Green Tea, the "Asian Paradox," and Cardiovascular Disease

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Archeologic findings have revealed that infusions of leaves from various wild plants, including the tea plant, might have been consumed for more than 500,000 years.[1] Legends from China and India indicate that use of tea occurred as far back as 2,737 years BC when the Chinese Emperor Shen Nung, "Divine Healer," found himself with a beverage harboring a pleasant aroma and refreshing taste after dried leaves accidentally blew into hot boiling water.[2] This ancient practice associated with medicinal purposes, lifestyle customs, and nutritional beliefs was progressively introduced to countries worldwide by tradesmen and travelers alike.[3] Tea was used to reduce inflammation, improve blood flow, treat infectious diseases, purify the body, and maintain mental equilibrium.[4] The people of Japan, China, India, and England elevated tea from a simple beverage to a social custom, bestowing tea consumption a preferential place in society.[3]

Scientific validation has slowly accumulated and green tea has attracted more followers as the word has spread about its health and medicinal properties. A recent survey conducted in the US among cancer patients using herbal remedies revealed that green tea was the most common herb used in 54% of patients.[5] Tea is the most widely consumed beverage in the world, second only to water,[6,7] with a worldwide per capita consumption of 40 L per year.[7] Approximately 3 billion kilograms of tea are produced and consumed annually and this number is growing at a rate of 2.1% per year.[8] In the Western World, black tea is preferred, and in the Asian countries green tea is the primary drink. The practice of drinking iced tea is spreading from the US, where it began during the early 20th century. It now accounts for 75% to 80%[7] of the 140 million cups of tea consumed each year by Americans.[2]

Next to green tea, one of the most highly consumed products in Asia is cigarettes. Evidence strongly associates cigarette smoking with cardiovascular events, including myocardial infarction, stroke, peripheral vascular disease, aggravation of stable angina pectoris, vasospastic angina, rethrombosis after thrombolysis, restenosis after angioplasty, and even sudden death, and malignancies.[9,10] These pathologic conditions occur as a result of a number of detrimental effects leading to atherogenesis, including an increase in levels of fatty acids, LDL, and very LDL, and a decreased turnover of HDL cholesterol. Smoking has also been correlated with aggravation of hypertension, promotion of platelet aggregation, and modulation and proliferation of vascular endothelial cells (EC) and smooth muscle cells (SMC).[10] Using a bovine aortic vascular SMC scrape injury model, as shown by our laboratory,[11] a mitogen-activated protein kinases p38 and p44/42 mediated SMC migration would result as a consequence of nicotine exposure.

Despite the high consumption of tobacco, Asia and Japan in particular have among the lowest incidences of arteriosclerosis and lung cancer per capita (Table 1). It has been postulated that this paradox, the "Asian Paradox," exists as a result of the high consumption of green tea in this region, and most benefits occur when approximately 1.2 L of green tea are consumed every day. For example, a Japanese epidemiologic study[12] involving 1,371 men older than 40 years of age reported the association between the consumption of $>$ 10 cups (1,500 mL) of green tea a day with a decreased serum concentration of total cholesterol, LDL, and triglycerides, and with an increased HDL concentration. A recent meta-analysis,[13] involving 10 cohort studies and 7 case-control studies, reported an 11% decrease in myocardial infarction when 3 cups of tea (tea type not specified) were consumed daily. Risk of myocardial infarction was seen to be reduced by 44% in individuals drinking $\geq$ 1 cup (237 mL) of tea per day compared with nondrinkers, in

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Acronyms and Abbreviations

EC = endothelial cells
EGCG = (-)-epigallocatechin-3-gallate
MMP = matrix metalloproteinase
ROS = reactive oxygen species
SMC = smooth muscle cells

a study involving 340 patients with age-, gender-, and community-matched controls.[14] In a prospective cohort study,[15] which involved 1,935 patients with a history of myocardial infarction, age- and gender-adjusted mortality was lower among moderate tea (green or black tea) drinkers (< 14 cups of tea/wk) presenting a relative risk of 0.69, and in heavy drinkers (14 cups of tea/wk) with a relative risk of 0.61, when compared with nondrinkers. Another prospective cohort study,[16] including 8,552 Japanese men and women, revealed a decreased relative risk for cardiovascular disease of 0.52 for men, 0.82 for women, and 0.72 for both genders for those consuming > 10 cups of green tea per day compared with those consuming < 3 cups. This same study demonstrated a decreased relative risk for cancer of 0.54 for men, 0.57 for women, and 0.59 for both genders, again for those consuming > 10 cups of green tea per day compared with those drinking < 3 cups per day. Among cancer patients, there was a delayed cancer onset for those who drank larger quantities of green tea. Cancer appeared up to 7 years later in women who drank ≥ 10 cups per day compared with those who drank ≤ 3. In the case of the men, there was also a delay, but of only 3 years. Epidemiologists from Japan have also reported in a case-control study[17] based on 139 cases of newly diagnosed gastric cancer and 278 gender-matched and year of birth-matched controls, a decreased risk of gastric cancer among subjects with green tea consumption > 10 cups per day.

