Topical Review

TEA IN PROMOTION OF HUMAN HEALTH

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ABSTRAC

Because of its special aroma, taste and low cost, next to water, tea has been the most common beverage consumed by humans. Tea leaves are primarily manufactured as black, green, or oolong, with black tea representing approximately 80% of tea products consumed worldwide. Even though health beneficial effects of tea are known for centuries, the concept of "use of tea for promotion of human health and prevention and cure of diseases" has become a subject of research interest in recent years. The health promoting effects of tea are attributed to the polyphenolic antioxidants present therein. Diseases for which tea drinkers appear to have lower risk are simple infections like bacterial – and viral- infectivity to chronic debalating diseases that include cancer, coronary heart disease, stroke and osteoporosis. Initial studies suggested that green tea possess human health promoting effects. In recent years the research efforts have also been expanded to black tea. From the research conducted in recent years around the world, it is becoming clear that both black and green teas have very similar beneficial attributes in lowering the risk of many human diseases. The strongest evidence gathered so far is for two most dreaded diseases: cancer and heart disease. For cancer prevention the evidence is so overwhelming that the Chemoprevention Branch of the National Cancer Institute, United States of America has initiated a plan for developing tea compounds as cancer chemopreventive drugs in human trials. The outcome of these and many other investigator initiated trials is eagerly awaited. Thus, modern medical research is confirming the ancient wisdom that therapy of many diseases may reside in an inexpensive beverage in a "teapot".

Key words : health promotion ; disease prevention; chemopreventive therapy; polyphenols; antioxidants; heart; osteoporosis; cancer.

1. Origin of Tea and its Health Promoting Effects

The tea plant, *Camellia sinensis,* has been grown and consumed in Southeast Asia for thousands of years. In China, emperor Shen Nung discovered tea for the first time in 2737 BC (Harbowy and Balentine1997). In ancient China, tea was considered to be useful in many ways including as medicinal remedies for headaches, body aches, depression, immune enhancement, digestion, detoxification, as an energizer, as an antioxidant and to prolong life. From China, around 800 AD, drinking of tea migrated to Japan from where it was introduced all over the world by traders and travelers. In present times, consumption of tea has been adopted and assimilated by many cultures around the world. 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."

Of all the beverages consumed today, tea is undoubtedly one of the oldest**,** and most widely consumed beverage and is second only to water in most parts of the world. Tea drinking is a pleasurable experience that is enjoyed either alone or shared at social gatherings. The Japanese tea ceremony and the English four o'clock tea are well-known examples of how important tea has become in the traditions of some of the cultures in the world. One thing that makes tea attractive is that it comes cheap and is available in a variety of flavors.

As we grow older, a major issue of health importance becomes how to remain disease-free. Thus, an understanding of what to eat and drink

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and what to avoid is of paramount importance for maintaining a healthy lifestyle. Evidence is accumulating that tea has some potential to help reducing the incidence of major diseases, especially when combined with a healthy lifestyle that includes plenty of exercise and minimizing 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 for thousands of years to play an important role in maintaining human health and improving the quality of life (Ames 1983; Block 1993).

Epidemiological observations as well as laboratory investigations have indicated that the consumption of tea is associated with a lower incidence of certain diseases (Trevisanato and Kim 2000; Liao *et al.* 2001). Among all types of teas consumed, data on green tea appears more abundant. However, in recent years, many studies have attempted to unravel the possible health-promoting and therapeutic benefits of green tea (Trevisanato and Kim 2000; Liao *et al.* 2001; Dufresne and Farnworth 2001). 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 (Figure 1: Please see cover page) (Katiyar and Mukhtar 1996; Dufresne and Farnworth 2001;Liao *et al.* 2001). Tea polyphenols 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.

