markedly increased PKCα and PKCε in the membrane and the cytosolic fractions of mouse hippocampus. The results suggested EGCG has protective effects against Aβ-induced neurotoxicity and regulates secretory processing of nonamyloidogenic APP via the PKC pathway. In another model, EGCG was found to impart prevention of NO-mediated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced Parkinson's disease in mice (14).

Tea effects on bacterial growth

Goto *et al.* (23) demonstrated that tea flavonoids given to elderly women on feeding tubes were found to reduce fecal odor and favorably altered the gut bacteria. Similar results were observed with bedridden patients not on feeding tubes in a separate study with green tea (24). These studies have also raised the possibility of using green tea in other settings where gut bacteria are disturbed, such as after taking antibiotics. Tea polyphenols modulate the composition of the microflora in the gastrointestinal tract. A high content of clostridia and a low percentage of bifidobacteria have been observed in the intestinal microflora of patients with colon cancer. Tea polyphenols selectively inhibit the growth of clostridia and promote bifidobacteria colonization contributing to a decrease in the pH of feces (82). Viruses, bacteria, and worms have been implicated in the development of cancers; hepatitis viruses, herpes viruses, *Helicobacter pylori,* and parasitic worms are some well-known causes of cancer (57). Generation of powerful oxidants to destroy the invaders and protect the cells could be the mechanism underlying the effect. Bacteria can also synthesize nitrosating agents endogenously and activate macrophages (53). Tea polyphenols can destroy these nitrosating agents that are potentially carcinogenic. VacA is a major virulence factor of the widespread stomach-dwelling bacterium *Helicobacter pylori.* It causes cell vacuolation and tissue damage by forming anion-selective, urea-permeable channels in plasma and endosomal membranes. Tombola *et al.* (76) recently reported that green tea that contains polyphenols potently inhibited the toxin. These observations suggested that tea polyphenols or their derivatives might be useful in the prevention or cure of *H. pylori*-associated gastric diseases.

Green tea polyphenols are believed to offer protection against tooth decay by (a) killing the causative bacteria, such as *Streptococcus mutans* (35), (b) inhibiting the collagenase activity of the bacteria resident below the gum line (59), and (c) increasing the resistance of tooth enamel to acid-induced erosion (88). All teas are a rich source of fluoride and thus can strengthen tooth enamel. Even one cup a day can provide a significant amount of fluoride. Tea can also reduce plaque formation on teeth that can lead to gum inflammation and bleeding and eventually lost teeth. On the negative side, tea compounds can discolor teeth.

Miscellaneous effects of tea

Tea, which on average accounts for 40% of our daily fluid intake, helps to replace fluids that are lost through day-to-day activities, which is why doctors recommend that we drink at least 1.5 liters of fluid per day to prevent dehydration. But perhaps the most important reason to drink plenty of tea is that it helps people maintain enough water in their tissues. This is especially important during the hot summer time. Active, outdoors people and the elderly are particularly prone to dehydration if they are overly exposed to hot temperatures.

Tea is a naturally refreshing drink and has no calorie value when taken without milk and sugar. When taken with milk, which is a popular way of tea consumption globally, four cups of tea a day can provide significant amounts of the following nutrients: approximately 17% of the recommended intake for calcium, 5% for zinc, 22% for vitamin B_2, 5% for folic acid, and trace amounts of vitamins B_1 and B_6.

CONCLUSIONS

The accumulated data available from studies that have been conducted over the past two decades have provided a scientific basis for the health-promoting effects of tea. The data strongly suggest a potentially significant prophylactic role in human health for certain tea constituents, but the studies justifying this lie well in the future. A linear association between *in vitro* studies, animal studies, and human efficacy rarely exist in pharmacology. This should be examined directly in human populations under carefully controlled conditions to get positive results. A major focus of interest in tea comes from its high levels of polyphenols, which are potent antioxidants. The antioxidant nature of tea polyphenols has a broad spectrum of health benefits, which include prevention and treatment of cancer, cardiovascular diseases, inflammatory conditions, arthritis, asthma, periodontal disease, liver disease, cataracts, and macular degeneration. Tea polyphenols are also known to decrease the rate of cell division, especially of transformed or damaged cells involved in cancer development. Thus, the concept of tea as a cancer chemopreventive agent has gained much attention. All teas—green, black, and oolong—are considered to have health-promoting potential.

Among the different types of teas, the beneficial effects of green tea are much clearer because most tea-research work has been done with it. Based on the available data, it appears that black tea possesses similar beneficial effects.

