Review

Mechanisms of chronic disease causation by nutritional factors and tobacco products and their prevention by tea polyphenols☆

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Summary

The beverage tea, from the top leaves of the plant *Camellia sinensis* is one of the most widely used beverages in the world, second only to water. Black and green tea have mostly similar actions. The active components are polyphenols, mainly epigallocatechin gallate in green tea, and the tea leaf polyphenol oxidase mediated oxidation to oolong and black tea, yielding other polyphenols, theaflavin and thearubigins. There is 40−50 mg caffeine in a 160-ml cup of tea. The chemopreventive effects of tea depend on: (1) its action as an antioxidant; (2) the specific induction of detoxifying enzymes; (3) its molecular regulatory functions on cellular growth, development and apoptosis; and (4) a selective improvement in the function of the intestinal bacterial flora. The oxidation of LDL cholesterol, associated with a risk for atherosclerosis and heart disease, is inhibited by tea. Many of cancers are caused by lifestyle elements. One is cigarette and tobacco use, leading to cancer in the oral cavity, esophagus and lung, inhibited by tea. Mice administered a tobacco nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), developed significantly fewer lung tumors than controls when given green tea or its major polyphenol, epigallocatechin gallate (EGCG). Tea suppressed the formation of 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA damage, in the lung DNA of mice given NNK. Gastric cancer, caused by a combination of *Helicobacter pylori* and salted foods, is lower in tea drinkers. Western nutritionally-linked cancers of the breast, colon, prostate and pancreas can be inhibited by tea. The formation of genotoxic carcinogens for these target organs during the cooking of meats, heterocyclic amines, and their effects were decreased by tea. Tea inhibited the formation of reactive oxygen species and radicals and induced cytochromes P450 1A1, 1A2 and 2B1, and glucuronosyl transferase. The higher formation of glucuronides represents an important mechanism in detoxification. The developmental aspects and growth of cancers through promotion are decreased by tea. The regular use of a widely available, tasty, inexpensive beverage, tea, has displayed valuable preventive properties in chronic human diseases. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Heart disease; Cancer; Growth; Tobacco; Nutrition; Heterocyclic amines; Tea; Caffeine; Enzyme induction; Glucuronosyl transferase

1. Introduction

This review deals with the multiple beneficial roles of black and green tea in lowering the risk of smoking- and tobacco-related diseases, and of nutritionally-linked illnesses, with emphasis on the underlying mechanisms.

Research in geographic pathology indicates that chronic diseases such as coronary heart disease, stroke and varied types of cancer have a lower incidence in countries where traditional nutritional habits involve the frequent intake of vegetables and fruits. Consumption of such foods can be interpreted to reflect an adequate intake of micronutrients, vitamins and minerals. Yet the major benefit of these foods is their content in protective antioxidant chemicals such as quercetin or genistein (Mazur and Adlercreutz, 2000). There is great scientific interest in the field of phytochemicals, as nutritional tools for chronic disease prevention, the definitive approach to disease control, to reach an old age in good health (Weisburger, 2000). A number of reviews on the worldwide role of tea in nutrition and disease provide background (Hirayama, 1990; Blot et al., 1997; Kohlmeier et al., 1997; Bravo, 1998; Bushman, 1998; Harman et al., 1998; Mukhtar and Ahmad, 2000; Ohigashi, 2000).

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2. Green and black tea

In the context of nutrition, research has established the favorable effects on health of a plant product that is not eaten, but consumed as a liquid, namely tea, an extract of the leaves of the plant *Camellia sinensis* with hot water. Humans have drunk tea for thousands of years. It was first mentioned almost 5000 years ago, (Weisburger and Comer, 2000). There have been descriptions of the use of tea to improve health and even to cure specific diseases. Even if there were no therapeutic benefits, tea is a tasty and inexpensive beverage that is easily prepared. It is an excellent means to meet the physiological needs for fluid intake about 2–3 l per day. Eight cups of tea a day would provide almost one-half of this requirement. Tea consumed at moderate temperatures has not displayed any acute or chronic toxic effects, and in fact, it is health promoting. Schwarz et al. (1994) described regular tea drinkers as individuals with a generally healthy lifestyle.