2. Tea and its Chemical Constituents

Tea from the leaves of *Camellia sinensis,* a plant of the Theaceae family, is cultivated in over 30 countries worldwide. Approximately 2.5 million metric tons of dried tea is produced annually. Green tea that 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 account for 78% of total tea consumed (Yang and Wang 1993; Katiyar and Mukhtar 1996). Oolong tea is consumed in Southeastern China and Taiwan and totals to a mere 2% of the consumption (Yang and Wang 1993; Katiyar and Mukhtar 1996). 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 tea plant.

Tea contains phenolic acids, mainly caffeic, quinic, and gallic acids (Dufresne and Farnworth 2001;Liao *et al.* 2001). Theanine is an amino acid found only in tea leaves that imparts a pleasantly sweet taste to tea (Liao *et al.* 2001). Theanine is degraded to glutamic acid and has been shown to have relaxation effects in humans. Tea contains up to one-third of dry weight of catechins and other polyphenols such as quercetin, myricitin and kaempferol (Dufresne and Farnworth 2001). 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.

The major antioxidant catechins present in green tea are (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), (-)-epicatechin (EC), (+)-gallocatechin, and (+)-catechin. Green tea also contains caffeine, theophylline, and theobromine, the principal alkaloids, and gallic acids and theanine, the phenolic acids. EGCG is the major polyphenolic

constituent present in green tea and constitutes 25 to 40% of the total catechin contents that is believed to be responsible for most of the beneficial effects in biological model system (Liao *et al.* 2001). A brewed cup of green tea contains up to 200 mg of EGCG. Black tea, in addition to the catechins, also contains thearubigins, theaflavins and caffeine (Katiyar and Mukhtar 1996; Dufresne and Farnworth 2001; Liao *et al.* 2001). Caffeine is a natural component of all teas. While a serving of tea usually contains less than half the caffeine of coffee, actual caffeine levels are dependent upon 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 thearubigns (Katiyar and Mukhtar 1996;Dufresne and Farnworth 2001; Liao *et al.* 2001).

3. Biochemical Properties of Tea

Some populations consume green tea to improve blood flow, combat cancer and cardiovascular disease, eliminate various toxins, and to improve resistance to various diseases. Many of these claims have supportive scientific evidences surfacing in recent times leading 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, protects cells against the adverse effects of damaging reactive oxygen species (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, this leads to cellular injury and cellular dysfunctions. ROS contributes to the etiology of many chronic health problems including cardiovascular diseases, inflammatory diseases, diabetes, obesity and cancer (Yang and Wang 1993; Katiyar and Mukhtar 1996; Dufresne and Farnworth 2001; Liao *et al.* 2001). The polyphenolic constituents of tea can act as scavengers of ROS and thereby prevent damage to cellular macromolecules. (Rice and Diplock 1993; Wei *et al.* 1996). The scavenging activity of the specific catechin molecules is related to the number of *o*-dihydroxy and *o*-hydroxyketo groups, C_2-C_3 double bonds, solubility, concentration, the accessibility of the active group to the oxidant, and the stability of the reaction product (Sergediene *et al.* 1999). It has been shown that tea catechins, especially EGCG, might also influence cellular mechanisms that are related to induction of mutagenesis, such as DNA synthesis and repair processes (Hyatsu *et al.* 1992).

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 (Liao *et al.* 2001). Also, this chelating activity is important since it protects iron-loaded hepatocytes from lipid peroxidation by removing iron-from these cells (Liao *et al.* 2001). EGCG may chelate the cations, which may contribute to its ability to inhibit angiotensin-converting enzyme (Liao *et al.* 2001). Polyphenols in all types of tea chelate copper ions and this mechanism has also been suggested to protect low-density lipoproteins from peroxidation (Yokozawa *et al.* 1997). Because of its chelating properties tea may additionally protect against toxicity due to heavy metals (Liao *et al.* 2001). 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 (Kao *et al.* 2000a). The beneficial effects of tea consumption in health are summarized in table 1 and the associated mechanisms by which it provides health benefits are outlined in table 2.