Due to our diversity in food habits, lifestyle, heredity, age, gender, and environment, interpreting the data on the effects of tea on human health is difficult. In epidemiological studies of the effects of tea consumption on health promotion, the confounding factors are generally more variable than the effect tested because of which the results are often inconclusive. This is an issue with most studies where the beneficial or adverse effects of a single nutrient in a complex diet consumed by humans are examined. However, as elaborated in this article, there is a reason to believe that the consumption of tea may have health-promoting effects in humans due to the presence of polyphenols that are novel for the chemoprevention of various diseases. Perhaps the most important reason to drink plenty of tea is that it also helps people to maintain enough water in their tissues. We believe that there is still a long way to go as far as the research on the health-promoting effect of tea is concerned. The challenge for the future is to interpret what diseases and which populations could benefit most by consuming tea or its bioactive components.

ABBREVIATIONS

Aβ, β-amyloid; AP-1, activator protein-1; APP, amyloid precursor protein; BYC, Bai-Yu-Cha; COMT, catechol-*O*-methyltransferase; EC, epicatechin; ECG, epicatechin gallate; EGC, epigallocatechin; EGCG, epigallocatechin-3-gallate; LDL, low density lipoprotein; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; sAPPα, soluble form of amyloid precursor protein; TRAMP, transgenic adenocarcinoma of mouse prostate.

REFERENCES

1. Afaq F and Mukhtar H. Effects of solar radiation on cutaneous detoxification pathways. *J Photochem Photobiol* 63: 61–69, 2001.
2. Afaq F, Adhami VM, Ahmad N, and Mukhtar H. Green tea constituent (−)-epigallocatechin-3-gallate inhibits ultraviolet B-mediated activation of nuclear factor kappa B signaling pathway in normal human epidermal keratinocytes. *Oncogene* 22: 1035–1044, 2003.
3. Ahmad N, Katiyar SK, and Mukhtar H. Cancer chemoprevention by tea polyphenols. In: *Nutrition and Chemical Toxicity*, edited by Ioannides C. West Sussex, U.K.: John Wiley and Sons Ltd., 1996, pp. 301–343.
4. Ahmad N, Feyes DK, Nieminen A-L, Agarwal R, and Mukhtar H. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. *J Natl Cancer Inst* 89:1881–1886, 1997.
5. Akiyama K, Shimizu Y, Yokoi I, Kabuto H, Mori A, and Ozaki M. Effects of epigallocatechin and epigallocatechin-3-*O*-gallate on catechol-*o*-methyltransferase. *Neuroscience* 15: 262–264, 1989.
6. Ames BN. Dietary carcinogens and anticarcinogens. *Science* 221: 1256–1264, 1983.
7. Aviram M, Dornfeld L, Kaplan M, Coleman R, Gaitini D, Nitecki S, Hofman A, Rosenblat M, Volkova N, Presser D, Attias J, Hayek T, and Fuhrman B. Pomegranate juice flavonoids inhibit low-density lipoprotein oxidation and cardiovascular diseases: studies in atherosclerotic mice and in humans. *Drugs Exp Clin Res* 28: 49–62, 2002.
8. Balentine DA, Wiseman SA, Bouwens LC. The chemistry of tea flavonoids. *Crit Rev Food Sci Nutr* 37: 693–704, 1997.
9. Bell SJ and Goodrick GK. A functional food product for the management of weight. *Crit Rev Food Sci Nutr* 42: 163–178, 2002.
10. Boolbol SK, Dannenberg AJ, Chadburn A, Martucci C, Guo XJ, Ramonetti JT, Abreu-Goris M, Newmark HL, Lipkin ML, DeCosse JJ, and Bertagnolli MM. Cyclooxygenase-2 overexpression and tumor formation are blocked by sulindac in murine model of familial adenomatous polyposis. *Cancer Res* 56: 2556–2560, 1996.
11. Bushman JL. Green tea and cancer in humans: a review of the literature. *Nutr Cancer* 31: 151–159, 1998.
12. Cao Y, Cao R, and Brakenhielm E. Antiangiogenic mechanisms of diet-derived polyphenols. *J Nutr Biochem* 13: 380–390, 2002.
13. Chan MM, Fong D, Ho CT, and Huang HI. Inhibition of inducible nitric oxide synthase gene expression and enzyme activity by epigallocatechin gallate, a natural product from green tea. *Biochem Pharmacol* 54: 1281–1286, 1997.
14. Choi JY, Park CS, Kim DJ, Cho MH, Jin BK, Pie JE, and Chung WG. Prevention of nitric oxide-mediated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice by tea phenolic epigallocatechin 3-gallate. *Neurotoxicology* 23: 367–374, 2002.
15. Chung JY, Huang C, Meng X, Dong Z, and Yang CS. Inhibition of activator protein 1 activity and cell growth by purified green tea and black tea polyphenols in H-ras-transformed cells: structure–activity relationship and mechanisms involved. *Cancer Res* 59: 4610–4617, 1999.
16. Cutler RG. Antioxidants and longevity of mammalian species. *Basic Life Sci* 35: 15–73, 1985.
17. Doucet E and Tremblay A. Food intake, energy balance and body weight control. *Eur J Clin Nutr* 51: 846–855, 1997.
18. Duffy SJ, Keaney JF Jr, Holbrook M, Gokce N, Swerdloff PL, Frei B, and Vita JA. Short- and long-term black tea consumption reverses dysfunction in patients with coronary artery disease. *Circulation* 104: 151–156, 2001.
19. Dulloo AG, Seydoux J, Girardier L, Chantre P, and Vandermander J. Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord* 24: 252–258, 2000.
20. Fujiki H, Suganuma M, Okabe S, Komori A, Sueoka E, Sueoka N, Kozu T, and Sakai Y. Japanese green tea as a cancer preventive in humans. *Nutr Rev* 54: S67–S70, 1996.
21. Gao YT, McLaughlin JK, Blot WJ, Ji BT, Dai Q, and Fraumeni JF Jr. Reduced risk of esophageal cancer associated with green tea consumption. *J Natl Cancer Inst* 86: 855–858, 1994.
22. Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, and Witteman JC. Inverse association of tea flavonoid

