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Mechanisms and Effects of Green Tea on Cardiovascular Health

Arpita Basu, PhD, and Edralin A. Lucas, PhD

Green tea, rich in antioxidant and anti-inflammatory catechins, especially epigallocatechin gallate (EGCG), has been shown to reduce surrogate markers of atherosclerosis and lipid peroxidation, particularly LDL oxidation and malondialdehyde concentrations, in several in vitro, animal, and limited clinical studies. Epidemiological observations in Southeast Asian countries indicate an inverse correlation exists between habitual consumption of green tea beverages and the incidence of cardiovascular events. A few short-term clinical studies have reported its effects in attenuating biomarkers of oxidative stress and inflammation among smokers, and an ability to decrease postprandial lipemia in hypercholesterolemic subjects has also been suggested. However, further investigations are needed to confirm the potential role of green tea beverages and the safety of green tea supplements in reducing body fat, as well as other biomarkers of cardiovascular disease risks.

Key words: epigallocatechin gallate, green tea, lipid peroxidation, smokers, weight loss

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INTRODUCTION

Tea, a beverage consumed worldwide, is a source of both pleasure and healthful benefits. Originally recommended in traditional Chinese medicine, green tea (*Camellia sinensis*) has gained considerable attention due to its antioxidant, anti-inflammatory, antihypertensive, antidiabetic, and antimutagenic properties. Green tea has been recommended in the past for treating headaches and body aches, aiding digestion and detoxification, and acting as an energizer.[1] Since the incidence of cardiovascular disease (CVD) continues to rise in industrialized countries, the role of bioactive compounds in foods has been an active area of scientific enquiry, with the flavonoids in tea being of interest, mainly for their exciting cardioprotective prospects.[2]

Green tea, due to its high content of polyphenolic flavonoids, mainly the catechins, has shown unique cardiovascular health benefits. Approximately 76% to 78% of the tea produced and consumed is black tea, and 80% of tea consumed in the USA is in the form of black iced tea. Green tea constitutes 20% to 22% of tea production and is principally consumed in China, Japan, Korea, and Morocco. Oolong tea production and consumption accounts for less than 2% and is popular in China and Taiwan.[3,4,5] Green tea, or non-fermented tea, contains the highest amount of flavonoids, in comparison to its partially fermented (oolong tea) and fermented (black tea) counterparts. In green tea, catechins comprise 80% to 90% of total flavonoids, with epigallocatechin gallate (EGCG), being the most abundant catechin (48–55%), followed by the other catechins, epigallocatechin (EGC; circa 9–12%), epicatechin gallate (ECG; circa 9–12%), and epicatechin (EC; circa 5–7%) (Figure 1).[6,7] One cup of green tea contains about 90 mg of EGCG.[3] In addition to catechins, the chemical composition of green tea also includes proteins (15%), amino acids (4%), fiber (26%), other carbohydrates (7%), lipids (7%), pigments (2%), and minerals (5%).[8]

The catechin content of green tea depends on several factors including how the leaves are processed before drying, preparation of the infusion, and decaffeination, as well as the form in which it is distributed in the market (e.g., instant preparations, iced, and ready-to-drink teas have been shown to contain fewer catechins).[9,10] Chen et al.[11] have further demonstrated the thermal conversion of EGCG to gallocatechin gallate in canned or bottled green tea drinks in Japan, which also contained fewer green tea catechins than the green tea prepared traditionally in a

Drs. Basu and Lucas are with the Department of Nutritional Sciences, 301 Human Environmental Sciences, Oklahoma State University, Stillwater, OK 74078-6141, USA.

Please address all correspondence to: Dr. Arpita Basu, Department of Nutritional Sciences, 416 Human Environmental Sciences, Oklahoma State University, Stillwater, OK 74078-6141, USA. Phone: +1-405-744-4437; Fax: +1-405-744-1357; E-mail: arpita.basu@okstate.edu

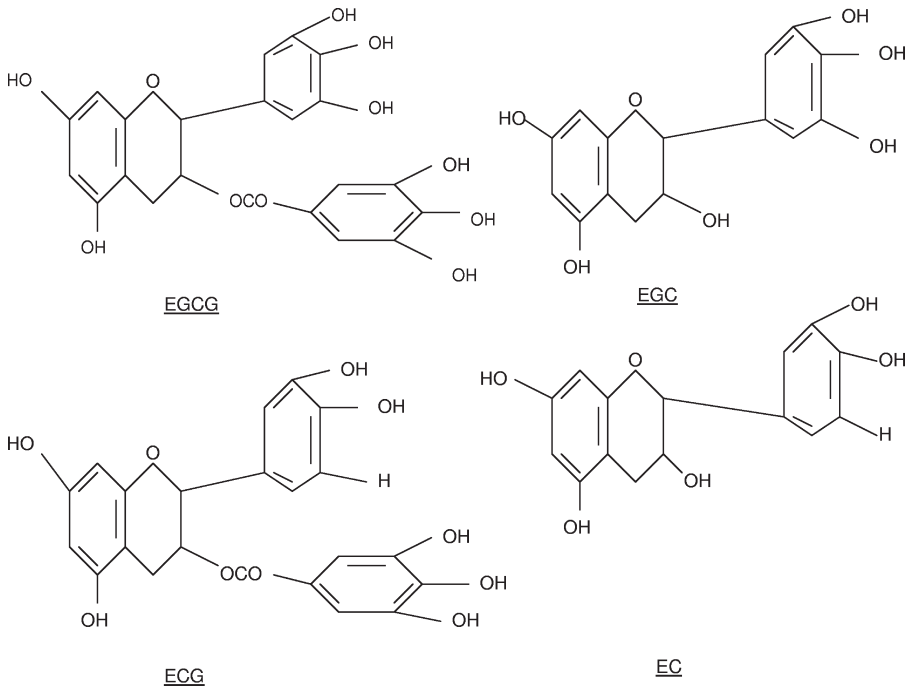

Figure 1. Major catechins in green tea. EGCG, epigallocatechin gallate; EGC, epigallocatechin; ECG, epicatechin gallate; EC, epicatechin.

porcelain cup or a teapot. The EGCG content of green tea dietary supplements have also been reported to vary widely, ranging from 12% to 143% of the label claims.[12] Thus, it is important to consider the large variations in the catechin content of green tea, as well as supplements containing green tea extracts, when assessing their biological effects on human health and disease.

BIOAVAILABILITY AND PHARMACOKINETICS OF GREEN TEA CATECHINS

The bioavailability of green tea catechins in humans is an important variable for evaluating their biological activity within target tissues. Catechin levels in human plasma have been shown to reach their peak within 2 to 4 hours following ingestion of green tea.[13] A study comparing the pharmacokinetics of equimolar doses of pure EGC, ECG, and EGCG in healthy volunteers reported that average peak plasma concentrations after a single dose of 1.5 mmol was the highest for EGC (5.0 μmol/L), followed by ECG (3.1 μmol/L) and EGCG (1.3 μmol/L), indicating that EGCG may be less bioavailable than other green tea catechins in humans.[14]