4. Tea in Disease Control and Prevention

4.1. Tea and Cardiovascular Diseases

Cardiovascular diseases are the greatest human killers in the world, and these than any other disease kill more people. One of the proposed mechanisms for the possible protective effect of

Table-1.
Beneficial effects of tea consumption

Disease	Evidence in Humans	Evidence in Animals	Key Reference
Cardiovascular	Strong	Moderate	Nakagawa *et al.* 1999, Hara 1992, Duffy *et al.* 2001 a and b, Kono *et al.* 1996, Sesso *et al.* 1999, Keli *et al.* 1996
Cancer	Population dependent	Strong	Lio *et al.* 2001, Katiyar and Mukhtar 1996, Drufresne and Farnworth 2001, Yang and Wang 1993, Mukhtar and Ahmad 1999, Ahmad *et al.* 1996, Gordon 1996, Kuroda and Hara 1999, Steele *et al.* 2000, Nakachi *et al.* 1998.
Diabetes	Suggestive	Moderate	Zhu *et al.* 1990, Murata *et al.* 1994, Kador *et al.* 1985, Waltner-Law *et al.* 2002.
Obesity	Suggestive	Moderate	Kao *et al.* 2000 b and c Dullo *et al.* 2000,Doucet and Trembley 1997.
Osteoporosis	Some	None	Hegarty *et al.* 2000, Kanis *et al.* 1999.
Arthritis	Suggestive	Some	Haqqi *et al.* 1999, Yang and Landau 2000
Neurological	Some	None	No *et al.* 1999, Akiyama *et al.* 1989.
Bacterial	Suggestive	Some	Horiba *et al.* 1991, Makimura *et al.* 1993, Yu H *et al.* 1995, Goto *et al.* 1998 and 1999,Weisburger 1999

tea against cardiovascular diseases is that tea polyphenols inhibit the oxidation of low-density lipoprotein (LDL), which is known to be involved in the development of atherosclerosis (Kono *et al.* 1996). 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 (Kono *et al.* 1996). Numbers of studies have been done in the field of cardiovascular disease chemoprevention using green tea. 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 (Nakagawa *et al.* 1999). A cross-sectional study revealed that people consuming more than ten cups of green tea per day had lower levels of serum cholesterol, LDL, very-low-density lipoprotein, and triglycerides, an increase in level of high-density lipoprotein, and a reduction in atherogenic index (Imai and Nakachi 1995). Polyphenols in tea (mainly catechins and

Table-2.
Cancer chemopreventive mechanisms of tea polyphenols

Mechanisms	References
Metabolism	
Enhancement of detoxification enzymes	Khan *et al.* 1992, Laskin *et al.* 1996, Afaq et al 2001
Inhibition of cytochrome P-450	Wang *et al.* 1988, Katiyar *et al* 2000
Inhibition of mutagenicity	Mukhtar *et al.* 1992,Wang *et al.* 1989, Kada *et al.* 1985
Inhibition of genotoxicity	Weisburger *et al.* 1994
Inhibition of urokinase activity	Jankun *et al.* 1997
Proliferation	
Induction of apoptosis and cell cycle arrest	Ahmad *et al.* 1997
Activation of mitogen activated protein kinases	Yu *et al.* 1997,Katiyar *et al* 2001a
Suppression of extracellular signals and cell proliferation	Liang *et al.* 1997, Afaq *et al* 2003
Oxidative Stress	
Scavenging of free radicals	Khan *et al.* 1992, Katiyar *et al.* 1993
Inhibition of reactive oxygen species	Khan *et al.* 1992, Katiyar *et al.* 1994, Terao et al 1994, Katiyar *et al* 2001b
Inhibition of tumor promoter-caused induction of cytokines	Katiyar *et al.* 1995

theaflavins) lower hypercholesterolemia to normal levels, reduce blood pressure, and decrease the risk of stroke in susceptible rats (Hara 1992). Recent studies by Duffy *et al.* . (2001a; b) 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.