intakes with incident myocardial infarction: the Rotterdam study. *Am J Clin Nutr* 75: 880–886, 2002.
23. Goto K, Kanaya S, and Nishikawa T. The influence of tea catechins on fecal flora of elderly residents in long-term care facilities. *Ann Long-Term Care* 6: 43–48, 1998.
24. Goto K, Kanaya S, Ishigami T, and Hara Y. The effects of tea catechins on fecal conditions of elderly residents in a long-term care facility. *J Nutr Sci Vitaminol (Tokyo)* 45: 135–141, 1999.
25. Gupta S and Mukhtar H. Green tea and prostate cancer. *Urol Clin North Am* 29: 49–57, 2002.
26. Gupta S, Ahmad N, Nieminen AL, and Mukhtar H. Growth inhibition, cell-cycle dysregulation, and induction of apoptosis by green tea constituent (−)-epigallocatechin-3-gallate in androgen-sensitive and androgen-insensitive human prostate carcinoma cells. *Toxicol Appl Pharmacol* 164: 82–90, 2000.
27. Gupta S, Hastak K, Ahmad N, Lewin JS, and Mukhtar H. Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. *Proc Natl Acad Sci U S A* 98: 10350–10355, 2001.
28. Hakim IA, Alsaif MA, Alduwaihy M, Al-Rubeaan K, Al-Nuaim AR, and Al-Attas OS. Tea consumption and the prevalence of coronary heart disease in Saudi adults: results from a Saudi national study. *Prev Med* 36: 64–70, 2003.
29. Han MK. Epigallocatechin gallate, a constituent of green tea, suppresses cytokine-induced pancreatic beta-cell damage. *Exp Mol Med* 35: 136–139, 2003.
30. Haqqi TM, Anthony DD, Gupta S, Ahmad N, Lee MS, Kumar GK, and Mukhtar H. Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. *Proc Natl Acad Sci U S A* 96: 4524–4529, 1999.
31. Harbour JW and Dean DC. Rb function in cell-cycle regulation and apoptosis. *Nat Cell Biol* 2: E65–E67, 2000.
32. Hegarty VM, May HM, and Khaw KT. Tea drinking and bone mineral density in older women. *Am J Clin Nutr* 71: 1003–1007, 2000.
33. Higdon JV and Frei B. Tea catechins and polyphenols: health effects, metabolism and antioxidant functions. *Crit Rev Food Sci Nutr* 43: 89–143, 2003.
34. Hirano R, Momiyama Y, Takahashi R, Taniguchi H, Kondo K, Nakamura H, and Ohsuzu F. Comparision of green tea intake in Japanese patients with and without angiographic coronary artery disease. *Am J Cardiol* 90: 1150–1153, 2002.
35. Horiba N, Maekawa Y, Ito M, Matsumoto T, and Nakamura H. A pilot study of Japanese green tea as a medicament: antibacterial and bactericidal effects. *J Endod* 17: 122–124, 1991.
36. Imai K and Nakachi K. Cross-sectional study of the effects of drinking green tea on cardiovascular and liver diseases. *Br Med J* 310: 693–696, 1995.
37. Imai K, Suga K, and Nakachi K. Cancer-preventive effects of drinking green tea among a Japanese population. *Prev Med* 26: 769–775, 1997.
38. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, and Tominaga S. Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. *Cancer Causes Control* 9: 209–216, 1998.
39. Jankun J, Selman SH, Swiercz R, and Skrzypczak-Jankun E. Why drinking green tea could prevent cancer. *Nature* 387: 561, 1997.
40. Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, and Fraumeni JF Jr. Green tea consumption and the risk of pancreatic and colorectal cancers. *Int J Cancer* 70: 255–258, 1997.
41. Kador PF, Kinoshita JH, and Sharpless NE. Aldolase reductase inhibitors: a potential new class of agents for the pharmacological control of certain diabetic complications. *J Med Chem* 28: 841–849, 1985.
42. Kao YH, Hiipakka RA, and Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. *Endocrinology* 141: 980–987, 2000.
43. Kao YH, Hiipakka RA, and Liao S. Modulation of obesity by a green tea catechin. *Am J Clin Nutr* 72: 1232–1233, 2000.
44. Katiyar SK and Mukhtar H. Tea in chemoprevention of cancer: epidemiological and experimental studies. *Int J Oncol* 8: 221–238, 1996.
45. Katiyar SK, Agarwal R, and Mukhtar H. Inhibition of spontaneous and photo-enhanced lipid peroxidation in mouse epidermal microsomes by epicatechin derivatives from green tea. *Cancer Lett* 79: 61–66, 1994.
46. Katiyar SK, Afaq F, Azizuddin K, and Mukhtar H. Inhibition of UVB-induced oxidative stress-mediated phosphorylation of mitogen-activated protein kinase signaling pathways in cultured human epidermal keratinocytes by green tea polyphenol (−)-epigallocatechin-3-gallate. *Toxicol Appl Pharmacol* 176: 110–117, 2001.
47. Katiyar SK, Afaq F, Perez A, and Mukhtar H. Green tea polyphenol (−)-epigallocatechin-3-gallate treatment of human skin inhibits ultraviolet radiation-induced oxidative stress. *Carcinogenesis* 22: 287–294, 2001.
48. Keli SO, Hertog MGL, Feskens EJM, and Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke. *Arch Intern Med* 156: 637–642, 1996.
49. Khan SG, Katiyar SK, Agarwal R, and Mukhtar H. Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer chemoprevention. *Cancer Res* 52: 4050–4052, 1992.
50. Kono S, Shinchi K, Ikeda N, Yanai F, and Imanishi K. Physical activity, dietary habits and adenomatous polyps of sigmoid colon: a study of self-defence officials in Japan. *J Clin Epidemiol* 44: 1255–1261, 1991.
51. Kono S, Shinchi K, Wakabayashi K, Honjo S, Todoroki I, Sakurai Y, Imanishi K, Nishikawa H, Ogawa S, and Katsurada M. Relation of green tea consumption to serum lipids and lipoproteins in Japanese men. *J Epidemiol* 6: 128–133, 1996.
52. Lala PK and Chakraborty C. Role of nitric oxide in carcinogenesis and tumour progression. *Lancet Oncol* 2: 149–156, 2001.
53. Lampe JW. Health effects of vegetables and fruits: assessing mechanisms of action in human experimental studies. *Am J Clin Nutr* 70(Suppl): 475S–490S, 1999.