In the US and other Western countries, arteriosclerosis and its clinical sequelae, such as myocardial infarction, stroke, and peripheral vascular disease, account for almost 40% of all mortality.[18] Concomitant evidence is emerging from Western nations that green tea, primarily because of the high concentration of polyphenolic flavonoids, is a potential tool in the prevention of arteriosclerosis. Hollman and colleagues[19] assessed the association between flavonol intake and cardiovascular disease through six prospective epidemiologic studies. In the Seven Countries Study,[20] the Zutphen Elderly Study,[21] and in a Finnish cohort,[22] a clear inverse correlation with mortality rates from coronary heart disease was observed. In vitro studies[23-25] indicate that the polyphenol (-)-epigallocatechin-3-gallate (EGCG) and, to a lesser extent, other catechins in green tea, decrease oxidation of LDL and inhibit SMC and EC proliferation, potentially reducing the risk of arteriosclerosis. These vascular effects of EGCG are thought to be a result of its antiox-

Table 1. Lifestyle Factors and Mortality from Cardiovascular Disease and Lung Cancer*

	Annual CAD mortality/100,000 population		Lung cancer mortality/100,000 population		Cigarette smokers (%)†	Cigarettes (per adult/y)‡	Tea consumption (kg/person/y)§
Country	Men	Women	Men	Women	Total	Total	Total
Ireland	422	183	50.0	29.0	—	2,316	1.5
China	401	276	34.9	17.4	35.6	1,780	—
United Kingdom	382	178	74.8	44.3	—	1,553	2.3
US	348	177	66.6	45.1	27.0	2,092	0.2
New Zealand	318	139	48.3	29.6	—	1,038	1.0
Canada	280	133	71.4	43.2	25.0	1,820	0.2
Rep of Korea	261	149	39.6	13.0	36.9	2,668	—
Italy	255	108	97.1	19.6	24.9	2,041	0.1
Australia	237	103	50.8	22.9	19.5	1,708	0.8
France	208	74	75.0	14.6	34.5	1,757	0.2
Japan	186	81	66.1	23.5	33.1	2,950	0.9

*Source: World Health Organization, http://www.who.int/en; Global Market Information. Database (Euromonitor), www.euromonitor.com/gmid.
†Percentage of total population who smoked at least one cigarette a day.
‡Data refers to estimates of apparent consumption based on cigarette production, imports, and exports during the most recent 3-y moving average between 1992 and 2000.
§1 kg = approximately 311 cups (60−70 lb leaves = 20 lb dry tea = 2,800 cups tea).
CAD, coronary artery disease.

idant properties.[26] EGCG has also been reported to prevent angiogenesis and tube formation, causing cessation of cancer growth[27-29] and preventing certain types of tumors from metastasizing.[30-35] Angiogenesis inhibition is thought to be due primarily to specific receptor blockage, which alters certain cell regulatory functions, including apoptosis of SMC and EC.[23,27-29] Vascular endothelial growth factor binding to its receptors can be reduced by EGCG, affecting downstream signaling.[28]

Data collected from the World Health Organization on lifestyle factors and mortality from cardiovascular disease and lung cancer, shown in Table 1, reveal increased levels of mortality in countries such as Ireland and the United Kingdom, where, in fact, black tea, and not green tea, is heavily consumed. Asian countries such as Japan and Korea, where green tea is consumed exclusively, on the other hand, have lower mortality rates, suggesting beneficial properties. In this article, the most recent and relevant data associated with green tea's putative cardiovascular protective effects will be reviewed to provide insight on the clinical significance of its phytochemicals.

COMPOSITION OF GREEN TEA

Tea derives from the leaves of the plant *Camellia sinensis*, and is reported to contain nearly 4,000 bioactive chemical compounds, one-third of which are polyphenols.[36] EGCG, the major catechin in tea, accounts for 10% of the total weight (Fig. 1).[3] *Camellia sinensis* is indigenous to India and the Far East countries, primarily China and Japan.[36] Three different types of tea: green (no "fermentation"), oolong (moderate "fermentation"), and black (complete "fermentation") tea can be derived from this plant.[7] When tea leaves at harvest are withered and immediately steamed or heated, the polyphenol oxidase that is present in the leaves is inactivated, yielding green tea. If the leaves are harvested, withered, rolled, and crushed, the polyphenol oxidase is liberated and is biochemically oxidized, which in turn leads to polymerization of the polyphenols. Polyphenols are converted to dimers and polymers, mainly theaflavins and thearubigins. These products are responsible for the characteristic yellowish-orange to reddish-brown color of these teas and for physiologic and biochemical properties comparable with those of catechins, but with considerably less antioxidant effects (Table 2). This process is stopped by drying the product in a stream of hot air. Oolong tea is produced when this reaction time is about 30 minutes, and black tea is the result of a 60- to 90-minute reaction time.[36]