The leaves of the plant *C. sinensis* contain about one-third of the dry weight as polyphenols, and also the enzyme, polyphenol oxidase. When the leaves are harvested, withered and immediately steamed or heated, the polyphenol oxidase is inactivated, yielding green tea, as was done originally in China (Graham, 1992; Balentine, 1997). However, if the leaves at harvest are withered, rolled and crushed, the polyphenol oxidase liberated converts the polyphenols into those typical of oolong tea with a 30-min reaction time, or black tea with a 60–90-min reaction time, after which the product is dried in a stream of hot air. Therefore, oolong and black teas stem from the biochemical oxidation of the tea polyphenols. In the trade, this process is called "fermentation", technically a wrong term that is misunderstood by lay people. Thus, black tea is not consumed in some Muslim countries, because "fermented" beverages are not allowed. The polyphenols in green tea are catechin derivatives, and the main product is the polyphenol epigallocatechin gallate. During the biochemical oxidation of these catechins oxidation yields the polyphenols in black tea, such theaflavin and thearubigins, a fairly complex number of polymeric chemicals, but that retain potent physiological and biochemical properties similar to the attributes of epigallocatechin gallate in green tea leaves (Weisburger, 1999).

The tea leaves, and hence green and black tea contain caffeine, but in lower amounts than coffee. A cup of tea has 40–55 mg caffeine, a cup of coffee 125–150 mg. Some beneficial effects of tea relate to the presence of caffeine, probably acting together with the tea polyphenols.

3. Tea and heart disease prevention

A mechanism involved in the causation of coronary heart disease is the oxidation of LDL-cholesterol, leading to damage of the vascular system and the heart (Cox and Cohen, 1996). Antioxidants in tea inhibit this oxidative step and may account for the lower risk of heart disease in tea drinkers (Hertog et al., 1995; Imai and Nakachi, 1995; Ishikawa et al., 1997; Katan, 1997; Kritz and Sinzinger, 1997; Yokozawa and Dong, 1997; Vinson and Dabbagh, 1998; Geleijnse et al., 1999; Sesso et al., 1999) (Table 1). Tea acts as an oxygen radical scavenger and exerts a hypocholesterolemic action (Hara, 2001). Milk does not affect the bioavailability of the tea polyphenols (Van het Hof et al., 1998). Addition of the International Standards Organization recommended amounts, 1.85% whole milk, to tea does not reduce the beneficial effect of tea (Weisburger et al., 1997). An as yet unclear question is why there is a high incidence of cardiovascular disease in Ireland and the United Kingdom, even though tea with milk is frequently consumed there.

4. Tea and cancer prevention

Cancer is a general term applicable to many distinct diseases, with different causative, enhancing, promoting, and also inhibiting elements. The mechanisms of carcinogenesis show that the induction of cancer involves a sequence of steps leading to clinical cancer (Weisburger, 2001; Table 1). The critical action is transformation of normal cells by genotoxic carcinogens (chemicals, radiation or viruses), which affect specific codons in DNA and represent a somatic mutation of oncogenes or tumor suppressor genes. Growth and development of cells with such a modified DNA, and additional alterations of the genetic elements, perhaps as a result of lower fidelity of the polymerases synthesizing DNA, eventually leads to typical of neoplastic cells with the characteristic gene structure and phenotypic expression (Loeb, 2001). Neoplastic cells carrying mutated, abnormal DNA, such as UV light-induced skin tumors in mice, displayed slower growth when the mice were on a black tea solution than controls drinking water (Lu et al., 1997; Liu et al., 1998; Conney et al., 1999). The tea solution lowered the bromodeoxyuridine labeling index and increased the apoptosis index in the tumor (Hayashi et al., 1996; Ahmad et al. 1997). Clearly, control of cell duplication rates plays an essential role in the expression of neoplasia, and it appears that tea can effectively decrease cell cycling, although the underlying molecular mechanisms require exploration (Lin and Lin, 1997; Liang et al., 1999).

Both DNA-reactive genotoxic and epigenetic carcinogens act in a dose-dependent fashion. Thresholds have been observed for both types of carcinogens in experimental animals and humans. The thresholds for DNA-reactive carcinogens vary greatly and may be low (Williams et al., 2000). Those for non-genotoxic

Table 1
Neoplastic diseases

Mechanisms: Carcinogens require biochemical activationand undergo detoxification. Metabolically generated reactivecarcinogens produce mutations in DNA and yield mutated oncogenesand tumor suppressor genes. Cells with mutated DNA, upon cellduplication, growth and development yield clinical cancer inlaboratory animals and in humans.