54. Levites Y, Amit T, Mandel S, and Youdim MB. Neuroprotection and neurorescue against Aβ toxicity and PKC-dependent release of non-amyloidogenic soluble precursor protein by green tea polyphenol (−)-epigallocatechin-3-gallate. *FASEB J* 17: 952–954, 2003.
55. Liang Y-C, Lin-Shiau S-Y, Chen C-F, and Lin J-K. Supression of extracellular signals and cell proliferation through EGF receptor binding by (−)-epigallocatechin gallate in human A431 epidermoid carcinoma cells. *J Cell Biochem* 67: 55–65, 1997.
56. Liao S and Hiipakka RA. Selective inhibition of steroid 5-α-reductase isoenzymes by tea epicatechin-3-gallate and epigallocatechin-3-gallate. *Biochem Biophys Res Commun* 214: 833–838, 1995.
57. Liao S, Kao YH, and Hiipakka RA. Green tea: biochemical and biological basis for health benefits. *Vitam Horm* 62: 1–94, 2001.
58. Lin JK, Liang YC, and Lin-Shiau SY. Cancer chemoprevention by tea polyphenols through mitotic signal transduction blockade. *Biochem Pharmacol* 58: 911–915, 1999.
59. Makimura M, Hirasawa M, Kobayashi K, Indo J, Sakanaka S, Taguchi T, and Otake S. Inhibitory effect of tea catechins on collagenase activity. *J Periodontol* 64: 630–636, 1993.
60. McArdle NJ, Clifford MN, and Ioannides C. Consumption of tea modulates urinary excretion of mutagens in rats treated with IQ. Role of caffeine. *Mutat Res* 441: 191–203, 1999.
61. McCarty MF. Polyphenol-mediated inhibition of AP-1 transactivating activity may slow cancer growth by impeding angiogenesis and tumor invasiveness. *Med Hypotheses* 50: 511–514, 1998.
62. Mills JJ, Chari RS, Boyer IJ, Gould MN, and Jirtle RL. Induction of apoptosis in liver tumors by the monoterpene perillyl alcohol. *Cancer Res* 55: 979–983, 1995.
63. Mukhtar H and Ahmad N. Cancer chemoprevention: future holds in multiple agents. *Toxicol Appl Pharmacol* 158: 207–210, 1999.
64. Mukhtar H, Wang ZY, Katiyar SK, and Agarwal R. Tea components: antimutagenic and anticarcinogenic effects. *Prev Med* 21: 351–360, 1992.
65. Murase T, Nagasawa A, Suzuki J, Hase T, and Tokimitsu I. Beneficial effects of tea catechins on diet-induced obesity: stimulation of lipid catabolism in the liver. *Int J Obes Relat Metab Disord* 26: 1459–1464, 2002.
66. Nakachi K, Suemasu K, Suga K, Takeo T, Imai K, and Higashi Y. Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Jpn J Cancer Res* 89: 254–261, 1998.
67. Nakachi K, Eguchi H, and Imai K. Can teatime increase one's lifetime? *Ageing Res Rev* 2: 1–10, 2003.
68. Nakagawa K, Ninomiya M, Okuba T, Aoi N, Juneja LR, Kim M, Yamanaka K, and Miyazawa T. Tea catechin supplementation increases antioxidant capacity and prevents phospholipid hydroperoxidation in plasma of humans. *J Agric Food Chem* 47: 3967–3973, 1999.
69. No JK, Soung DY, Kim YJ, Shim KH, Jun YS, Rhee SH, Yokozawa T, and Chung HY. Inhibition of tyrosinase by green tea components. *Life Sci* 65: L241–L246, 1999.
70. Oguni I, Nasu K, Kanaya S, Ota Y, Yamamoto S, and Nomura T. Epidemiological and experimental studies on the anti-tumor activity by green tea extracts. *Jpn J Nutr* 47: 93–102, 1989.