Polyphenols are bonded benzene rings with multiple hydroxyl groups (Fig. 1). Polyphenols are categorized by structure into flavonoids and nonflavonoids, with the chemicals found in tea being mainly flavonoids. All three types of teas contain compounds called catechins; which are currently thought to be primarily responsible for the beneficial effects of tea.[23-26,37] Green tea has the highest concentration of catechins per gram of dried leaves compared with black and oolong teas and is the best dietary source of this compound. In green tea, catechins represent 80% of flavonoids, although in black tea they only represent 20% to 30% (Fig. 1).[4] Each tea contains primarily four different types of catechins including: (-)-epicatechin, (-)-epicatechin-3-gallate, (-)-epigallocatechin, and (-)-epigallocatechin-3-gallate (EGCG).[38] Other important dietary sources of catechins are red wine, black grapes, apples, and chocolate.[39-41] The most important flavonols in tea are quercetin, kaempferol, and rutin. They are more widely distributed and can also be found in red wine, black grapes, apples, onions, cherries, berries, grapefruits, and cruciferous vegetables.[19,40-42] Tea also contains phenolic acids, including mainly caffeic, gallic, and quinic acids, and is an excellent source of methylxanthines, containing approximately one-third the amount of caffeine compared with coffee.[3] A cup of tea contains 40 to 55 mg of caffeine, and a cup of coffee contains 125 to 150 mg.[36]

METABOLISM AND BIOAVAILABILITY

In healthy volunteers, drinking green tea resulted in a catechin concentration in plasma between 0.2% to 2% of the ingested amount, with a maximal concentration after 1.4 to 2.4 hours after consumption.[43-45] The half-life of EGCG is about 5 hours, although that for (-)-epigallocatechin and epicatechin are shorter, between 2.5 and 3.4 hours.[45] The latter two can be partly recovered in urine, although EGCG cannot. In humans, a study[46] using radioactively labeled catechins demonstrated the efficient metabolism of this flavonoid. Little is known about the bioavailability of theaflavins and thearubigins, the black tea polyphenols; they both appear to be absorbed. Adding milk to the beverage, as customized in Great Britain, does not reduce polyphenols' bioavailability as this produces no change in the blood polyphenol concentration.[46] On the other hand, milk has been reported to reduce the antioxidant activity of tea in vivo.[47] The effects of green tea might be less

	occurence (% dry weight)		structure
	green tea	black tea	
Catechins	**30-42**	**10-12**	
epigallocatechin gallate	11		**B** (-)2,3-cis R1=OH R2=**A**
epicatechin gallate	2		**B** (-)2,3-cis R1=H R2=**A**
gallocatechin gallate	2		**B** (+)2,3-trans R1=OH R2=**A**
epicatechin	10		**B** (-)2,3-cis R1=R2=H
epigallocatechin			**B** (-)2,3-cis R1=OH R2=H
gallocatechin			**B** (+)2,3-trans R1=OH R2=H
catechin			**B** (+)2,3-trans R1=R2=H
Teaflavin		**3-6**	
theaflavin-3-gallate			**C** R1=OH R2=OH
theaflavin-3'-gallate			**C** R1=**A** R2=OH
theaflavin-3,3'-digallate			**C** R1=OH R2=**A**
Thearubigens		**12-18**	**C** R1=**A** R2=**A**
Theogallin	**2-3**		
Proanthoocyanidin			
Flavonols	**5-10**	**6-8**	
quercetin			**D** R1=OH R2=H R3=OH
kaempferol			**D** R1=R2=H R3=OH
rutin			**D** R1=OH R2=H R3=O-rutinose
Methylxanthines	**7-9**	**8-11**	
caffeine	3-5		**E** R1=R2=CH_3
theobromine	0.1		**E** R1=H R_2=CH_3
theophylline	0.02		**E** R= CH_3 R2=H
Amino acids			
theanine	4-6		**F**
Organic acids			
caffeic acid			
quinic acid	2		
gallic acid			
Volatiles			
linalool			
delta-cardinene			
geraniol			
nerolidol			
alpha-terpineol			
cis-jasmone			
indole			
beta-ionone			
1-octanal			
indole-3-carbinol			
beta-caryophyllene			