Prevention: Tea and tea polyphenols lower activation, andincrease detoxification carcinogens through increased formation ofglucuronides. Tea decreases growth of early cancer cells throughseveral mechanisms, lower cytolethality and cell duplication rates,improve cell to cell communication, and favor apoptosis.

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epigenetic carcinogens, particularly of the promoter class, appear to be high and are a function of classic pharmacologic and toxicologic phenomena, and display an S-shaped dose−response curve. The inhibition of these effects by tea involves several distinct mechanisms.

Tea can block the formation of mutagens and carcinogens from precursors (Weisburger et al., 1994; Yen and Chen, 1996; Kuroda and Hara, 1999; Weisburger, 1999). Tea and the polyphenols inhibit the biochemical activation of genotoxic carcinogens. They increase their detoxification through the induction of higher levels of glucuronosyl transferases (Embola et al., 2001). Tea polyphenols influence molecular events at the level of the gene. Thus, epigallocatechin gallate affected the action of tumor promoters on transcription factors such as AP-1 or NF-κB, leading to control of the activity of transforming growth factors TGF-α and TGF-β (Meyer et al., 1994; Lin and Lin, 1997; McCarty, 1998; Chen et al., 1999; Ripple et al., 1999; Fujiki et al., 2000).

Subsequent steps in the development of neoplasia involve the growth control of the early neoplastic cells. These phenomena, involving promoting and enhancing elements, are a function of the amounts and potency of the promoting stimuli. The active ingredients in tea can decrease effectively these sequences (Sigler and Ruch, 1993; Chen et al., 1998; Yang et al.; 1998; Weisburger, 1999).

Genotoxic carcinogens and also oxidative processes in cells lead to the formation of reactive oxygen species that alter DNA (Kasai et al., 2000). One key indicator of such alterations is the presence of 8-hydroxydeoxyguanine (8-OHdG) in hydrolyzed fractions of DNA (Liebler et al., 1998; Cadenas and Packer, 1999; Allen and Tresini, 2000). The polyphenols in tea are effective inhibitors of oxidative damage (Hasaniya et al., 1997; Wei et al., 1999), which accounts for prevention of heart disease, cancer and even aging (Weisburger, 2000). Tea polyphenols inhibit xanthine oxidase associated with the formation of reactive oxygen species and radicals (Aucamp et al., 1997). The effect of promoters involves blockage of cellular growth control messages through gap junctions, and the tea polyphenols restore effective gap junction communication and hence inhibit the action of promoters (Valcic et al., 1996; Katiyar and Mukhtar, 1997; Fujiki et al., 2000; Trosko, 2001).

Wattenberg (1997) coined the phrase "chemoprophylaxis" in 1966, when he discovered that cruciferous vegetables induced metabolic enzymes, now known as cytochrome P450s, and related phase I enzymes, and phase II enzymes. Our group, and others, have demonstrated that green tea and black tea induced specific cytochrome P450s, namely 1A1, 1A2 and 2B1, but no others. It was important that glucuronosyl transferase, a phase II enzyme, was higher in tea-drinking animals, which may account for the protective effects associated with the intake of tea (Sohn et al., 1994; Embola et al., 2001). Suganuma et al. (1998) noted that epigallocatechin gallate acted on cellular membranes and affected tumor necrosis factor formation and gene expression. Prostaglandin E in the rectal mucosa was decreased by green tea (August et al., 1999). Also, nitric oxide (NO) synthetase gene expression and enzyme activity was inhibited, in turn affecting the associated activation and binding of nuclear factor κB to the inducible NO synthetase promoter, accounting for the inhibition of this cellular process by tea (Chan et al., 1997; Lin and Lin, 1997; Liebler et al., 1998).

Metabolic changes yielding lower body weight through decreased fat storage and accumulation were observed by intake of green tea (Sayama et al., 2000). Increases in energy expenditures and fat oxidation in humans consuming green tea were reported (Dulloo et al., 1999). Suggestions that tea polyphenols might prevent the absorption of essential mineral are not correct. It was found, for example, that iron is fully available (Record et al., 1996).