71. Sachinidis A, Skach RA, Seul C, Ko Y, Hescheler J, Ahn HY, and Fingerle J. Inhibition of the PDGF beta-receptor tyrosine phosphorylation and its downstream intracellular signal transduction pathway in rat and human vascular smooth muscle cells by different catechins. *FASEB J* 16: 893–895, 2002.
72. Sadakata S, Fukao A, and Hisamichi S. Mortality among female practitioners of Chanoyu (Japanese "tea ceremony"). *Tohoku J Exp Med* 166: 475–477, 1992.
73. Schwarz B, Bischof HP, and Kunze M. Coffee, tea and lifestyle. *Prev Med* 23: 377–384, 1994.
74. Sesso HD, Gazlano JM, Buring JE, and Hennekens CH. Coffee and tea intake and the risk of myocardial infarction. *Am J Epidemiol* 149: 162–167, 1999.
75. Steele VE, Kelloff GJ, Balentine D, Boone CW, Mehta R, Bagheri D, Sigman CC, Zhu S, and Sharma S. Comparative chemopreventive mechanisms of green tea, black tea and selected polyphenol extracts measured by in vitro bioassays. *Carcinogenesis* 21: 63–67, 2000.
76. Tombola F, Campello S, De Luca L, Ruggiero P, Del Giudice G, Papini E, and Zoratti M. Plant polyphenols inhibit VacA, a toxin secreted by the gastric pathogen *Helicobacter pylori*. *FEBS Lett* 543: 184–189, 2003.
77. Waltner-Law ME, Wang XL, Law BK, Hall RK, Nawano M, and Granner DK. Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production. *J Biol Chem* 277: 34933–34940, 2002.
78. Wang ZY, Das M, Bickers DR, and Mukhtar H. Interaction of epicatechins derived from green tea with rat hepatic cytochrome P-450. *Drug Metab Dispos* 16: 98–103, 1988.
79. Wang ZY, Cheng SJ, Zhou ZC, Athar M, Khan WA, Bickers DR, and Mukhtar H. Antimutagenic activity of green tea polyphenols. *Muta Res* 223: 273–285, 1989.
80. Wei H, Zhang X, Zhao JF, Wang ZY, Bickers D, and Lebwohl M. Scavenging of hydrogen peroxide and inhibition of ultraviolet light-induced oxidative DNA damage by aqueous extracts from green and black teas. *Free Radic Biol Med* 26: 1427–1435, 1996.
81. Weisburger JH. Evaluation of the evidence on the role of tomato products in disease prevention. *Proc Soc Exp Biol Med* 218: 140–143, 1998.
82. Weisburger JH. Tea and health: the underlying mechanisms. *Proc Soc Exp Biol Med* 220: 271–275, 1999.
83. Weisburger JH, Nagao M, Wakabayashi K, and Oguri A. Prevention of heterocyclic amine formation by tea and tea polyphenols. *Cancer Lett* 83**:** 143–147, 1994.
84. Yamada J and Tomita Y. Antimutagenic activity of water extract of black tea and oolong tea. *Biosci Biotechnol Biochem* 12: 2197–2200, 1994.
85. Yoshioka H, Akai G, Yoshinaga K, Hasegawa K, and Yoshioka H. Protecting effect of a green tea percolate and its main constituents against gamma ray-induced scission of DNA. *Biosci Biotechnol Biochem* 60: 117–119, 1996.
86. Young W, Hotovec RL, and Romero AG. Tea and atherosclerosis. *Nature* 216: 1015–1016, 1967.
87. Yu GP, Hsieh CC, Wang LY, Yu SZ, Li XL, and Jin TH. Green-tea consumption and risk of stomach cancer: a