Studies have suggested that consumption of green tea is associated with protection against atherosclerosis in the Japanese population (Kono *et al.* 1996). Tea consumption was found to reduce the risk of death from coronary heart disease and stroke (Young at al 1967; Hertog *et al.* 1993). 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 (Geleijnse *et al.* 1999 and 2002). 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 (Sesso *et al.* 1999). 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) (Keli *et al.* 1996). A recent study has suggested that there is no inverse association between green tea intake and Coronary Artery diseases (CAD), however its intake of $\geq$ 1 cup/day significantly decreases Myocardial Infarcation. (Hirano *et al.* 2002)

4. 2. Tea and Cancer

Cancer is not a single disease but rather a conglomeration of several diseases. In spite of the fact that black tea shares 80% of worldwide consumption, 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. 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, fore stomach, duodenum, pancreas, colon, and breast (Yang and Wang 1993; Ahmad *et al.* 1996; Katiyar and Mukhtar 1996; Mukhtar and Ahmad 1999; Dufresne and Farnworth 2001; Liao *et al.* 2001). Based on recent studies, 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 (Yang and Wang 1993; Ahmad *et al.* 1996; Katiyar and Mukhtar 1996; Mukhtar and Ahmad 1999). However, it is not clear whether the different polyphenolic constituents of green tea work through similar or different mechanisms. Green tea catechins act as antioxidants (ROS scavengers) 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. EGCG inhibits the action of enzymes to prevent the activation of procarcinogens, resulting in their inactivation and finally excretion (Gordon 1996 and Lin *et al.* 1999). Consumption of both green tea and black tea aqueous extracts influences the excretion of mutagens and promutagens in the urine of animals (McArdle *et al.* 1999). Intake of green tea increases the excretion of heterocyclic aryl amines formed during cooking of meat, poultry, fish etc. (Embola *et al.* 2001).

Tea flavonoids can directly neutralize the procarcinogens by their strong ROS scavenging action before cell damage occurs. EGCG was found to exhibit substantial protection against DNA scissions, mutations, and in nonenzymatic interception of superoxide anions in Ames test and superoxide tests (Yamada and Tonita 1994; Yoshioko *et al.* 1996). Black, green, and oolong teas were found to significantly decrease 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 (Yamada and Tonita 1994;Kuroda and Hara 1999; Steele *et al.* 2000). Green tea polyphenols have been shown to reduce the occurrence of chromosomal aberrations during mutagen exposure (Sasaki *et al.* 1993; Weisburger *et al.* 1994). EGCG and theaflavin-3-3'-digallate (the major polyphenol in black tea) block activated protein-1 (AP-1), a signal transducer that may play critical role in the development of skin cancer, and can inhibit the mitotic signal transducers responsible for cell proliferation (Chung *et al.* 1999).

Several epidemiological studies have suggested that tea and its associated compounds may prevent certain types of cancers (Trevisanato and Kim 2000; Liao *et al.* 2001). 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 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.

Green tea users have an approximate 50% reduction in risk for both esophageal cancer (Gao *et al.* 1994) and stomach cancer (Yu GP *et al.* 1995). Inhabitants of tea-producing districts in Japan have a lower mortality due to stomach cancer, possibly due to regular consumption of green tea (Kono *et al.* 1988; Oguni *et al.* 1989). 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 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 USA; and colon cancer amongst retired male self-defense officials in Japan (Kono *et al.* 1991; Schwarz *et al.* 1994; Liao *et al.* 2001). Cohort studies suggest a protective effect of green tea for colon, urinary bladder, stomach, pancreatic, and esophageal cancer (Bushman 1998; Landau *et al.* 1998). In a Japanese population survey, an overall protection together with a slowdown of the increase of cancer incidence with age was reported (Imai *et al.* 1997). The effects were found to be more pronounced when the consumption of tea was over 10 cups per day. According to a study, consumption of seven or more cups per day of green tea significantly decreased the risk of stomach cancer (by 31%) compared with no green tea consumption (Inoue *et al.* 1998). Regular drinkers of tea experienced a 12% and 53% lower incidence of cancer among males and females, respectively, compared with non-tea drinkers (Ji