4.1. Tobacco and cancer

Cancers in the lung, oral cavity and esophagus are associated with cigarette smoking or tobacco use. Green or black tea lowers the risk of these cancers in humans. Green tea and its main components—epigallocatechin gallate (EGCG) and caffeine—inhibit lung tumorigenesis induced by the nicotine-derived tobacco carcinogen nitrosamines, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) in strain A mice (Xu et al., 1992) and in F344 rats (Chung et al., 1998; Chung, 1999). Caffeine may have contributed to the effect of tea (Table 2). The mechanism of inhibition may be due to its antioxidant activity, as both green tea and EGCG suppressed

Table 2
Effects of green tea, EGCG and caffeine on NNK-induced lung adenomas in A/J mice

Treatment group	% Of mice with tumors	Number of animals	Tumors/mouse (±S.D.)
1. NNK	100	30	22.5±4.7
2. Tea + NNK	100	25	12.2±4.3[a]
3. EGCG + NNK	100	25	16.1±5.3[a]
4. Caffeine + NNK	100	15	19.2±4.8[a]
5. Tea	7	15	0.1±0.2
6. EGCG	20	15	0.3±0.6
7. Caffeine	20	15	0.3±0.6

[a] Adapted from Chung (1999).
$P < 0.05$ as compared to group 1.

Table 3
Effects of green tea and EGCG on the 8-OH-dG levels in lung and liver DNA of A/J mice 2 h after treatment with NNK[a]

Treatment	Number of mice	8-OH-dG/10 dG	
		Lung	Liver
1. Control	11	1.7±1.2[b]	3.9±0.6
2. NNK	10	3.2±1.7[c]	4.7±1.1
3. NNK + tea	11	1.9±1.0[d]	4.3±1.4
4. NNK + EGCG	12	2.1±1.1[d]	4.3±1.2
5. EGCG	10	1.8±0.9[d]	4.1±1.2
6. Tea	11	1.8±0.7[d]	4.0±1.4

Adapted from Chung (1999).
[a] Mice that drank water, green tea or EGCG solution as drinking water were administered NNK in corn oil (23 mg/kg body weight) by gavage three times weekly for 3 weeks. Mice were sacrificed 2 h after the last NNK treatment.
[b] Mean±S.D.
[c] $P < 0.01$ as compared to Group 1.
[d] $P < 0.05$ as compared to Group 2.

Table 4
Lung cancer mortality ratios for men in Japan and USA

Parameter	Japanese study	ACS 25-state study
No. of cigarettes smoked per day		
Non-smoker	1.00	1.00
1–9	2.06	4.62
10–19	4.00	8.62
20–39	6.24	14.69
40+	6.24	18.71
Age at start of smoking (years)		
Non-smoker	1.00	1.00
⩾25	4.35	4.08
20–24	4.35	10.08
<20	5.71	18.23

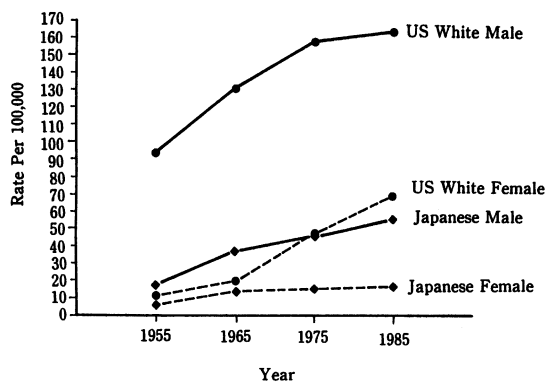Adapted from Chung et al. (1997). ACS, American Cancer Society.

Fig. 1. Sex-specific age-adjusted mortality rates due to lung cancer in the United States of America and Japan, 1955–1985; from Wynder et al. (1990).

8-hydroxydeoxyguanosine (8-OHdG) formation in the lung DNA of mice treated with NNK (Table 3; Chung and Xu, 1992; Xu et al., 1992; Dreosti, 1996; Chung, 1999). In addition, an increase of 8-OHdG levels was noted in the lung DNA of strain A mice treated with the carcinogens benzo[a]pyrene (BaP) and N-nitrosodimethylamine (NDMA) (Chung et al., 1997). Mutations by tobacco carcinogens were inhibited by tea (Lee et al., 1997). In transgenic mice, the effect of BaP in the lung was inhibited by the polyphenol from green tea (Muto et al., 1999). Japanese male smokers are at a lower risk of lung cancer than their US counterparts even though they smoke more cigarettes per day (Fig. 1; Table 4; Wynder et al., 1990; Ohno et al., 1995; Chung et al., 1997; Imai et al., 1997; Chung, 1999; Fujiki et al., 1996, 1999). The mechanism involves diet, that in Japan is lower in fat and cholesterol and higher in flavanoids in green tea and vegetables (Tominaga and Kato, 1992). Tea drinkers had a lower risk of lung cancer in smokers

in Uruguay, so that the protective mechanism may be quite general (Mendilaharsu et al., 1998; De Stefani et al., 1999).