Chow et al.[15] administered one of the following orally for a period of 4 weeks to 40 healthy men and women with Fitzpatrick skin type II or III: 1) a bolus dose of 800 mg of EGCG or Polyphenon E (a decaffeinated green tea polyphenol mixture); 2) 400 mg of EGCG or Polyphenon E twice daily; or 3) a placebo. These skin types allow evaluation of the ultraviolet light-induced erythema response without causing a painful burn, which is useful for evaluating the cancer-preventive properties of green tea. Though the intervention had no effects on erythema, the area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of EGCG or Polyphenon E were higher following the 800 mg dose compared to the 400 mg dose. Also, following repeat administration of the 800 mg dose, the AUC was significantly higher, versus no change associated with a twice-daily supplementation of a 400 mg dose. The AUC of total EGC and EC (free and conjugated) showed no significant change following repeat dosing of either 800 mg or 400 mg of EGCG or Polyphenon E, though the AUC was significantly higher after the first dose of 800 mg versus 400 mg. The authors suggest the mechanism of inhibition of presystemic elimination of EGCG or Polyphenon E at a higher bolus dose of 800 mg, versus 400 mg, may contribute to the observed increase in AUC. This study further reported the safety of a bolus dose of EGCG or Polyphenon E, based on the fact that the participants experienced only mild events, such as upset stomach, nausea, dizziness, headache, and muscle pain, with similar events being reported in the placebo group as well.[15]

Little data is available on the distribution of catechins in tissue following green tea consumption. A 28-day study in rats, which were given 0.6% green tea polyphenols in their drinking water, showed an increased accumulation of EGC and EC in the esophagus, large

intestine, kidney, bladder, lung, and prostate, whereas, EGCG levels were higher in the esophagus and large intestine.[16] Thus, there is a difference in the bioavailability of different green tea catechins that is influenced by dosing schedule; it may also differ by genotype and the presence of other nutrients or polyphenols as part of the natural food matrix.

MECHANISMS OF ACTION OF GREEN TEA POLYPHENOLS

Findings from both in vitro and animal models demonstrate the cardiovascular benefits of green tea and its catechins and provide insight into some of the mechanisms of action by which they exert cardiovascular-protective effects. Tables 1 and 2 summarize the effects of green tea catechins on markers related to CVD, as reported by studies using in vitro systems and animal models. Green tea extract and tannin mixtures have been shown to scavenge nitric oxide and superoxides, and the flavan-3-ol linked to gallic acid is an important structural property that confers this activity.[17] The effects of green tea catechins on copper-induced oxidation of low-density lipoprotein (LDL) have been investigated in several in vitro studies.[18-20] The activity of green tea catechins against copper-induced oxidation of LDL is in the order of EGCG=ECG>EC=C>EGC.[18] Moreover, green tea catechins have been shown to prolong lag time,[20-21] inhibit formation of oxidized cholesterol, and decrease linoleic acid and arachidonic acid concentrations.[18] Studies also show that green tea catechins reduce LDL oxidation, thiobarbituric acid reactive substances (TBARS) formation, cellular oxidation, and superoxide production.[22,23] In human hepatoma cells, green tea catechins were shown to prevent TBARS and glutathione disulfide formation and alpha-tocopherol depletion while enhancing the glutathione content of the cell.[24]

In addition to having antioxidant properties, green tea catechins have also been shown to reduce smooth muscle cell proliferation,[25] which may be attributed to inhibition of protein tyrosine kinase activity, reducing c-jun mRNA expression and inhibiting JNK1 activation.[26] Moreover, green tea polyphenols inhibit p44/42 MAP kinase expression[27] and induce the death of smooth muscle cells in a p53- and NF-kappaB-dependent manner.[28] Proliferation of vascular smooth muscle cells (VSMC) stimulated with advanced glycation end products or native LDL was dose-dependently inhibited by green tea polyphenols.[29,30] [3] Thymidine incorporation stimulated with platelet-derived growth factor-BB and Ang II in VSMC was also inhibited by green tea catechins.[31,32] Catechins inhibit the Ang II-stimulated VSMC proliferation via inhibition of the Ang II-stimulated activation of MAP kinase and activator protein-1 signaling pathways.[32,33] EGCG was also shown to have anti-invasive and anti-metalloproteinase activities in aortic smooth muscle cells.[34] Findings from in vitro studies demonstrate that green tea catechins exert cardiovascular benefits through their antioxidant properties by inhibiting LDL-oxidation, reducing TBARS formation, cellular oxidation and superoxide production, and inhibiting smooth muscle cell proliferation.

The positive findings reported from studies using in vitro systems were also observed using animal models. Rats fed a cholesterol-rich diet and given Chinese green tea or jasmine tea for 8 weeks had significantly lower cholesterol levels in serum and liver. The investigators attributed these hypocholesterolemic effects to the ECG and EGCG content of the tea.[35] Another study using Chinese green tea demonstrated that the hypocholesterolemic effect of green tea is mediated through increased fecal bile acid and cholesterol excretion.[36] The activities of three major lipid-metabolizing enzymes, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, cholesterol 7alpha-hydroxylase, and fatty acid synthase, were not affected by green tea.[37] Another mechanism by which green tea exerts hypolipidemic effects may be due to inhibition of intestinal absorption of cholesterol and dietary fat, as observed in rats and hamsters.[37-39] Findings by Raederstoff et al.[40] confirmed that the cholesterol-lowering effect of green tea is mainly elicited by EGCG, and that the effect occurs through decreased cholesterol absorption. Green tea polyphenols were also shown to be as effective as probucol, an antioxidant hypocholesterolemic agent, in inhibiting LDL oxidation and elevating serum antioxidative activity.[41]

In addition to lowering cholesterol, green tea has been shown to possess anti-atherosclerotic effects.[42-46] In New Zealand white rabbits, consumption of green tea led to a reduction in atherosclerosis, a decrease in vascular endothelial growth factor expression in the atherosclerotic plaque,[43] and prolongation of the lag phase of LDL oxidation.[42] Similar anti-atherosclerotic effects of green tea extracts were observed in rats and attributed to a significant increase in tissue inhibitor of matrix metalloproteinases (MMP)-2 expression and a significant reduction of gelatinolytic net activity and activated MMP-2 levels in the injured arteries.[44] In apolipoprotein E-null mice, EGCG treatment differentially reduced evolving atherosclerotic lesions without influencing established atherosclerosis.[45] Another mechanism by which green tea exerts a cardiovascular-protective effect is through its effect on blood pressure. Systolic and diastolic blood pressure was significantly lower in stroke-prone male, spontaneously hypertensive rats given green tea polyphenol, which can be explained by the antioxidant properties of green tea.[47]

Table 1. Summary of in vitro studies on the cardiovascular effects of green tea and its catechins