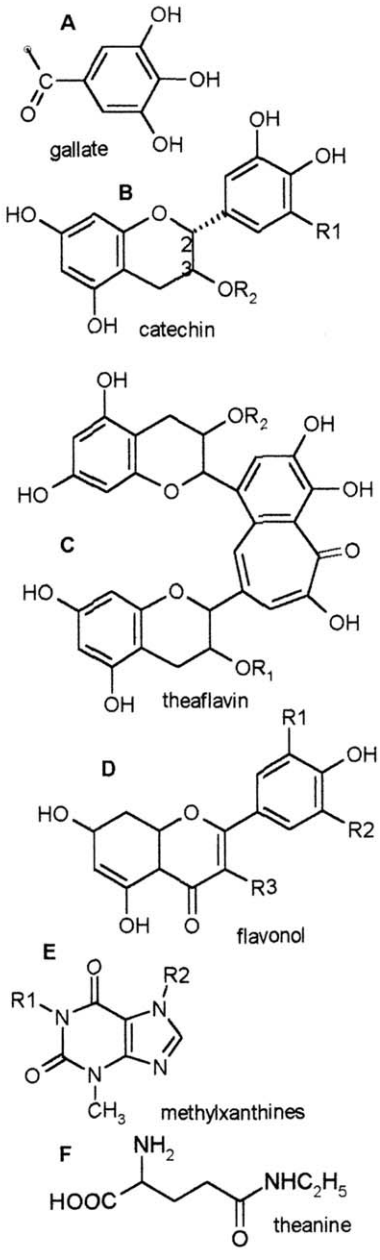

Figure 1. Biochemical composition of green tea. (Reprinted from: Dufresne CJ, Farnworth ER. A review of latest research findings on the health promotion properties of tea, J Nutr Biochem 2001;12:405, with permission).

variable than black tea in this respect, as milk is not used for green tea in Japan or other Asian countries.

Polyphenols have an especially strong affinity for proline rich proteins such as casein, milk, gelatin, and saliva, and also interfere with the absorption of other compounds in the diet.[3] The most effective binding capacity is held by the large, flexible, and poorly water soluble polyphenols.[46] By binding to digestive enzymes, tannins can reduce lipid, starch, and protein digestibility, affect insulinemic and glycemic responses, increase excretion of fats, and reduce absorption of cholesterol.[48] Tea polyphenols have an important interaction with transition metal ions, strongly inhibiting nonhaem iron absorption in the gastrointestinal tract by forming insoluble complexes with this metal.[46,48,49] With a varied diet, iron absorption is unaffected; in vegetarian diets, it is advised

Table 2. Tea Biochemical Compounds Responsible for Taste, Flavor, and Color

Biochemical compounds	Taste
Polyphenol	Astringency
Theaflavins	Astringency
Thearubigin	Slight astringency and ashyness
Amino acids	Brothyness
Caffeine	Bitterness and briskness
	Flavor
Phenyl ethanol, Benzaldehyde, Nerolidol, Methyl salicylate	Fruity
Linalool, Linalool oxide	Sweet
Geraniol, Phenylacetaldehyde	Floral
Trans-2-Hexenal, n-Hexanal, Cis-3-Hexenol Grassy, b-Ionone	Fresh flavor
	Color
Flavonol glycosides	Light yellow
Theaflavins	Yellow-brown
Thearubigins	Red-brown
Carotene	Yellow
Pheophorbide	Brown
Pheophytin	Black

that green tea be consumed between meals to avoid a reduction in the already limited amount of available iron.[3] In rats, zinc absorption inhibition has been observed, although results for copper remain unclear. Polyphenols also affect the bioavailability of sodium and aluminum; it does not interfere with that of calcium, manganese, or magnesium.[48]

POLYPHENOL ANTIOXIDANT ACTIVITY

Free radicals are molecules or atoms with an unpaired electron. The unpaired electron results in a high level of reactivity because the free radical "seeks" another electron to fulfill a pair. Free radicals are a natural byproduct of cellular metabolism, but are also generated by the external action of ultraviolet radiation, toxic substances, ozone, cigarette smoke, microbial attacks, and even intensive exercise.[50-54] These free radicals include: hydroxyl radical, nitric oxide, hypochlorous acid, peroxynitrite, singlet oxygen, and alkoxyl radical, among others.[54,55] Reactive oxygen species (ROS) deleterious effects on cellular membranes and internal structures might contribute to the onset of cardiovascular disease, cancer, and impairment of the immune function by altering the metabolism. DNA, LDL, and other intracellular and extracellular molecules are susceptible to damage by free radicals. When a free radical attacks LDL, it changes its structure and contributes to atherogenesis in several ways. First, oxidized LDL has cytotoxic properties that can promote endothelial injury. It can also act as a chemoattractant for circulating monocytes, leading to their increased accumulation within plaques. Oxidized LDL has also been reported to inhibit the egression of macrophages from plaques. Lipid and protein oxidation have been correlated with an increase in arteriosclerosis, diabetic complications, and a reduction in the immune system.[56]

To prevent cell injury, free radicals can be inhibited by antioxidants and by compartmentalization. The detoxification process occurs through a multistage enzyme system, where molecules activated by phase I enzymes such as NADPH, p450, and cytochrome, are converted into electrophilic water soluble compounds. They are then conjugated for their inactivation to detoxifying molecules, such as glutathione and UDP-glucoronosyl, before their excretion.[3] Antioxidants from nutrients such as tocopherol, ascorbic acid, and carotenoids, which includes lycopenes and polyphenols, contribute to the overall protection of cell integrity and the immune function, in conjunction with the cell's constitutive enzymatic and nonenzymatic protection against ROS.[54,56-62]