4.2. Cancer of the stomach

A major type of cancer in the Orient, and in northern and eastern Europe—cancer of the stomach—is associated with a high intake of salted or salt-preserved foods (Howson et al., 1986; Tominaga and Kato, 1992). A bacterium, *Helicobacter pylori*, enhances cell cycling in the gastric mucosa through mucosal damage that raises the risk (Hwang et al., 1994). Tea and the tea polyphenols are bacteriostatic and bactericidal. Thus, they lower the titers of *H. pylori* and the associated gastric cancer (Hara, 2001). Chronic gastritis and clinical stomach cancer was decreased by tea (Setiawan et al., 2001). In addition, tea reacts with nitrosating agents and, therefore, gives rise to lower titers of possible gastric carcinogens (Chen et al., 1996). In vitro studies described the effect of green tea on human stomach cancer explants and cells (Okabe et al., 1999).

Table 5
Prevention of formation of heterocyclic aromatic amines by tea and tea polyphenols

	MeIQx fraction (%)	PhIP Fraction (%)
A[a]	100	100
A + Green tea	100	34
A + Black tea	79	32
B[b]	100	100
B + EGCG	42	44
B + TFG	29	58

Adapted from Weisburger et al. (1994).

[a] A for MeIQx, heat 1 mmol glycine, 1 mmol creatinine, 0.5 mmol glucose at 160 °C for 1 h in 3.33 ml diethyleneglycol–water (10:1); for PhIP, the same, but using phenylalanine.

[b] B same, but at 0.2 mmol level and using 0.1 mmol epigallocatechin gallate (EGCG) or theaflavin gallate (TFG). Reaction mixtures, in triplicate, were processed using blue cotton to absorb and desorb heterocyclic amine formed. Mass spectrometry (positive chemical ionization) of an aliquot of A gave $m + 1 = 214$, and of B gave $m + 1 = 225$, the same as authentic MeIQx and PhIP, respectively.

4.3. Western nutritionally-linked cancers

The carcinogens, heterocyclic amines (HCAs), associated with a high incidence of cancers in the Western world, cancer of the breast, colon, prostate and pancreas, occur in cooked meats (Sugimura, 2000). The amount of HCAs consumed by humans is low, but their effect is strongly potentiated by the types and amounts of fats consumed in Western nutrition. Fats lead to promoting events, through increased levels of bile acids, promoters in the colon, or of estrogen, promoters in endocrine organs. Epidemiologic investigations recorded an increased risk of breast or colon cancer in people who eat well-done meat (Sinha et al., 1999). HCA formation is inhibited by tea (Weisburger et al., 1994; Hernaez et al., 1998; Table 5). The HCAs require a two-step metabolic activation to DNA-reactive genotoxins, and also lead to an oxidative modification of DNA. These reactions are inhibited by tea or the tea polyphenols (Dashwood et al., 1999). Tea lowered mammary gland carcinogenesis in rats induced by the classic carcinogens 7,12-dimethylbenz[a]anthracene (Weisburger et al., 1997; Rogers et al., 1998).

4.4. Effect on metabolic enzymes

Rats drinking a 2% solution of green or black tea have increased levels of hepatic cytochromes P450 1A1, 1A2 and 2B1, but not the other cytochromes P450. Importantly, glucuronosyl transferase was raised significantly (Sohn et al., 1994; Table 6). Thus, even if cytochrome P450 results in an increased formation of the N-hydroxy metabolites of heterocyclic amines, immediate conjugation with the glucuronide moiety would yield the detoxified N-hydroxyglucuronide, readily eliminated in urine (Embola et al., 2001). This is the

Table 6
Phase I and II enzymes in male F344 rat liver are modified by green and black tea intake

Enzymes	Water (%)	Green tea (%)	Black tea (%)
Cytochrome P450 1A1	100	164[a]	184[a]
Cytochrome P4501A2	100	540[a]	623[a]
Cytochrome P450 2B1	100	147[a]	154[a]
UDP-glucuronyl transferase	100	130[a]	148[a]

Rats 8 weeks of age, fed a semi-purified starch based AIN-76A diet were given water, or 2% solutions, freshly made three times per week, of research grade black or green tea for 6 weeks. The cytochrome P450 and UDP-GT enzymes were measured in the hepatic microsome fractions.