Reference	Cell type and treatment	Findings
Nakagawa et al.[17]	Nitric oxide- and superoxide-generating systems treated with green tea extract and green tea tannin mixtures.	Green tea extract and green tea tannin mixtures showed direct scavenging activity against nitric oxide and superoxide.
Osada et al.[18]	Cu^{++} catalyzed oxidation of human LDL incubated with varying levels of crude catechin mixture (THEA-FLAN 40) and purified C, EC, ECG, EGC, and EGCG. AAPH-mediated oxidation of LDL from rats fed a diet containing 0.5% ECG or EGCG for 5 days.	Antioxidative potency of GTC against Cu^{++} catalyzed LDL oxidation: EGCG=ECG>EC=C>EGC. EGCG and ECG inhibited formation of oxidized cholesterol and decreased linoleic and arachidonic acids. EGCG and ECG inhibited oxygen consumption and formation of conjugated dienes.
Miura et al.[19]	Cu^{++} catalyzed oxidation of porcine LDL incubated with different tea polyphenols.	Tea polyphenols suppressed the oxidative modification of LDL ($P<0.05$). Prolongations of the lag time were in the order of EGC < C < EC < ECG < EGCG.
Ishikawa et al.[20]	Cu^{++} catalyzed oxidation of human LDL incubated with catechins or theaflavins.	Among the catechins, EGCG exerted the most marked effect, prolonging the oxidation lag time more than vitamin E at the same molar concentration ($P<0.01$).
Yamanaka et al.[21]	Cu^{++} catalyzed oxidation of human LDL incubated with different tea polyphenols (EC and EGC).	In the initiation phase, the oxidation of LDL was inhibited by EC and EGC; in the propagation phase, EC or EGC worked as an accelerator of oxidation.
Yang et al.[22]	Human umbilical cord vascular endothelial cell (HUVEC) LDL oxidation; incubated with Lung Chen tea extract.	Catechin-rich fraction of Lung Chen tea dose-dependently reduced LDL oxidation ($P<0.001$), TBARS ($P<0.001$), and cellular cholesterol ($P<0.01$).
Yoshida et al.[23]	Mouse peritoneal macrophages and HUVEC LDL oxidation; incubated with tea flavonoids.	Inhibition of Cu^{++}-mediated LDL oxidation was in the order of theaflavin digallate>theaflavin≥EGCG>EGC>gallic acid ($P<0.05$). Theaflavin digallate pretreatment decreased superoxide production of macrophages and chelated iron ions significantly ($P<0.05$).
Murakami et al.[24]	Human hepatoma cells (HepG2) incubated with tea catechins.	Inhibition of TBARS accumulation in HepG2 cells: EGCG>EGC≥ or ECG>EC ($P<0.05$).
Lorenz et al.[25]	Rat aortic rings and endothelial cells incubated with EGCG.	EGCG-induced endothelium-dependent vasodilatation; caused rapid activation of eNOS by a phosphatidyl-inositol 3-kinase-, PKA-, and Akt-dependent increase in eNOS activity ($P<0.05$).
Yokozawa et al.[26]	Smooth muscle cells exposed to green tea tannin.	Among four types of gallate-free tannin, EGC, EC, and C showed significant dose-dependent inhibition of smooth muscle cell proliferation ($P<0.05$).
Lu et al.[27]	Rabbit vascular smooth muscle cell (VSMC) stimulated by serum mixed with tea catechins.	Catechins dose-dependently inhibited the proliferative response stimulated by serum in rabbit cultured vascular smooth muscle cells ($P<0.05$)
Ouyang et al.[28]	Rat VSMCs stimulated by native LDL and exposed to green tea polyphenols.	Green tea polyphenols inhibited high levels of LDL-induced proliferation of phosphorylated p44/42 MAPK expression in rat VSMCs ($P<0.05$).

Table 1. (Cont'd) Summary of in vitro studies on the cardiovascular effects of green tea and its catechins

Reference	Cell type and treatment	Findings
Hofmann et al.[29]	Aortic smooth muscle cell exposed to green tea polyphenols.	EGCG inhibits growth ($P=0.019$) and induces death of SMCs in a p53- and NF-kappaB-dependent manner ($P<0.05$).
Ouyang et al.[30]	Rat vascular smooth muscle cells (VSMCs) stimulated by advanced glycation end products (AGEs) and exposed to green tea polyphenols.	Green tea polyphenols dose-dependently inhibited AGE-stimulated VSMC proliferation and the p44/42 MAPK activity was significantly enhanced ($P<0.05$).
Locher et al.[31]	Human VSMCs stimulated by native LDL and exposed to green tea catechins.	Cell proliferation stimulated by native LDL was concentration-dependently inhibited by EGC, EGCG, green tea polyphenols, and the nonspecific antioxidant N-acetylcysteine ($P<0.05$).
Kim et al.[32]	Rat carotid artery injury model exposed to green tea catechins.	Green tea catechins dose-dependently decreased [3H]thymidine incorporation stimulated with platelet-derived growth factor-BB. The GTC-treated group also showed a significant reduction in luminal diameter and neointimal formation compared with the control group. The effects of EGCG were similar to those of GTC ($P<0.05$).
Won et al.[33]	Rat aortic VSMC exposed to tea catechins.	EC, ECG, or EGCG significantly inhibited the Ang II-induced [3H]thymidine incorporation into the primary cultured rat aortic VSMC ($P<0.01$). EGCG pretreatment inhibited the Ang II-induced phosphorylation of ERK 1/2, JNK 1/2, or p38 MAPK and the expression of c-jun or c-fos mRNA ($P<0.01$).
Maeda et al.[34]	Culture bovine aortic SMC exposed to catechins.	EGCG inhibited the gelatinolytic activity of MMP-2 and concanavalin A (ConA)-induced pro-MMP-2 activation without the influence of membrane-type MMP expression in SMCs ($P<0.001$).

AAPH-2,2', azobis(2-amidinopropane) hydrochloride; AGEs, advanced glycation end products; Ang II, angiotensin II; C- (+), catechin; EC- (-), epicatechin; ECG- (-), epicatechin gallate; EGC- (-), epigalocatechin; EGCG- (-), epigalocatechin gallate; eNOS, endothelia nitric oxide synthase; ERK ½, extracellular signal-regulated protein kinase ½; GTC, green tea catechin; HepG2, human hepatoma cells; HUVEC, human umbilical cord vascular endothelial cell; JNK ½, c-jun-N-terminal kinase ½; LDL, low density lipoprotein; MAPK, mitogen-activated protein kinase; MMP-2, matrix metalloproteinase-2; PKA, cAMP-dependent protein kinase; SMC, smooth muscle cells; TBARS, thiobarbituric acid reactive substances; VSMC, vascular smooth muscle cells

In summary, the cardiovascular benefits of green tea consumption were demonstrated in both in vitro studies and animal models. EGCG was demonstrated to be the most potent of the green tea catechins in exerting its cardiovascular benefits. Some of the mechanisms by which green tea exerts these positive effects include antioxidative, antiatherosclerotic, and hypolipidemic effects.

GREEN TEA INTERVENTION IN ADULT SMOKERS

According to recently published data from the INTERHEART study, tobacco use is one of the most important causes of the progression of heart disease and its culmination in acute myocardial infarction among men.[48] Cigarette smoke contains large amounts of free radicals, which have been shown to promote lipid peroxidation in the circulation. Keeping in mind the fact that green tea polyphenols, containing EGCG, are effective scavengers of free radicals,[49] some investigators have examined their effects on biomarkers of oxidative stress and surrogate markers of cardiovascular risk factors among smokers.