population-based case-control study in Shanghai, China. *Cancer Causes Control* 6: 532–538, 1995.
88. Yu H, Oho T, and Xu LX. Effects of several tea components on acid resistance of human tooth enamel. *J Dent* 23: 101–105, 1995.
89. Zatonski WA, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, and Walker AM. Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. *Int J Cancer* 53: 601–607, 1993.
90. Zhu DY, Li XY, Jiang FX, Yang YD, Zhou J, and Kubo M. Studies on anti-diabetic principles from Bai-Yu-Cha. *Planta Med* 56: 684–685, 1990.

Address reprint requests to:
Hasan Mukhtar, Ph.D.
Helfaer Professor of Cancer Research
Director and Vice-Chair for Research
Department of Dermatology
University of Wisconsin
Medical Sciences Center, Room B-25
1300 University Avenue
Madison, WI 53706

E-mail: hmukhtar@wisc.edu

Received for publication October 7, 2003; accepted February 19, 2004.

This article has been cited by:

1. Susanne M. Henning, Piwen Wang, Jonathan Said, Clara Magyar, Brandon Castor, Ngan Doan, Carmen Tosity, Aune Moro, Kun Gao, Luyi Li, David Heber. 2012. Polyphenols in brewed green tea inhibit prostate tumor xenograft growth by localizing to the tumor and decreasing oxidative stress and angiogenesis. *The Journal of Nutritional Biochemistry* . [CrossRef]
2. C. H. S. Ruxton, P. Mason. 2012. Is black tea consumption associated with a lower risk of cardiovascular disease and type 2 diabetes?. *Nutrition Bulletin* no-no. [CrossRef]
3. Pawan Kumar Maurya, Siya Prakash. 2011. Intracellular uptake of (-)epicatechin by human erythrocytes as a function of human age. *Phytotherapy Research* **25**:6, 944-946. [CrossRef]
4. Chwan-Li Shen, Jay J. Cao, Raul Y. Dagda, Thomas E. Tenner, Ming-Chien Chyu, James K. Yeh. 2011. Supplementation with Green Tea Polyphenols Improves Bone Microstructure and Quality in Aged, Orchidectomized Rats. *Calcified Tissue International* **88**:6, 455-463. [CrossRef]
5. Joshua D. Lambert, Ryan J. Elias. 2010. The antioxidant and pro-oxidant activities of green tea polyphenols: A role in cancer prevention. *Archives of Biochemistry and Biophysics* **501**:1, 65-72. [CrossRef]
6. Preeti Roy, Nidhi Nigam, Madhulika Singh, Jasmine George, Smita Srivastava, Hasnain Naqvi, Yogeshwer Shukla. 2010. Tea polyphenols inhibit cyclooxygenase-2 expression and block activation of nuclear factor-kappa B and Akt in diethylnitrosoamine induced lung tumors in Swiss mice. *Investigational New Drugs* **28**:4, 466-471. [CrossRef]
7. Petros Efthimiou, Manil Kukar. 2010. Complementary and alternative medicine use in rheumatoid arthritis: proposed mechanism of action and efficacy of commonly used modalities. *Rheumatology International* **30**:5, 571-586. [CrossRef]
8. Qin Shen, Fen Tian, Ping Jiang, Yanqiu Li, Li Zhang, Jingjing Lu, Jiawen Li. 2009. EGCG enhances TRAIL-mediated apoptosis in human melanoma A375 cell line. *Journal of Huazhong University of Science and Technology [Medical Sciences]* **29**:6, 771-775. [CrossRef]
9. Chwan-Li Shen, James K. Yeh, Jay J. Cao, Jia-Sheng Wang. 2009. Green tea and bone metabolism. *Nutrition Research* **29**:7, 437-456. [CrossRef]
10. Chwan-Li Shen, James K. Yeh, Barbara J. Stoecker, Ming-Chien Chyu, Jia-Sheng Wang. 2009. Green tea polyphenols mitigate deterioration of bone microarchitecture in middle-aged female rats. *Bone* **44**:4, 684-690. [CrossRef]
11. Shinya Toyokuni. 2008. Molecular mechanisms of oxidative stress-induced carcinogenesis: From epidemiology to oxygenomics. *IUBMB Life* **60**:7, 441-447. [CrossRef]
12. C.-L. Shen, P. Wang, J. Guerrieri, J. K. Yeh, J.-S. Wang. 2008. Protective effect of green tea polyphenols on bone loss in middle-aged female rats. *Osteoporosis International* **19**:7, 979-990. [CrossRef]
13. Kana Hayashi, Shinji Takai, Rie Matsushima-Nishiwaki, Yoshiteru Hanai, Kanefusa Kato, Haruhiko Tokuda, Osamu Kozawa. 2008. (-)-Epigallocatechin gallate reduces transforming growth factor #-stimulated HSP27 induction through the suppression of stress-activated protein kinase/c-Jun N-terminal kinase in osteoblasts. *Life Sciences* **82**:19-20, 1012-1017. [CrossRef]
14. HSIU-CHIN HUANG, HSIAO-YU CHEN, CHIA-YANG CHEN, TANG-LONG SHEN, JOHN HUANG, NENG-YU LIN, SHAO-YIN SUM, MEI-IENG CHE, MIN-CHUAN HUANG. 2008. AMMONIUM HYDROXIDE EXTRACTS FROM BLACK TEA INHIBIT GROWTH, MIGRATION AND INVASION OF COLON CANCER CELLS. *Journal of Food Biochemistry* **32**:2, 201-215. [CrossRef]
15. P ABBOUD, P HAKE, T BURROUGHS, K ODOMS, M OCONNOR, P MANGESHKAR, H WONG, B ZINGARELLI. 2008. Therapeutic effect of epigallocatechin-3-gallate in a mouse model of colitis. *European Journal of Pharmacology* **579**:1-3, 411-417. [CrossRef]