et al. 1997). 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 (Ji *et al.* 1997). Another case-control study from Poland reported a significant reduction in risk of pancreatic cancer with increasing lifetime consumption of tea (Zatonski *et al.* 1993). 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) (Nakachi *et al.* 1998). Contrary to the above, however, two recent studies did not find any association between green tea consumption and stomach or colon cancer (Cerhan *et al.* 2001; Hoshiyama *et al.* 2002).

In vitro studies revealed that catechin gallates selectively inhibit 5-a-reductase. This enzyme is responsible for the conversion of testosterone to 5-a-dihydrotestosterone (Satsung *et al.* 1995), 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 (Gupta and Mukhtar 2002). 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 (Gupta *et al.* 2001). Prostate cancer is an attractive target 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 (Gupta *et al.* 2001). From this and other previous studies it is now generally believed that tea drinking has cancer chemopreventive effects (Schwarz *et al.* 1994; Yu GP *et al.* 1995).

A proper understanding of the mechanisms of the biological effects of tea is essential in designing better strategies for cancer chemoprevention. Recent studies have evaluated the molecular mechanisms involved in the biological effects of tea polyphenols. The protective effects of these substances have been attributed to the inhibition of enzymes such as cytochrome P450, which are involved in the bio-activation of some carcinogens (Yu R *et al.* 1997). EGC was also found to reduce 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 (Lu *et al.* 1998; Sachinidis *et al.* 2002). Nitric oxide (NO) is a bioactive molecule that plays an important role in inflammation and carcinogenesis (Lala and Chakraborty 2001). Gallic acid, EGC, and EGCG were found to inhibit the protein expression of inducible NO-synthase as well as the generation of NO (Chan and Huang 1997; Lin and Lin 1997). Because many studies have suggested that the activation of AP-1 plays an important role in tumor promotion, the down-regulation of this transcription factor has been suggested a general therapeutic strategy against cancer (McCarty 1998). 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 (Jankun *et al.* 1997). 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 (Fesus *et al.* 1995). On one hand, several cancer chemopreventive agents have been shown to induce apoptosis, whereas, on the other hand, the tumor promoting agents inhibit apoptosis (Mills *et al.* 1995;Boolbol *et al.* 1996). 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. At present, only a limited number of chemopreventive agents are known to cause

apoptosis (Jiang *et al.* 1996). Our studies have shown that EGCG induces apoptosis and cell cycle arrest in some cancer cell types (Ahmad *et al.* 1997). 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 (Harbour and Dean 2000). Studies from our laboratory have shown that EGCG treatment of human carcinoma cells resulted in inhibition of cell growth and the arrest of cells and induction of apoptosis (Gupta *et al.* 2000). These studies have been verified in a variety of other cell systems in many laboratories worldwide.

4.3. Tea and Diabetes

Tea and its various preparations have been extensively used in China, for the treatment of diabetes. Bai-Yu-Cha (BYC), one such preparation, 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 body weight of mice), orally administered to mice, protects against experimentally induced damage of pancreatic islets, the major cause of diabetes (Zhu *et al.* 1990). Orally administered BYC at a dose of 1.5 g/kg also decreases the blood glucose concentration in normal rabbits (Zhu *et al.* 1990). EC, EGC, GC, and caffeine individually do not have any anti-diabetic 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 (Zhu *et al.* 1990). The blood-lowering effect of the prescription mixture is comparable to that of clinically used antidiabetic drugs (Zhu *et al.* 1990).