Polyphenols' antioxidant activity can prevent DNA damage,[63] lipid hydroperoxide formation,[64-66] and photograph-enhanced lipid peroxidation.[67] They present scavenging activity against free radicals,[41,68] superoxide radicals,[63,68] and peroxynitrite.[55,69,70] They also alter many catalytic activities of enzymes, notably the oxidative ones,[55] and can modify the process of protein phosphorylation.[71] Polyphenols can inhibit the formation of the harmful N-nitroso compound, which is the result of the reaction of endogenous or exogenous nitrosating agents when exposed to nitrogen-containing compounds.[61] They prevent formation of metal-catalyzed free radicals by chelating iron and copper.[41] Flavonoids can contribute to cells overall antioxidant protection mechanism by sparing β-carotene, urate, and vitamins C and E.[72]

EGCG and a variety of other polyphenols are antioxidants and have the ability to neutralize free radicals. The antioxidant potential of EGCG is far greater than vitamins E and C,[26] which, along with glutathione and superoxide dismutase, are the cell's main internal defense.[3] EGCG and other antioxidants have the ability to prevent and protect against oxidative damage occurring on LDL molecules, and have an antiatherosclerotic effect.[24] EGCG

inhibition of oxidative damage is dose-dependent. A low concentration of EGCG of 0.25 μM resulted in an antioxidant protective effect of 13%, although a concentration of 10.00 μM had a 68% effect. EGCG is a potent antioxidant because it has three polyphenolic benzene rings, yielding eight hydroxyl hydrogens per molecule. Each hydroxyl hydrogen enhances the ability of EGCG to be a potent antioxidant because the polyphenolic hydrogens will attract free radicals displacing LDL and other biologic molecules.[4] Catechin's scavenging activity is associated with the number of o-dihydroxy and o-hydroxyketo groups, the number of C2-C3 double bonds, the concentration, the solubility, accessibility to the antioxidant by the active group, and the stability of the reaction product.[3,73,74] In green tea, EGCG has the most potent antioxidant effects because of its four dihydroxy groups.[36]

POLYPHENOL MODULATION OF PLATELET AGGREGATION

Cardiovascular disease can be the result of numerous stimuli, one being platelet aggregation. Platelets will aggregate in blood vessels for a variety of reasons, including vessel damage and disease. The primary purpose of platelets is to aid in the repair of the damaged blood vessel by forming clots that plug holes in the vessel wall preventing additional blood loss. Platelet aggregation can sometimes lead to adverse consequences, including strokes and myocardial infarctions.

EGCG can act on platelets and other cells to prevent platelet aggregation. It can inhibit platelet-activating factor, decreasing the "stickiness" of platelets and decreasing the probability of platelet aggregation.[75,76] Kang and colleagues[77] investigated the effects of EGCG on murine pulmonary thrombosis in vivo, human platelet aggregation ex vivo and in vitro, and on coagulation parameters. In mice, they observed that EGCG prevented death caused by pulmonary thrombosis in a dose-dependent manner and considerably prolonged bleeding time. Ex vivo, adenosine diphosphate- and collagen-induced rat platelet aggregation was inhibited. EGCG also inhibited adenosine diphosphate-, collagen-, epinephrine-, and calcium ionophore A23187-induced human platelet aggregation without changing the activated partial thromboplastin time, prothrombin time, or thrombin time. EGCG has also been demonstrated to block tyrosine phosphorylation and reduce gene expression of platelet-derived growth factor-β receptor. In diabetic rats,[78] green tea has been reported to affect phospholipase A2 activity and the antithrombotic reaction of platelets. This data suggest that green tea polyphenols have antithrombotic action explained primarily by antiplatelet activity, with relative sparing of the coagulation function.

POLYPHENOL EFFECTS ON VASOMOTOR TONE

Hypertension is an important risk factor for development of cardiovascular complications.[79] Antioxidants, like those found in green tea, are very useful in protecting and restoring endothelial function.[3] The balance in the endothelium between vasodilators, such as nitric oxide and ROS, and vasoconstrictors, such as thromboxane and isoprostane, contributes to vascular resistance and endothelium-dependent contraction.[79] There is clinical and experimental evidence that tea phytochemicals can also improve endothelial function.[80,81] In an epidemiologic study, tea consumption was shown to be inversely associated with systolic blood pressure.[82] In a clinical trial[6] involving 1,507 men and women from Taiwan ages 20 years and older, researchers found that the habitual consumption of $\geq$ 120 mL/d of moderate strength green or oolong tea for at least 1 year, considerably reduced risk of hypertension developing. After adjusting for different confounding factors, such as age, gender, personal and family medical history, dietary and lifestyle factors, they observed that compared with nonhabitual tea drinkers, risk of hypertension developing decreased by 46% for those who drank 120 to 599 mL/d, and was reduced by 65% for those who drank $\geq$ 600 mL on a daily basis.