[a] $P < 0.05$ with respect to control group on water; modified from Sohn et al. (1994).

plausible mechanism whereby tea serves to detoxify polycyclic and heterocyclic reactive metabolites. Polyphenols from tea also affected other biochemical parameters, such as glucuronide formation of hormones (Conney et al., 1999). We demonstrated such an effect with the inhibiting action of phenobarbital on the carcinogen 2-acetylaminofluorene (Matsushima et al., 1972).

4.5. Tea and cancer development

Green tea inhibited promoting elements in prostate cancer (Gupta et al., 1999). At the cellular level, promoters operate by increasing the rate of cell cycling and lower cell to cell communication (Trosko, 2001). The tea polyphenols exert a protective effect in cancer development through such mechanisms (Mukthar and Ahmad, 2000; Schwab et al., 2000). Also, tea inhibits the rate of cell duplication in the colon of rats, and thus affected the development of colorectal cancer in humans (Hartman et al., 1998; Inoue et al., 1998). This important area, bearing on tea in adjuvant therapy, is interesting and deserves further documentation. Tea modified the action of UV light as a carcinogen on the p53 tumor suppressor gene (Conney et al., 1999; Yang and Landau, 2000). Metastatic cancer in humans may be reproduced by the growth, decreased by tea, of transplantable cancers in animals (Javed and Shukla, 2000). The endogenous cellular effectors exert a controlling action that is modified by tea.

4.6. Tea and intestinal bacterial flora

The intestinal microflora affects the metabolism of endogenous and exogenous compounds, present in the intestines either by direct migration of food or food components after oral intake, or more often, by secretion in the bile of metabolites from the liver. The intestinal flora contains enzymes with numerous functions, including hydrolytic and reductive reactions. Tea

and tea polyphenols lead to a reduction in Enterobacteriaceae that produce ammonia, skatole, and other amines, sources of unpleasant odor of stools. Tea increases the level of *Lactobacilli* and *Bifidobacteria* that have beneficial odor-free metabolites (Hayatsu and Hayatsu, 1993; Goto et al., 1999; Reddy, 1999; Bengmark, 2000; Hara, 2001). There is also a decrease in the pH of the intestinal contents through increased formation of organic acids, inhibiting carcinogenesis.

5. Absorption and metabolism of tea polyphenols

The results described indicate that the active components of tea, the antioxidant polyphenols, are absorbed to generate the effects noted. This has been determined directly through a number of analytical methods, such as HPLC and other chromatographic procedures, to measure plasma levels in humans (Kiehne and Engelhardt, 1996; Maiani et al., 1997; Arce et al., 1998; Bravo, 1998; Suganuma et al., 1998; Benzie, et al., 1999; Okushio et al., 1999a; Kohri et al., 2001; Shahrzad et al., 2001; Zhu et al., 2001). A more complex thermospray-liquid chromatography-mass spectrometry has been applied. The in vivo antioxidant effects in humans and the direct measurements of metabolites of epigallocatechin gallate utilized the tritiated chemical (Kohri et al., 2001). As is true for other catechols, the tea polyphenols undergo methylation on one of the hydroxy groups (Okushio et al., 1999b). It seems likely that the phenolic hydroxy groups are subject to conjugation by phase II enzymes, and excretion of the products in urine.