It has been suggested that tea extracts might be useful as functional foods for diabetic patients (Murata *et al.* 1994). Catechins in tea inhibit the formation of sugars that cause diabetic complications, such as cataracts, retinopathy, neuropathy, and nephropathy (Kador *et al.* 1985). EGCG has been shown to 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 (Waltner-Law *et al.* 2002).

4.4. Tea and Obesity

Long-term use of green tea is considered to be beneficial in oriental countries for keeping a healthy body weight. However, supporting evidence for this became evident only recently. EGCG given to rats by intraperitoneal injection at a dosage of 50 to 90 mg EGCG/kg body wt daily could within 2 to 7 days reduce body weight by about 20 to 30% (Kao *et al.* 2000 b). Other structurally related catechins, such as EC, EGC, and ECG, are not effective at the same dose. Reduction of body weight appears to be due to EGCG-induced reduction in food intake, although the loss of appetite might involve neuropeptide(s) in tea. The effective dose of EGCG is, at first, 30 to 50 mg EGCG/kg body weight; however, rats gradually adapt and within one week higher doses of EGCG (100 mg/kg) are needed to reduce or prevent weight gain. The weight loss is reversible when EGCG administration is stopped (Kao *et al.* 2000 c). 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 (Kao *et al.* 2000 b and c). EGCG may interact specifically with a component of leptin receptor-independent appetite control pathway and reduce food intake. Green tea increases the 24-hour energy expenditure suggesting a role in weight reduction (Bell and Goodrick 2002). 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

(Dulloo *et al.* 2000). Obesity has also often been associated to a 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 aiding in weight loss (Astrup *et al.* 1995; Doucet and Trembley 1997).

4.5. Tea and Longevity

There is some evidence that tea drinking may also promote longevity expressed as low mortality rates among Japanese females who are traditional practitioners of the tea ceremony (Sadakata 1995). It has been shown, for example, that the higher the concentration of the antioxidants in the bodies of animals, the longer they live (Cutler 1985). This suggests that active consumption of agents that are effective antioxidants may slow the aging process. Green tea is rich in antioxidizing compounds. It has recently been demonstrated that catechins in green tea are far stronger antioxidants than the well known antioxidant vitamin E (about 20 times stronger) (Rice- Evans 1999). 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 8500 participants in Saitama Prefecture. Those who had more than 3 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 more than 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 over 10 cups of green tea a day, and, importantly, green tea consumption also had life-prolonging effects on cumulative survival (Fujiki *et al.* 1996). Our studies have shown that consumption of 0.1% GTP to TRAMP mice prolongs their overall survival more than two fold (Gupta *et al.* 2001). Confirmation of these findings to other disease models needs verification before a generalize statement could be made.

4.6. Tea and Osteoporosis

Low bone-mineral density known as osteoporosis is the biggest cause of fractures among elderly women. Hormone deficiencies are the leading cause of this disease where bones and joints become thin and fragile. A recent study suggests that drinking daily one to six cups of tea may significantly reduce the risk of bone fracture by increasing bone mineral density. Studies suggest that isoflavonoids in tea increase bone mineral density and help reduce the risk of fractures in old age (Hegarty *et al.* 2000). Of the 1256 women between the ages of 65 and 76 were surveyed, 1134 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 (Hegarty *et al.* 2000). Tea is reported to protect against hip fractures in a population-based study (Kanis *et al.* 1999).

4.7. Tea, Arthritis and Inflammation

In a study in mice, we found that consumption of green tea polyphenols produces a significant reduction in arthritis incidence with a marked reduction of inflammatory mediators, of neutral endopeptidase activity, of IgG and type II collagen-specific IgG levels in arthritic joints (Haqqi *et al.* 1999). Many published studies have suggested that green tea has anti-inflammatory properties and new research is beginning to explain reasoning behind these effects. Previous animal studies and other laboratory researches had found that polyphenols in green tea are potent anti-inflammatory agents, but the mechanism behind this action is not well understood. EGCG inhibits the expression of the interleukin gene involved in the inflammatory response (Suganuma *et al.* 2000).