Several animal studies have also reported a consistent hypotensive effect on rats exposed to green tea extracts.[83-87] In precontracted aortic rings in rats, purified catechins evoked endothelium-dependent vasorelaxation by means of nitric oxide release from the endothelium.[80] EGCG acts as a natural activator of endothelial nitric oxide synthase in EC by increasing its phosphorylation by a phosphatidylinositol-3-OH-kinase-, cAMP-dependent protein kinase-, and Akt-dependent pathway, leading to endothelial-dependent vasorelaxation.[88] In an in vivo study[89] involving stroke-prone spontaneously hypertensive rats, green and black tea effects on blood pressure were assessed. The amounts of polyphenols used for this experiment correspond to those present in approximately 1 L of tea. Systolic and diastolic pressures were observed to be substantially lower in both groups compared with the control group. Green

and black tea considerably decreased phosphorylated myosin light chains that were measured in the aorta using Western blotting. Protein expression of catalase was also studied, and was found elevated only in the green tea group. 2-amino-5-(N-ethylcarboxyamido)-pentoic acid, a nynhydrin-positive compound from unprocessed tea leaves, has been observed to be a potent inhibitor of thrombin-stimulated thromboxane formation.[75] This compound has been reported to be inhibited in rats taking green tea, but not in those given processed tea extracts. Theanin given at high doses to spontaneously hypertensive rats has also been reported to markedly decrease blood pressure.[84]

POLYPHENOL EFFECTS ON CHOLESTEROL

In hypercholesterolemic rats, green tea considerably reduced serum and liver cholesterol, the atherogenic index, and liver weight by lowering the deposition of lipids.[90] The levels of HDL-cholesterol and triglycerides in this study remained unchanged. Other investigators[91] reported that consumption by rats of tea plant leaves for a long period of time decreased serum levels of triglyceride and total cholesterol, produced superoxide dismutase enhancement, and increased the activity of phase II enzymes in the liver. In hamsters fed a normal or a high cholesterol diet, green tea, and black tea exhibited improved plasma lipid profiles, and reduction in LDL and very LDL oxidation.[92] Reduction of blood cholesterol levels might be explained by precipitation of lipids and their fecal elimination.[82,93] A study in rats[94] suggested that squalene epoxidase, a rate-limiting enzyme found in tea and involved in cholesterol biogenesis, might also be responsible for this effect.

Green tea reduces the levels of cholesterol and triglycerides, inhibits the action of digestive lipase, and decreases fat absorption, reducing body weight.[91,95] Obesity increases the risk for cardiovascular disease and cancer, and a lower body weight would reduce the risk of suffering from these conditions. Through sympathetic activation thermogenesis, green tea plays a role in the control of body composition and produces weight loss.[96] Studies have indicated that preadipocyte apoptosis can be induced through EGCG by demonstrating a decrease in Cdk2 expression and an increase in caspase-3 activity. The treatment of Cdk2 overexpression with caspase-3 inhibitor prevented preadipocytes apoptosis through the induction of DNA fragmentation, suggesting the EGCG apoptotic effects of Cdk2- and caspase-3-inhibitors.[97] Tea can also prevent obesity and a fatty liver by enhancing noradrenaline-induced lipolysis and inhibiting pancreatic lipase activity, as observed in high-fat diet obese mice.[98]

POLYPHENOL INHIBITION OF CELL PROLIFERATION AND MIGRATION

Green tea has been shown to inhibit SMC invasion through the basement barrier, a key event involved in development and progression of arteriosclerosis and injury-induced vascular remodeling. Matrix metalloproteinases (MMP) are considered important in migration and growth of EC and SMC,[99,100] and in vitro studies[27,28] indicate that EGCG reduces expression of MMP. In bovine aortic SMC, EGCG has been found to inhibit concanavalin A-induced pro-MMP-2 activation and the gelatinolytic activity of MMP-2.[23] EGCG also inhibits SMC invasion through the basement membrane barrier, in a dose-dependent manner. In a rat carotid artery balloon injury model,[101] vascular remodeling was assessed when green tea extracts were added. Green tea reduced the area of the intima in the injured arteries by 30%, and the intimal to the medial area ratio by 36.2% compared with controls in vessels after 14 days of injury. Green tea catechins administration substantially increased expression of tissue inhibitor of MMP-2, and reduced the levels of active MMP-2 and of the gelatinolytic net activity. This evidence suggests to some extent an association between the antiatherogenic action of catechins and the antiinvasive and antimetalloproteinase activity.