Princen et al.[50] reported no effects of green tea consumption (900 mL/day for 4 weeks) on plasma lipids, LDL oxidation, and plasma levels of antioxidants like

Table 2. Summary of animal studies on the cardiovascular effects of green tea and its catechins

Reference	Animal model and treatment	Findings
Yang et al.[35]	Rats fed a cholesterol-rich diet and treated with different tea extracts for 8 weeks.	Chinese green tea and jasmine tea significantly lowered serum ($P=0.001$) and liver cholesterol ($P=0.02$ and 0.05, respectively). All tea treatments lowered the atherogenic index ($P=0.01$) and increased the HDL-total cholesterol ($P=0.01$).
Yang et al.[36]	Hypercholesterolemic Sprague-Dawley rats given Lung Chen tea for 8 weeks.	Lung Chen tea administration (2% and 4%) significantly lowered serum cholesterol ($P<0.05$ and $P<0.02$, respectively) and significantly increased excretion of fecal bile acids ($P<0.05$) and cholesterol ($P<0.05$).
Loest et al.[37]	Ovariectomized rats infused with green tea extracts for 8 hours.	Green tea extracts dose-dependently reduced ($P<0.05$) the lymphatic absorption of (14)C-cholesterol.
Chan et al.[38]	Hamsters fed a high-fat, high-cholesterol diet containing green tea extract for 4 weeks.	GTE dose-dependently lowered ($P<0.05$) serum total cholesterol and triacylglycerols but did not affect liver fatty acid synthase. GTE increased ($P<0.05$) fecal excretions of total fatty acids, neutral sterols, and acidic sterols compared with the control group ($P<0.05$).
Hasegawa et al.[39]	Male Zucker rats fed a 50% sucrose diet containing 15% butter supplemented with green tea powder for 10 days.	Powdered green tea depressed body weight ($P<0.01$) and lowered plasma total cholesterol ($P<0.01$). Liver total cholesterol was unaffected.
Raederstoff et al.[40]	Wistar rats fed a diet high in cholesterol and fat containing EGCG for 4 weeks.	Total cholesterol ($P=0.004$) and LDL ($P=0.013$) levels were significantly reduced in the group fed 1% EGCG. Plasma triglycerides and HDL levels did not change significantly. Intestinal cholesterol and total fat absorption ($P<0.05$) was reduced with EGCG.
Yokozawa et al.[41]	Cholesterol-fed rats given green tea polyphenols compared to probucol in a 5-week treatment period.	Green tea polyphenol effectively inhibited LDL oxidation and elevated serum antioxidative activity ($P<0.001$) to the same degree as probucol. Green tea polyphenols increased ($P<0.001$) the levels of HDL cholesterol, leading to dose-dependent improvement of the atherogenic index, an effect that was not seen with probucol.
Tijburg et al.[42]	New Zealand white rabbits fed a high-fat semi-purified diet supplemented with cholesterol and given black tea or green tea in drinking water for 21 weeks.	Green tea consumption tended ($P=0.11$) to reduce aortic lesion formation, while black tea, vitamin E, and beta-carotene had no effects. Green and black tea induced a prolongation of the LDL lag phase ($P<0.05$) with a correspondingly lower oxidation rate.
Kavantzas et al.[43]	Male New Zealand white rabbits given a hypercholesterolemic diet with green tea for 17 weeks.	Consumption of green tea led to a reduction of atherosclerosis as well as a significant decrease of VEGF expression ($P=0.0016$) in the atherosclerotic plaque of rabbit aorta ($P=0.001$).

Table 2. (Cont'd) Summary of animal studies on the cardiovascular effects of green tea and its catechins

Reference	Animal model and treatment	Findings
Cheng et al.[44]	Male Wistar rats fed drinking water with or without green tea extracts for 14 days.	Tea extract reduced the area of the intima ($P=0.0245$) and the ratio of the intimal area to the medial area ($P=0.0012$) in injured arteries. Compared with the control group, there was a significant increase in TIMP-2 expression ($P<0.001$) as well as a significant reduction of gelatinolytic net activity ($P<0.01$) and activated MMP-2 levels in the injured arteries.
Chyu et al.[45]	Apolipoprotein E-null mice with evolving and established atherosclerotic lesions given EGCG intraperitoneal injections for 42 days.	EGCG treatment resulted in an increase in the antioxidant capacity in local vascular tissue and systemic circulation ($P<0.05$) and reduced vascular smooth muscle cell proliferation and redox-sensitive gene activation in vitro ($P<0.05$).
Miura et al.[46]	Atherosclerosis-susceptible C57BL/6J, apoprotein (apo)E-deficient mice fed an atherogenic diet for 14 weeks along with drinking water supplemented with green tea extracts.	No effects on plasma cholesterol or triglyceride concentrations. Plasma lipid peroxides were reduced ($P<0.01$) in the tea group. Atheromatous areas in the aorta from the arch to the femoral bifurcation and aortic weights were both significantly attenuated by 23% in the tea group ($P<0.01$).
Negishi et al.[47]	Male SHRSP rats fed water, black, or green tea polyphenols for 3 weeks.	Systolic and diastolic BP were significantly lowered ($P<0.05$) in the BTP and GTP groups compared with the controls. GTP significantly increased catalase expression ($P<0.05$), and BTP and GTP significantly decreased MLC-p expression ($P<0.05$) in the aorta.

BP, blood pressure; BTP, black tea polyphenols; EGCG- (-), epigalocatechin gallate; GTE, green tea extract; GTP, green tea polyphenols; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMP-2, matrix metalloproteinase-2; SHRSP, stroke-prone spontaneously hypertensive; TIMP-2, tissue inhibitor of matrix metalloproteinase; VEGF, vascular endothelial growth factor

vitamin C, E, β-carotene, and uric acid in subjects who smoked at least 10 cigarettes per day. The study further reported that polyphenol extracts of green tea (3.6 g/day for 4 weeks) decreased plasma vitamin E levels and reduced LDL oxidation in vitro, but had no effect on ex vivo LDL oxidation. It should be noted that this study did not measure other biomarkers of oxidative stress, and the small sample size ($n=15$ in the green tea group) may have contributed to the null effects.[50] In contrast, Klaunig et al.[51] reported that green tea consumption (6 g of green tea extracted into 300 mL of hot water or 32 oz of 2.75% green tea) in two separate study groups (China and the United States) caused a significant decrease in oxidative DNA damage, lipid peroxidation, and free radical generation among heavy smokers following either a 1-day or a 1-week intervention. The biomarkers that were found to be affected by the green tea intervention were 8-hydroxydeoxyguanosine in white blood cells and urine, and malondialdehyde and 2,3-dihydroxyl benzoic acid in urine. The non-smokers also showed a decrease in oxidative stress, following green tea consumption.[51] Further improvements were observed in a group of 20 male smokers. In this group, green tea consumption (400 mL) providing 61.8 mg/dL of EGCG was shown to significantly improve postprandial endothelium-dependent vasodilatation, and it significantly decreased urinary 8-iso-prostaglandin-F2α, a biomarker of lipid peroxidation.[52]

In a more recently reported study, Lee et al.[53] examined biomarkers of oxidative stress and inflammation, suggestive of endothelial dysfunction, in male smokers who consumed 600 mL of green tea for 4 weeks. While no effects were seen regarding the lipid profile, total antioxidant capacity, C-reactive protein, or soluble cellular adhesion molecules in plasma, there was a significant reduction in P-selectin and oxidized LDL at 2 and 4 weeks of green tea ingestion, suggesting decreased platelet aggregation and increased antioxidant effects of green tea.

Interestingly, while ex vivo LDL oxidation with Cu^{++} ions showed no protective effects of green tea catechins, a direct quantitation of oxidized LDL in plasma revealed significant antioxidant effects of green tea polyphenols.[53] The cardioprotective effects of green tea consumption on endothelial function has also been examined by Kim et al.[54] in chronic smokers. Green tea consumption (8 g/day for 2 weeks) caused a significant improvement in endothelial progenitor cell levels as well as flow-mediated endothelium-dependent vasodilatation, elucidating the role of green tea polyphenols in reversing endothelial cell injury and reducing the risks of cardiovascular events. This study further reported no effect of green tea consumption on the plasma lipid profile.[54] However, in the absence of a control group, the results from these studies should be interpreted with caution.

Since smokers tend to have an elevated level of oxidative stress and a consequent risk of developing CVD, green tea consumption may be beneficial in ameliorating these risk factors, though its impact on selected biomarkers of oxidative stress and inflammation need to be further defined in relation to the dose of EGCG. Table 3 summarizes the green tea beverage/extract supplementation in human volunteers and their effects on biomarkers of oxidative stress and inflammation as well as other CVD risk factors (1997–2006).