6. Role of caffeine

We have described the slightly improved antimutagenicity of regular tea containing caffeine compared to the decaffeinated version (Table 7). The finding that regular tea seems more active suggests that caffeine may play a role. Independent study of caffeine has described an antimutagenic effect against heterocyclic amines of caffeine in a dose-related fashion (Sanyal et al., 1997; Weisburger et al., 1998). In mice exposed to UV light, decaffeinated tea was somewhat less active than regular tea and caffeine itself displayed an inhibiting effect (Huang et al., 1997; Lou et al., 1999; Lu et al., 2000). Caffeine induced specific cytochromes, and in particular cytochrome P450 1A2 (Chen et al., 1996; Bu-Abbas et al., 1998). In vitro, tea and caffeine inhibited the growth of several human cancer cell lines. Serum concentrations of hormones and the hormone-binding globulin in women were also altered by caffeine (Nagata et al., 1998). Tumor prevention by tea in rats and humans displayed improved effects with regular tea compared to decaffeinated tea, basis for the conclusion that caffeine was involved in the effect observed. In a lung cancer model, caffeine had an inhibiting effect (Chung et al., 1998). Caffeine lowered stomach (Nishikawa et al., 1995) and breast cancer (Welsch, 1994) development.

It can be concluded that the relatively small amounts of caffeine, about 50 mg per 150 ml cup of tea, made with 2.25 g of dry tea leaves, exerts an important interactive effect with the polyphenols. There seems to be a joint effect between caffeine and tea polyphenols, since the effects described have not been observed with coffee (Barone and Roberts, 1996; Harland, 2000). The limited amount of caffeine present in tea is adequate to exert a desirable stimulant effect. Investigations field on the possible interaction between caffeine and the tea polyphenols in various physiological and biochemical parameters would be of great relevance.

7. Conclusion

Green tea and black tea, beverages second only to water as regards their worldwide usage, contain important phytochemicals, the polyphenols, with four documented beneficial actions (Table 8). They increase the level of cellular antioxidant defenses, and thus lower the risk of diseases involving adverse oxidative reactions such as heart disease and a number of types of cancer (Table 9).

Green and black teas have similar protective effects in most of the tests conducted. Caffeine in tea plays a role in the effects observed, since regular tea usually displays a slightly better effect than decaffeinated tea. Yet the purified tea polyphenols are active as such at the concentrations studied. Epidemiologic data and laboratory approaches indicate that the amount of polyphenols in four cups or less of tea (about 600 ml of a 1.5% solution) is insufficient to provide significant preventive

Table 7
Inhibition by regular black and decaffeinated black tea of the mutagenicity of the genotoxic dietary carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine

Tea (mg/plate)	Regular tea	Decaffeinated tea
0.0	1	–
0.125	0.62	0.72
0.25	0.69	0.76
0.5	0.55	0.65
1.0	0.25a	0.38[a]

Data adapted from Weisburger et al. (1998).
[a] $P < 0.05$; the ID_{50} for regular tea was 0.57 mg and for decaffeinated tea it was 0.76.

Table 8
Mechanisms of action of tea on parameters bearing on health

Action of tea and tea polyphenols	Consequences
1. Display potent antioxidant activity	Lower risk of heart disease; decreased formation of oxidizednucleotides in DNA and possibly inhibition of carcinogenesis
2. Selectivity induced Phase I and II metabolic enzymes	Increased formation of detoxified metabolites of carcinogens
3. Inhibit cell proliferation rates	Decreased growth of abnormal cells and neoplasms
4. Selectivity modify intestinal bacterial flora	Undesirable components of the flora replaced by beneficialbacteria, with improved metabolic profiles.

Table 9
Oxidative reactions in chronic disease causation

Coronary heart disease:
  Oxidation of LDL-cholesterol
  Oxidation by nitrogen oxides
  Oxidation by xanthine oxidase

Neoplastic diseases:
  Generation of active oxygen, reactive oxygen species
  Peroxy compounds, $H_2O_2 \cdot OH$ radicals, other radicals

Antioxidant attributes of tea polyphenols can inhibit adverse effects due to undesirable oxidation reaction by reactive oxygen or nitrogen species.

effects in chronic diseases. Intake of 6−10 cups of tea per day has been shown to constitute a useful dietary habit to assist in lowering the risk of a number of chronic diseases, especially as part of health-promoting nutritional traditions, low in total fat and low in salt, with adequate vegetables and fruits, bran cereal insoluble fiber, and sources of soluble fiber (Weisburger, 2000). Total fluid intake in adults should be about 2.5 l, of which tea can be 0.9−1.4 l. Even children, who often consume few vegetables, might benefit by drinking 3−5 cups decaffeinated tea, rather than some of the high-sugar beverages associated with obesity. Prevention is the definitive "cure" of major chronic diseases conditions, including most types of cancer, for which current therapy is difficult and expensive.

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