For new blood vessels to form, angiogenesis, EC, and SMC must migrate. EGCG has been demonstrated to prevent angiogenesis through several mechanisms, including inhibition of EC and SMC migration, regulating EC and SMC growth and survival, and inhibiting tube formation. EGCG induces the transcription factor nuclear factor-κB, promoting SMC death. The sum of these effects results in the cessation and potentially the reversal of various vascular diseases and cancer growth. Vascular endothelial growth factor is a key protein involved in angiogenesis.[102-109] It binds to the surface of EC and activates various cell functions including tube formation. It has been demonstrated that certain catechins, especially EGCG, inhibit vascular endothelial growth factor. One hundred micrometers of EGCG resulted in a cell growth inhibition rate of 55% and prevented tube formation.[27,28]

CANCER AND OTHER HEALTH BENEFITS

Similar to atherogenesis, many factors related to diet, metabolism, and the external environment modulate the initiation, promotion, and progression of cancer development. Cancer pathogenesis is influenced by the modification of DNA structure, enzymatic activity, and defense mechanisms, which are a result of the accumulation of ROS.[110] In vitro studies have shown tea catechins as potent inhibitors of carcinogenesis at the three stages of cancer development.[30,63,111,112] With regard to cancer initiation, in vitro studies have shown that polyphenols from green tea can prevent formation of nitrosamines, which are carcinogens also found in tobacco.[113,114] Phenolics in tea have also been found to inhibit heterocyclic amine formation.[67] These molecules are genotoxic carcinogens found in cooked meat and fish, and are associated with pancreatic, colon, and breast cancers. EGCG exhibits the strongest effects against mutations, DNA scissions, and nonenzymatic interception of superoxide anions.[3] On the other hand, (-)-epicatechin-3-gallate is one of the most efficient enzymatic scavengers, directly neutralizing procarcinogens, as observed in scavenging superoxide tests and in DNA damage assays.[63,110] With respect to cancer promotion, EGCG inhibits the protein kinase activator, an enzyme involved in the cell activation process leading to promotion of tumors by blocking the interaction and binding between proteins and ligands.[115] EGCG induces cellular senescence by strongly inhibiting telomerase activity, limiting cancer cells' lifespan in leukemia and in solid tumors.[116] Studies have also reported that EGCG and theaflavin-3 to 3′-digallate causes the blockage of activator protein-1, a signal transducer associated with development of skin cancer and other tumors.[117] With regard to cancer progression, numerous reports[63,118,119] indicate that tea polyphenols inhibit the growth of malignant cells and can induce apoptosis. Theaflavin-3,3′-digallate and EGCG have antiproliferative activities on tumors through the blockage of growth factor binding,[120,121] although EGCG has also been reported to block cell division in G_1.[122] In addition, EGCG inhibits urokinase, a proteolytic enzyme necessary for cancer growth, tissue invasion, and metastasis.[123] In animals, tea has been shown to be bioactive against carcinogenesis in liver, skin, lung, gastrointestinal tract, and hormonal-dependent cancers.[124-130] In humans, consumption of $>$ 10 cups (1,800 mL, approximately 300 to 400 mg of EGCG) per day among women and men was associated with a marked decrease in cancer incidence with age.[16] Cohort studies suggest a protective effect of green tea for esophageal, stomach, pancreatic, colon, and urinary bladder carcinogenesis, among other cancers.[131,132]

It should be emphasized that although green tea appears to be widely associated with protective effects for cancer, other factors such as genetic differences, geographic regions, and lifestyles should be taken into consideration. A population-based, case-control study of breast cancer among Chinese, Japanese, and Filipino women was conducted in Los Angeles County, where 501 breast cancer patients and 594 control subjects were interviewed. Detailed information on lifestyle factors, including diet and the intake of black and green tea, was collected. It was found that decreased breast cancer risk was unrelated to black tea intake. On the other hand, green tea consumption showed a substantially reduced risk. The adjusted odds ratios being 1.00, 0.71, and 0.53 respectively, in association with 0.0, 0 to 85.7 and $>$ 85.7 mL green tea per day.[133] This study suggests that the decreased cancer risk was irrespective of genetics, geographic location, and food consumption.

Green tea has also been associated with prevention and treatment of many other systemic disorders. Of importance in diabetes, green tea can reduce blood glucose levels in aged rats[134] and suppress the activity of glucose transporters in the intestinal epithelium, reducing dietary glucose intake.[135] Green tea has antiinflammatory properties and EGCG has been reported to considerably inhibit histamine release by 90% in rat cell culture.[136] Quercetin also produces a concentration-dependent inhibition of histamine release, and in antigen-activated cells, provides an antiinflammatory effect.[137] A marked reduction in the incidence of arthritis is produced by green tea polyphenols, as demonstrated in arthritic joints in mice. This is explained by a strong reduction of inflammatory mediators, neutral endopeptidase activity, and levels of type II collagen-specific IgG.[138] In terms of renal pathology, catechins increase sodium and prostaglandin E_2 excretion and improve renal circulation.[139] Progression of renal failure is suppressed, and mesangial proliferation and glomerular sclerotic lesions are attenuated by consumption of green tea, as shown in nephrectomized rats.[140] Modulation of the activity of the intestinal microflora and improvement in bowel function has also been demonstrated.[141] Extracts from tea have been reported to inhibit the effects of *Campylobacter jejuni*, *C*