GREEN TEA INTERVENTION IN HEALTHY NONSMOKING VOLUNTEERS

Several investigators have postulated that green tea has an effect in increasing the plasma antioxidant capacity in healthy human volunteers.[55-57] Green tea extract supplementation (3 g/day) has also been shown to reduce plasma malondialdehyde (MDA) concentrations in comparison to placebo in healthy female volunteers consuming a diet high in linoleic acid. However, no effects were observed with regard to serum lipids and antioxidants, plasma coagulation factors, urinary indicators of oxidative stress, thromboxane, and nitric oxide formation.[58] Since green tea extracts were administered together with a diet high in linoleic acid, which has been shown to reduce serum cholesterol and triglyceride concentrations,[59] the exclusive role of green tea extracts in reducing lipid peroxidation in healthy volunteers remains to be elucidated.

Erba et al.[60] showed a significant decrease in plasma peroxide levels, DNA oxidative damage, and plasma LDL-cholesterol, as well as a significant increase in total antioxidant activity in the plasma of healthy volunteers who consumed 2 cups of green tea per day in addition to a balanced and controlled diet. The data remained significant when compared to the control group, which received a similar diet that was controlled for vegetable and fruit intake. However, the balanced and controlled diet itself may play a role in the reported effects.[60] Hirano-Ohmori et al.[61] further demonstrated that drinking 7 cups of green tea per day for a period of 2 weeks did not affect plasma LDL-cholesterol concentrations in healthy volunteers, but it significantly decreased the serum malondialdehyde-LDL (MDA-LDL) levels and the ratio of MDA-LDL/LDL-cholesterol in these subjects.[61] Thus, green tea beverages may act synergistically with a healthy diet in affecting the biomarkers of oxidative stress in healthy individuals.

GREEN TEA AND WEIGHT LOSS

Abdominal obesity and percentage body fat, which are independent risk factors for CVD, have also been parameters of interest for researchers in green tea intervention. Epidemiological studies have shown an inverse correlation between habitual tea consumption practiced for more than 10 years and body fat percentage and distribution.[62] The anti-obesity effects of green tea have been investigated in various in vitro and in vivo models, including animal and human studies. They have been demonstrated to reduce adipocyte differentiation and proliferation, lipogenesis, fat mass, and body weight, and to increase beta-oxidation and thermogenesis.[63] Chantre and Lairon[64] examined the anti-obesity effects of the green tea extract AR25 (Exolise) in 70 moderately obese patients. Following a 3-month administration of AR25, providing a total of 375 mg catechins or 270 mg EGCG, the subjects experienced a 4.6% decrease in body weight and a 4.48% decrease in waist circumference, and the study further reported the safety of EGCG supplements in these participants.

In vitro studies with AR25 reported direct inhibition of gastric and pancreatic lipases and stimulation of thermogenesis by inhibiting enzymatic degradation of noradrenalin, which suggest the mechanisms of the weight-reducing effects of green tea extract AR25.[64] Kovacs et al.[65] conducted a randomized, parallel, placebo-controlled trial among 26 males and 78 females, involving the administration of green tea extracts (573 mg catechins, of which 323 mg was EGCG and 104 mg caffeine) for a duration of 13 weeks, which was a weight maintenance period, following a 4-week weight loss regimen. The study findings revealed that subjects in the green tea treatment group with a habitually higher caffeine intake regained more weight than those with a lower caffeine intake; however, this did not affect overall weight maintenance after a weight loss period. Also, while the researchers indicated a lack of effect on weight regain by green tea treatment, the macronutrient intake during the weight maintenance period was not described adequately and could have influenced weight regain in these subjects.[65]

In a subsequent study, the same group of researchers further reported the effects of green tea (270 mg

Table 3. Summary of clinical trials on the effects of green tea (GT) or green tea polyphenol (GTP) supplementation on cardiovascular risk factors and biomarkers of oxidative stress and inflammation

Reference	Duration	Study design	No. of participants	Control	GT/GTP	Daily dose	Significant results
van het Hof et al.[90]	4 weeks	Randomized parallel comparison trial	45 healthy adults (24 male, 21 female)	Mineral water	GT	6 cups	No effects on serum lipids or ex vivo LDL oxidation
Princen et al.[50]	4 weeks	Randomized placebo-controlled trial	43 smokers (22 male, 21 female; 13–16/group)	Water	GT and GTP	6 cups; 3.6 g	Plasma vitamin E (P= 0.016); LDL oxidation in vitro
Klaunig et al.[51]	1 day or 1 week	Randomized placebo-controlled trial	67 (52 smokers, 15 nonsmokers; 55 male, 12 female)	Hot water/ placebo drink	GT	300 mL; 32 oz of 2.75%	8-OHdG in WBC and urine; MDA and 2,3-DHBA in urine (P<0.05)
Freese et al.[58]	4 weeks	Randomized placebo-controlled trial	20 healthy nonsmoking females	Placebo	GTP	3 g	Plasma MDA (P<0.05)
Benzie et al.[55]	1 day	Crossover study: baseline vs postintervention	10 healthy volunteers (5 male, 5 female)	Water	GT	400 mL	Plasma & urinary FRAP; urinary total phenolic concentrations (P<0.05)
Nakagawa et al.[56]	1 day	Clinical trial: baseline vs post-intervention	18 healthy volunteers (gender not mentioned)	None	GTP	254 mg catechin	Plasma PCOOH; plasma antioxidant capacity (P<0.05)
Hodgson et al.[91]	1 day	Randomized crossover study	20 healthy male nonsmokers	Water; water with matched caffeine content	GT	400 mL	No effects on ex vivo lipoprotein oxidation (P=0.17)
Serafini et al.[57]	1 day	Randomized crossover study	5 healthy volunteers (gender not mentioned)	Water	GT	300 mL	Plasma TRAP; in vitro LDL oxidation (P<0.05)
Maron et al.[72]	12 weeks	Randomized placebo-controlled parallel-group trial	240 adults (100 male, 140 female) with mild to moderate hypercholesterolemia	Placebo	Theaflavin-enriched green tea extract	375 mg	Total and LDL-C (P=0.01)
Nagaya et al.[52]	1 day	Randomized crossover study	20 male smokers	Hot water	GT	400 mL	Urinary 8-iso-PGF2α; forearm blood flow (P<0.05)
Unno et al.[73]	3 days	Randomized triple-crossover trial	9 males with mild or borderline hypertriglyceridemia	10 mg green tea catechins	GTP (EGCG and ECG)	224 mg or 674 mg	Postprandial AUC of plasma triglycerides (P<0.05); postprandial elevation of remnant-like particle cholesterol (P<0.01)
Lee et al.[53]	4 weeks	Clinical trial: baseline vs post-intervention	20 male smokers	None	GT	600 mL	sP-selectin (P<0.001); oxidixed LDL (P<0.05)
Hirano Ohmori et al.[61]	2 weeks	Randomized crossover study	22 healthy male nonsmokers	Water	GT	7 cups	MDA-LDL (P<0.05); MDA-LDL/LDL-C ratio (P<0.02)
Erba et al.[60]	42 days	Randomized controlled trial	24 healthy females	Controlled diet	Controlled diet + GTE	320 mg	Plasma total antioxidant capacity; plasma peroxide levels, DNA oxidative damage, LDL cholesterol (P<0.05)