4.8. Tea and Neurological Effects

Tea components such as EGCG and ECG competitively inhibit tyrosinase, the rate-limiting enzyme in the synthesis of melanin, L-dihydroxyphenylalanine, norepinephrine, and

epinephrine (No *et al.* 1999). EGCG and EGC competitively inhibit COMT, one of the major enzymes in the metabolism of catecholamines, which are associated with Parkinson's disease (Akiyama *et al.* 1989). A high activity of prolylendopeptidase is found in-patients with Alzheimers disease and other neuropathological disorders and some studies have shown that this enzyme could be inhibited by EGCG (Fan *et al.* 1999).

4.9 Tea Effects on Bacterial Growth

Green tea polyphenols are believed to offer protection against tooth decay by: (i) killing the causative bacteria, such as *Streptococcus mutans* (Horiba *et al.* 1991); (ii) inhibiting the collagenase activity of the bacteria resident below the gum line (Makimura *et al.* 1993); and (iii) increasing the resistance of tooth enamel to acid induced erosion (Yu H *et al.* 1995). 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.

In Japan, tea flavonoids given to elderly women on feeding tubes were found to reduce fecal odor and favorably altered the gut bacteria (Goto *et al.* 1998). The study was repeated in bedridden patients not on feeding tubes, and again green tea was shown to improve their gut bacteria (Goto *et al.* 1999). These studies have also raised the possibility of using green tea in other settings where gut bacteria are disturbed, such as after taking antibiotics. In the gastrointestinal tract tea polyphenols modulate the composition of the microflora. A high content of Clostridia and a low percent 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 (Weisburger 1999). 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 (Liao *et al.* 2001). Tea can play another role in the prevention of cancer through its antimicrobial activity (Weisburger 1999). It has been demonstrated that tea can inhibit the growth of *Helicobacter pylori*, which is associated with gastric cancer (Ernest 1999). The cellular process involved could be the generation of powerful oxidants to destroy the invaders and protect the cells. Bacteria can also synthesize nitrosating agents endogenously and activate macrophages (Lamne 1999). Nitrosating agents that are potentially carcinogenic and can be destroyed by polyphenols.

4.10 Miscellaneous Effects of Tea

Tea is a naturally refreshing drink and when taken without milk and sugar has no calorie value. 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 B2, 5% for folic acid, and trace amounts of vitamins B1 and B6.

Tea helps to replace fluids that are lost through day-to-day activities, which is why doctors recommend that we drink at least 1.5 litres 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 elderly are particularly prone to dehydration if they are overly exposed to hot temperatures. Tea, which on average accounts for 40% of our daily fluid intake, can help reach the daily target of 1.5 litres.

5. Conclusions

Studies that have been conducted over past one and a half decades have provided a scientific basis for the health promoting effects of tea. A major focus of interest in tea comes from its high levels of polyphenols, which are potent antioxidants. Due to its antioxidant nature, tea polyphenols have 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 also 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 of tea-research work has been done with it. Based on the available data, it appears that black tea possesses similar beneficial effects.

Studies of the effect of tea on human populations are very complex. Due to our diversity in food habits, lifestyle, heredity, age, gender and environment, the interpretation of the data 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 chapter, there is a reason to believe that the consumption of tea may have health-promoting effects in humans. Perhaps the most important reason to drink plenty of tea is that it also helps people to maintain enough water in their tissues. Active, outdoors people are particularly prone to dehydration if they are overly exposed to hot temperatures especially in summers. Scientists believe that there's still a long way to go as far as the research on health promoting effect of tea is concerned. The challenge for the future is to decipher what diseases and which populations could benefit most by consuming tea or its bioactive components.

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