16. Ismail Celik, Yasin Tuluce. 2007. Elevation protective role ofCamellia sinensis andUrtica dioica infusion against trichloroacetic acid-exposed in rats. *Phytotherapy Research* **21**:11, 1039-1044. [CrossRef]
17. J YAMAUCHI, S TAKAI, R MATSUSHIMANISHIWAKI, Y HANAI, T DOI, H KATO, S OGURA, K KATO, H TOKUDA, O KOZAWA. 2007. (-)-Epigallocatechin gallate inhibits prostaglandin D2-stimulated HSP27 induction via suppression of the p44/p42 MAP kinase pathway in osteoblasts. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **77**:3-4, 173-179. [CrossRef]
18. H. Raza, A. John. 2007. In vitro protection of reactive oxygen species-induced degradation of lipids, proteins and 2-deoxyribose by tea catechins. *Food and Chemical Toxicology* **45**:10, 1814-1820. [CrossRef]
19. Imtiaz A SIDDIQUI, Mohammad SALEEM, Vaqar M ADHAMI, Mohammad ASIM, Hasan MUKHTAR. 2007. Tea beverage in chemoprevention and chemotherapy of prostate cancer. *Acta Pharmacologica Sinica* **28**:9, 1392-1408. [CrossRef]
20. E J Gardner, C H S Ruxton, A R Leeds. 2007. Black tea – helpful or harmful? A review of the evidence. *European Journal of Clinical Nutrition* **61**:1, 3-18. [CrossRef]
21. Lidwine Johannot, Shawn M Somerset. 2006. Age-related variations in flavonoid intake and sources in the Australian population. *Public Health Nutrition* **9**:08, 1045. [CrossRef]
22. T-F Hsu, A Kusumoto, K Abe, K Hosoda, Y Kiso, M-F Wang, S Yamamoto. 2006. Polyphenol-enriched oolong tea increases fecal lipid excretion. *European Journal of Clinical Nutrition* **60**:11, 1330-1336. [CrossRef]
23. K.V.P. Chandra Mohan , R. Subapriya , Y. Hara , Dr. S. Nagini . 2006. Enhancement of Erythrocyte Antioxidants by Green and Black Tea Polyphenols During 7,12-Dimethylbenz[a]anthracene-Induced Hamster Buccal Pouch Carcinogenesis. *Journal of Medicinal Food* **9**:3, 373-377. [Abstract] [Full Text PDF] [Full Text PDF with Links]
24. Dr. Shinya Toyokuni . 2006. Novel Aspects of Oxidative Stress-Associated Carcinogenesis. *Antioxidants & Redox Signaling* **8**:7-8, 1373-1377. [Abstract] [Full Text PDF] [Full Text PDF with Links]
25. L WU, H HSU, Y CHEN, C CHIU, Y LIN, J HO. 2006. Antioxidant and antiproliferative activities of red pitaya. *Food Chemistry* **95**:2, 319-327. [CrossRef]
26. D MANDAL, L LAHIRY, A BHATTACHARYYA, S BHATTACHARYYA, G SA, T DAS. 2006. Tumor-induced thymic involution via inhibition of IL-7R# and its JAK-STAT signaling pathway: Protection by black tea. *International Immunopharmacology* **6**:3, 433-444. [CrossRef]
27. Imtiaz A. Siddiqui, Vaqar M. Adhami, Mohammad Saleem, Hasan Mukhtar. 2006. Beneficial effects of tea and its polyphenols against prostate cancer. *Molecular Nutrition & Food Research* **50**:2, 130-143. [CrossRef]
28. Shinya Toyokuni, Shinya Akatsuka. 2006. What has been Learned from the Studies of Oxidative Stress-induced Carcinogenesis: Proposal of the Concept of Oxygenomics. *Journal of Clinical Biochemistry and Nutrition* **39**:1, 3-10. [CrossRef]
29. Arindam Bhattacharyya, Lakshmishri Lahiry, Debaprasad Mandal, Gaurisankar Sa, Tanya Das. 2005. Black tea induces tumor cell apoptosis by Bax translocation, loss in mitochondrial transmembrane potential, cytochrome c release and caspase activation. *International Journal of Cancer* **117**:2, 308-315. [CrossRef]
30. Bradford Frank, Sanjay Gupta. 2005. A Review of Antioxidants and Alzheimer's Disease. *Annals of Clinical Psychiatry* **17**:4, 269-286. [CrossRef]
31. Imtiaz A. Siddiqui, S. Raisuddin, Yogeshwer Shukla. 2005. Protective effects of black tea extract on testosterone induced oxidative damage in prostate. *Cancer Letters* **227**:2, 125-132. [CrossRef]
32. Minakshi Nihal, Nihal Ahmad, Hasan Mukhtar, Gary S. Wood. 2005. Anti-proliferative and proapoptotic effects of (?)-epigallocatechin-3-gallate on human melanoma: Possible implications for the chemoprevention of melanoma. *International Journal of Cancer* **114**:4, 513-521. [CrossRef]

33. Christos N Papandreou. 2005. The Proteasome as a Target for Cancer Treatment. *American Journal of Cancer* **4**:6, 359-372. [CrossRef]

34. Shinya Toyokuni . 2004. Redox Control of Carcinogenesis and Tumor Biology. *Antioxidants & Redox Signaling* **6**:3, 481-482. [Citation] [Full Text PDF] [Full Text PDF with Links]