Table 3. (Cont'd) Summary of clinical trials on the effects of green tea (GT) or green tea polyphenol (GTP) supplementation on cardiovascular risk factors and biomarkers of oxidative stress and inflammation

Reference	Duration	Study design	No. of participants	Control	GT/GTP	Daily dose	Significant results
Fukino et al.[74]	2 months	Randomized controlled trial	66 patients (53 male, 13 female) with borderline diabetes or diabetes	Control	GTP	456 mg catechins	No effects on insulin resistance and inflammation vs. control ($P>0.05$)
Kim et al.[54]	2 weeks	Clinical trial: baseline vs post-intervention	20 smokers (4 male, 16 female	None	GT	8 g in 1 L	EPC levels ($P<0.001$); FMD ($P<0.001$)
Ryu et al.[75]	4 weeks	Randomized crossover study	55 patients (31 male, 24 female) with type 2 diabetes	Water	GT	9 g in 900 mL	No effects on inflammation, insulin resistance, pulse wave velocity (P0.05)

2,3-DHBA, 2,3-dihydroxyl benzoic acid; 8-iso-PGF2α, 8-iso-prostaglandin F2alpha; 8-OHdG, 8-hydroxydeoxyguanosine; AUC, area under time versus concentration curve; EPC, endothelial progenitor cells; FRAP, ferric-reducing ability of plasma; LDL-C, low-density lipoprotein-cholesterol; MDA, malondialdehyde; PCOOH, plasma phosphatidylcholine hydroperoxide; TRAP, total radical-trapping antioxidant parameter; WBC, white blood cells

EGCG and 150 mg caffeine) in reducing body weight, waist circumference, respiratory quotient, and body fat during a 13-week weight-maintenance period in subjects with low habitual caffeine intake. However, no effects of green tea mixture were noted in high-quantity caffeine consumers.[66] A daily 12-week consumption of green tea (690 mg catechins, of which 136 mg was EGCG and 75 mg caffeine) or placebo (oolong tea with 3 mg EGCG and 78 mg caffeine), in conjunction with a low-calorie diet, was shown to significantly reduce body weight and fat mass in 35 overweight males.[67] Figure 2 shows a moderately strong positive correlation between dose of EGCG and reduction in fat mass (kg) in different weight loss programs using EGCG-rich green tea extracts.[64-69]

With regard to fat oxidation and thermogenesis in humans, a single administration of green tea extract or green tea beverage has been shown to increase energy expenditure due to increased fat oxidation among healthy males and females with a normal weight (BMI 20–25).[70,71] None of the studies reported any undesirable side effects associated with green tea or green tea extract

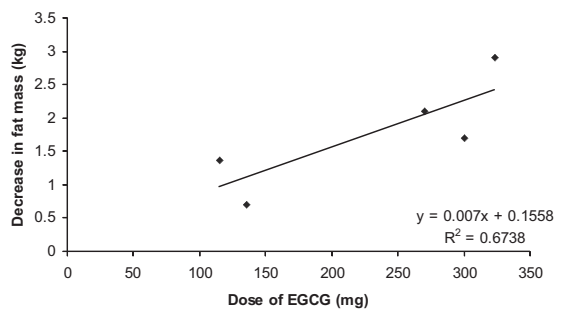

Figure 2. Positive correlation between dose of EGCG and decrease in fat mass based on clinical trials.[64-69]

supplementation. These initial, encouraging results need to be confirmed by future clinical trials.

GREEN TEA INTERVENTION IN INDIVIDUALS AT RISK FOR CARDIOVASCULAR DISEASE

The role of green tea flavonoid supplementation in reducing the risk of cardiovascular disease makes it an attractive therapeutic target. A 12-week daily supplementation of theaflavin-enriched green tea extract (375 mg) or placebo was given to 240 men and women with mild-to-moderate hypercholesterolemia who were already following a low-fat diet. In comparison to the baseline values, the tea intervention significantly reduced total and LDL-cholesterol levels (–11.3% and –16.4%, respectively; $P<0.01$), while no changes were observed in the placebo group.[72] Furthermore, no significant adverse events were reported with tea extract supplementation, which was a combination of theaflavins, green tea catechins, and other tea polyphenols. The authors suggest various mechanisms that explain the cholesterol-lowering effects of tea polyphenols, including reduced micellar solubility and intestinal cholesterol absorption, increased fecal excretion of cholesterol, reduced hepatic cholesterol concentration, and up-regulation of hepatic LDL receptors. Thus, the lipid-lowering effects may reflect a synergistic action between low-fat diet and tea polyphenols, or among the various tea polyphenols, and not the effects of green tea catechins per se.[72] In another randomized, triple-crossover study, moderate and high doses of green tea catechins (224 mg and 674 mg of EGCG and ECG, respectively) were shown to reduce the postprandial incremental area under the plasma triacylglycerol curves by 15.1% and 28.7%,

respectively, in comparison to the control. The subjects were nine adult males with mild or borderline hypertriglyceridemia who consumed one slice of white bread with 20 g of butter along with the test beverage containing different amounts of green tea catechins. Furthermore, green tea catechins were shown to inhibit the rapid elevation of remnant-like particle cholesterol 2 hours postprandial.[73] Since postprandial hypertriglyceridemia has been shown to be an independent risk factor for atherosclerosis and CVD, the consumption of green tea with or before meals may be an effective strategy to attenuate postprandial lipemia in at-risk individuals.

In a 2-month randomized controlled trial, 66 patients with borderline diabetes or diabetes were given green tea catechins supplemented at a daily dose of 456 mg. The results did not show any clear effects on insulin resistance and biomarkers of inflammation in comparison with the control group. Though body weight, systolic and diastolic blood pressure readings, blood glucose levels, hemoglobin A_{1C}, and insulin levels were lower in the intervention group in comparison with their baseline values, the parameters did not differ from those in the control group. However, the study suggested a positive correlation exists between green tea polyphenol intake and insulin levels, which warrants further investigation.[74]

In a recently reported study by Ryu et al.[75], no effects of green tea consumption (900 mL for 4 weeks) were noted on inflammation, insulin resistance, and pulse wave velocity in type 2 diabetic patients. The short duration of the study and absence of data showing compliance with regard to plasma catechin levels, may contribute to the null effects reported by the researchers. Thus, there is limited and conflicting clinical data on the therapeutic effects of green tea catechin. It is expected that further studies will reveal its long-term metabolic effects in the management of cardiovascular diseases.

CORRELATION BETWEEN GREEN TEA INTAKE AND CARDIOVASCULAR DISEASE: EPIDEMIOLOGICAL STUDIES

While tea drinking in general has been associated with cardioprotective benefits,[76] green tea consumption, specifically, has been correlated with a reduced risk of cardiovascular events and other surrogate markers of CVD in Chinese and Japanese cohorts. Recently reported data from the Ohsaki study, which included 40,530 Japanese adults who were followed up for up to 11 years (1995–2005), showed an inverse association between green tea consumption and mortality due to all causes and cardiovascular disease.[77] As early as 1992, Kono et al.[78] reported an inverse correlation between total cholesterol levels in serum and consumption of nine cups or more of green tea per day in 1306 Japanese males; however, no association was noted for serum triglycerides and high-density lipoprotein cholesterol, even after adjusting for dietary variables like soybean products, which are known to influence serum cholesterol.[78] Imai and Nakachi[79] also reported a significant inverse correlation between green tea consumption (>3 cups/day) and the levels of cholesterol and triglycerides in the serum of 1371 Japanese men. However, following extensive multivariate adjustments for nondietary and dietary covariates, Tsubono and Tsugane[80] failed to show any effects of green tea consumption on the lipid levels in 371 middle-aged Japanese males and females. The relatively small sample size may have contributed to the null results of this study.