coli, *Helicobacter pylori*, vibrio cholerae, *Salmonella*, shigella, clostridium, mycoplasma, pseudomona, and *Cryptococcus*.[136,141-144] Tea has also been shown to have antiviral effects, strongly inhibiting rotavirus in monkey cell culture and influenza A in animal cell culture, among other viruses.[63,145] In addition, flavonoids, including EGCG and (-)-epicatechin-3-gallate, have been reported to inhibit reverse transcriptase and propagation of the retrovirus human immunodeficiency virus.[145]

In conclusion, epidemiologic evidence suggests that chronic diseases, such as cardiovascular disease and cancer, have a lower incidence in countries with a high intake of tea, particularly green tea. It is possible that those who do or do not drink tea differ in some other way that affects cardiovascular disease, ie, cigarette smoking, dietary, and lifestyle factors. The "Asian Paradox" refers to the very low incidence of both heart disease and cancer in Asia, even though consumption of cigarettes is greater than in most other countries. This discrepancy is thought to have occurred as a result of a voluminous intake of green tea, approximately 1.2 L per day. In vitro and in vivo studies have shown that the main polyphenolic component of green tea, EGCG, is responsible for these protective qualities (Table 3). One of the reasons green tea is so beneficial to our health is the result of its strong antioxidant nature, being stronger than oolong and black teas. Since EGCG is an antioxidant, it is able to prevent LDL oxidation, which has been shown to play a key role in the pathophysiology of arteriosclerosis.

Another phenomenon that increases the risk of arteriosclerosis is platelet aggregation. EGCG has been shown to effectively reduce the amount of platelet aggregation by inhibiting certain events at the molecular level. Green tea's actions on the vasomotor tone as a lipid regulator, and in SMC proliferation and migration can enhance these cardiovascular protective effects. Studies have also shown that through several means EGCG effectively prevents angiogenesis, causing cessation of certain types of tumor growth. It has been reported that tea can improve gastrointestinal function, ethanol metabolism, kidney, liver, and pancreatic function, stomach injuries, skin and eye protection, and alleviation of arthritis. It has also been used in the management and prevention of allergies, diabetes, bacterial and viral infections, dental caries, to improve neurologic and psychological health, and to ameliorate or cure other diseases that have an inflammatory component.

Despite the plethora of information, more studies are necessary to fully elucidate and better understand green tea's method of action, particularly at the cellular level. In this manner, we can determine the active components involved in this process, perhaps with the goal of preparing extracts specifically for those individuals who cannot drink tea or simply dislike it. The evidence is strong that green tea consumption is a useful dietary habit to lower the risk and treat a number of chronic diseases. Prevention is by far the best cure. The consumption of 6 to 10 cups of tea per day might constitute an aid to increased health, longevity, and quality of life. Tea is becoming a popular drink and, to some extent, it seems to be a potential solution to some of the major health problems of the elderly

Table 3. Putative Mechanisms of Green Tea's Cardioprotective Effects

Antioxidant
Free radical scavenger[55,63,68-70]
Metal ion chelator[41]
Sparing of antioxidants (vitamins E and C, β-carotene)[72]
Alteration of catalytic activity of enzymes[55]
Modification of protein phosphorylation[71]
Platelet aggregation modulator
Inhibition of PAF[75,76]
Inhibition of ADP[77]
Inhibition of PDGF β receptor[77]
Modification of phospholipase activity[78]
Vasorelaxation
NO release[80,88]
eNOS activation
Inhibition thromboxane[75]
Lipids regulator
Enhance superoxide dismutase[91]
Enhance phase II enzymes activity[91]
Precipitation and fecal elimination of cholesterol[82,93]
Inhibition of digestive lipase activity
Inhibition of pancreatic lipase activity
Inhibition of squalene epoxide[94]
Reduce LDL and VLDL oxidation[92]
Enhancement of noradrenaline-induced lipolisis[97]
Inhibition of SMC proliferation and vascular hyperplasia
Cell cycle arrest[146]
DNA strand breakage
Inhibition of MMPs[23,27,28]
TIMP-2 overexpression[100]
Inhibition of VEGF[27,28]
SMC apoptosis[147,148]

eNOS, endothelial nitric oxide synthase; MMP, matrix metalloproteinase; NO, nitric oxide; PAF, platelet-aggregating factor; PDGF, platelet-derived growth factor; SMC, smooth muscle cell; TIMP-2, tissue inhibitor metalloproteinase; VEGF, vascular endothelial growth factor; VLDL, very low-density lipoprotein.

and society. It is important to reveal its role and mechanism of action in today's lifestyle-related diseases.

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