In an interesting community-based study conducted in Taiwan, China, habitual green tea intake of 120 mL or more per day for 1 year was significantly correlated with a reduction in the risk of developing hypertension in 39.8% of the study population (N=1507) compared to nonhabitual tea drinkers. Following adjustments for several covariates, there was a 46% reduction in the risk of developing hypertension in those who drank 120 ml and 599 mL of green tea per day, and a further 65% reduction in those who consumed 600 mL or more per day.[81]

Regarding the risk of mortality due to heart disease, Hertog et al.[82] reported an inverse correlation between catechin intake and coronary heart disease-related mortality after a 25-year follow-up of 12,763 men from seven different countries. The Boston Area Health Study further reinforced this observation by presenting data that revealed a 44% reduction in the risk of myocardial infarction among those who drank one or more cups of green tea per day versus non-tea-drinkers.[83] Sasazuki et al.[84] reported a weak but protective association between green tea consumption (>2 cups/day) and coronary artery disease (CAD) in men, which inhibited the progression of coronary atherosclerosis, but this was not found in women. An inverse association of green tea intake and myocardial infarction and its genetic variation has also been suggested by Hirano et al.[85] and Ohmori et al.[86] Green tea consumption (5.9 cups/day) was also significantly associated with a lower incidence of CAD in a Japanese population of 203 patients who underwent coronary angiography. After a follow-up of cardiovascular and cerebrovascular events in these patients and an analysis of predictors of CAD, the level of green tea consumption was found to be significantly higher in patients without CAD versus those with CAD (5.9 cups versus 3.5 cups/day, respectively; $P<0.001$). The authors further mention that individuals who drink green tea frequently may also consume traditional Japanese foods, like fish, vegetables, and soybeans that also con-

tain cardioprotective nutrients and dietary factors like omega-3-fatty acids and flavonoids, and this may additionally contribute to the reduced incidence of CAD.[87]

In a more recently reported retrospective cohort study, Iso et al.[88] suggested that a reduced risk of self-reported type 2 diabetes exists among Japanese adults who regularly consume green tea. When compared with participants who did not consume green tea, there was a 33% risk reduction for diabetes among those who were drinking six or more cups of green tea per day. No significant correlations were detected between the consumption of black tea or oolong tea and the risk for diabetes. The authors further discussed the role of green tea antioxidants, especially EGCG, which may contribute to improved insulin sensitivity and glucose metabolism.[88] Since type 2 diabetes mellitus is an independent risk factor for CVD,[89] these data suggest green tea flavonoids have a role in CVD risk reduction and prevention.

Thus, while most of the epidemiological studies showing an inverse correlation between habitual green tea consumption and CVD have been conducted in China and Japan, such results have not yet been documented in Western countries, where green tea intake is limited and sporadic. Also, differences in the results reported from observational studies may be due to variations in sample size and lack of information regarding other confounding variables, like the amount of dietary fat, intensity of smoking and alcohol consumption, and lifestyle factors, all of which impact CVD risk. The methods of green tea preparation and differences in tea strength, if unaccounted for, may affect the bioavailability, plasma catechin levels, and their functional properties and effects on the risk of cardiovascular diseases.

SAFETY OF GREEN TEA SUPPLEMENTS

While green tea beverage consumption is considered part of a healthy lifestyle, at least in China, Japan, and Korea, green tea extracts or EGCG supplements should be used with caution. Studies have shown that EGCG doses of up to 800 mg per day, administered for 4 weeks, is safe and associated with few side effects that were comparable to those in the placebo group.[15] However, very high doses of green tea extracts (6 g–240 g) have been associated with hepatotoxicity in patients who used them as health or weight-loss supplements for a duration of 5 to 120 days. The changes in biochemical parameters included an elevation of serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin levels. The case studies further reported a reversal of symptoms when subjects stopped taking the green tea supplement.[90] Thus, while it may be safe to use doses below 1 g of EGCG, subjects should take higher doses under close medical supervision.

CONCLUSIONS

The role of green tea polyphenols in reducing lipid peroxidation, particularly LDL oxidation and malondialdehyde concentrations, have been reported from several in vitro, animal, and limited clinical studies. However, its hypocholesterolemic effects have not been demonstrated in humans, and further investigations are needed to confirm the potential role of green tea in reducing body fat and being an effective component of a weight-loss diet. While green tea intake may benefit smokers who are at increased risk of developing CVD, its role in reducing the biomarkers of oxidative stress and inflammation in hypercholesterolemic subjects, or in those with borderline diabetes, remains to be elucidated. Nevertheless, a diet rich in functional foods containing antioxidant polyphenols, like green tea beverages, combined with physical activity and lifestyle changes may offer primary prevention against cardiovascular disease. While future clinical trials could further elucidate the cardioprotective benefits of green tea beverages or green tea extracts, on the basis of existing reports, freshly prepared green tea appears to be a healthy dietary choice to consider.

REFERENCES

1. Cabrera C, Artacho R, Gimenez R. Beneficial effects of green tea—a review. J Am Coll Nutr. 2006;25:79–99.
2. Kris-Etherton PM, Lefevre M, Beecher GR, Gross MD, Keen CL, Etherton TD. Bioactive compounds in nutrition and health-research methodologies for establishing biological function: the antioxidant and anti-inflammatory effects of flavonoids on atherosclerosis. Ann Rev Nutr. 2004;24:511–538.
3. Wu CD, Wei GX. Tea as a functional food for oral health. Nutrition. 2002;18:443–444.
4. Zuo Y, Chen H, Deng Y. Simultaneous determination of catechins, caffeine and gallic acids in green, Oolong, black and Pu-erh teas using HPLC with a photodiode array detector. Talanta. 2002;57:307–316.
5. Ilyasova D, Martin C, Sandler RS. Tea intake and risk of colon cancer in African-Americans and whites: North Carolina colon cancer study. Cancer Causes Control. 2003;14:676–772.
6. Balentine DA, Wiseman SA, Bouwens LC. The chemistry of tea flavonoids. Crit Rev Food Sci Nutr. 1997;37:693–704.
7. Shahidi F. Antioxidants in food and food antioxidants. Nahrung. 2000;3:158–163.
8. Belitz DH, Grosch W. Quimica de los Alimentos. Zaragoza: Acribia, 1997.
9. Hakim I, Harris R, Weisgerber U. Tea intake and squamous cell carcinoma of the skin: Influence of type of tea beverages. Cancer Epidemiol Biomarkers Prev. 2000;9:727–731.

10. Arts I, Van de PB, Hollman O. Catechins contents of foods commonly consumed, in the Netherlands. Tea, wine, fruit juices, and chocolate milk. J Agric Food Chem. 2000;48:1752–1757.
11. Chen Z-Y, Zhu QY, Tsang D, Huang Y. Degradation of green tea catechins in tea drinks. J Agric Food Chem. 2001;49:477–482.
12. Seeram NP, Henning SM, Niu Y, Lee R, Scheuller HS, Heber D. Catechin and caffeine content of green tea dietary supplements and correlation with antioxidant capacity. J Agric Food Chem. 2006;54: 1599–1603.
13. Yang CS, Chen L, Lee MJ, Balentine D, Kuo MC, Schantz SP. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. Cancer Epidemiol Biomarkers Prev. 1998;7:351–354.
14. Higdon JV, Frei B. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. Crit Rev Food Sci Nutr. 2003;43:89–143.
15. Chow HH, Cai Y, Hakim IA, et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and Polyphenon E in healthy individuals. Clin Cancer Res. 2003;9:3312–3319.
16. Kim S, Lee MJ, Hong J, Li C, Smith TJ, Yang GY, Seril DN, Yang CS. Plasma and tissue levels of tea catechins in rats and mice during chronic consumption of green tea polyphenols. Nutr Cancer. 2000; 37:41–48.
17. Nakagawa T, Yokozawa T. Direct scavenging of nitric oxide and superoxide by green tea. Food Chem Toxicol. 2002;40:1745–1750.
18. Osada K, Takahashi M, Hoshina S, Nakamura M, Nakamura S, Sugano M. Tea catechins inhibit cholesterol oxidation accompanying oxidation of low density lipoprotein in vitro. Comp Biochem Physiol C Toxicol Pharmacol. 2001;128:153–164.
19. Miura S, Watanabe J, Tomita T, Sano M, Tomita I. The inhibitory effects of tea polyphenols (flavan-3-ol derivatives) on Cu2+ mediated oxidative modification of low density lipoprotein. Biol Pharm Bull. 1994;17:1567–1572.
20. Ishikawa T, Suzukawa M, Ito T, Yoshida H, Ayaori M, Nishiwaki M, Yonemura A, Hara Y, Nakamura H. Effect of tea flavonoid supplementation on the susceptibility of low-density lipoprotein to oxidative modification. Am J Clin Nutr. 1997;66:261–266.
21. Yamanaka N, Oda O, Nagao S. Green tea catechins such as (-)-epicatechin and (-)-epigallocatechin accelerate Cu2+-induced low density lipoprotein oxidation in propagation phase. FEBS Lett. 1997;401: 230–234.
22. Yang TT, Koo MW. Inhibitory effect of Chinese green tea on endothelial cell-induced LDL oxidation. Atherosclerosis. 2000;148:67–73.
23. Yoshida H, Ishikawa T, Hosoai H, et al. Inhibitory effect of tea flavonoids on the ability of cells to oxidize low density lipoprotein. Biochem Pharmacol. 1999;58:1695–1703.
24. Murakami C, Hirakawa Y, Inui H, Nakano Y, Yoshida H. Effect of tea catechins on cellular lipid peroxidation and cytotoxicity in HepG2 cells. Biosci Biotechnol Biochem. 2002;66:1559–1562.
25. Lorenz M, Wessler S, Follmann E, Michaelis W, Dusterhoft T, Baumann G, Stangl K, Stangl V. A constituent of green tea, epigallocatechin-3-gallate, activates endothelial nitric oxide synthase by a phosphatidylinositol-3-OH-kinase-, cAMP-dependent protein kinase-, and Akt-dependent pathway and leads to endothelial-dependent vasorelaxation. J Biol Chem. 2004;279:6190–6195.
26. Yokozawa T, Dong E. Influence of green tea and its three major components upon low-density lipoprotein oxidation. Exp Toxicol Pathol. 1997;49:329–335.
27. Lu LH, Lee SS, Huang HC. Epigallocatechin suppression of proliferation of vascular smooth muscle cells: correlation with c-jun and JNK. Br J Pharmacol. 1998;124:1227–1237.
28. Ouyang P, Peng WL, Lai WY, Xu AL. Green tea polyphenols inhibit low-density lipoprotein-induced proliferation of rat vascular smooth muscle cells. Di Yi Jun Yi Da Xue Xue Bao. 2004;24:975–979.
29. Hofmann CS, Sonenshein GE. Green tea polyphenol epigallocatechin-3 gallate induces apoptosis of proliferating vascular smooth muscle cells via activation of p53. FASEB J. 2003;17:702–704.
30. Ouyang P, Peng WL, Xu DL, Lai WY, Xu AL.Green tea polyphenols inhibit advanced glycation end product-induced rat vascular smooth muscle cell proliferation. Di Yi Jun Yi Da Xue Xue Bao. 2004;24: 247–251.
31. Locher R, Emmanuele L, Suter PM, Vetter W, Barton M. Green tea polyphenols inhibit human vascular smooth muscle cell proliferation stimulated by native low-density lipoprotein. Eur J Pharmacol. 2002; 434:1–7
32. Kim DW, Park YS, Kim YG, et al. Local delivery of green tea catechins inhibits neointimal formation in the rat carotid artery injury model. Heart Vessels. 2004;19:242–247.
33. Won SM, Park YH, Kim HJ, Park KM, Lee WJ. Catechins inhibit angiotensin II-induced vascular smooth muscle cell proliferation via mitogen-activated protein kinase pathway. Exp Mol Med. 2006; 38:525–534.
34. Maeda K, Kuzuya M, Cheng XW, Asai T, Kanda S, Tamaya-Mori N, Sasaki T, Shibata T, Iguchi A. Green tea catechins inhibit the cultured smooth muscle cell invasion through the basement barrier. Atherosclerosis. 2003;166:23–30.
35. Yang TT, Koo MW. Hypocholesterolemic effects of Chinese tea. Pharmacol Res. 1997;35:505–512.
36. Yang TT, Koo MW. Chinese green tea lowers cholesterol level through an increase in fecal lipid excretion. Life Sci. 2000;66:411–423.
37. Loest HB, Noh SK, Koo SI. Green tea extract inhibits the lymphatic absorption of cholesterol and alpha-tocopherol in ovariectomized rats. J Nutr. 2002;132:1282–1288.
38. Chan PT, Fong WP, Cheung YL, Huang Y, Ho WK, Chen ZY. Jasmine green tea epicatechins are hypolipidemic in hamsters (*Mesocricetus auratus*) fed a high fat diet. J Nutr. 1999;129:1094–1101.
39. Hasegawa N, Yamda N, Mori M. Powdered green tea has antilipogenic effect on Zucker rats fed a high-fat diet. Phytother Res. 2003;17:477–480.
40. Raederstorff DG, Schlachter MF, Elste V, Weber P.

Effect of EGCG on lipid absorption and plasma lipid levels in rats. J Nutr Biochem. 2003;14:326–332.
41. Yokozawa T, Nakagawa T, Kitani K. Antioxidative activity of green tea polyphenol in cholesterol-fed rats. J Agric Food Chem. 2002;50:3549–3552.
42. Tijburg LB, Wiseman SA, Meijer GW, Weststrate JA. Effects of green tea, black tea and dietary lipophilic antioxidants on LDL oxidizability and atherosclerosis in hypercholesterolaemic rabbits. Atherosclerosis. 1997;135:37–47.
43. Kavantzas N, Chatziioannou A, Yanni AE, Tsakayannis D, Balafoutas D, Agrogiannis G, Perrea D. Effect of green tea on angiogenesis and severity of atherosclerosis in cholesterol-fed rabbit. Vascul Pharmacol. 2006;44:461–463.
44. Cheng XW, Kuzuya M, Sasaki T, et al. Green tea catechins inhibit neointimal hyperplasia in a rat carotid arterial injury model by TIMP-2 overexpression. Cardiovasc Res. 2004; 62:594–602.
45. Chyu KY, Babbidge SM, Zhao X, et al. Differential effects of green tea-derived catechin on developing versus established atherosclerosis in apolipoprotein E-null mice. Circulation. 2004;109:2448–2453.
46. Miura Y, Chiba T, Tomita I, et al. Tea catechins prevent the development of atherosclerosis in apoprotein E-deficient mice. J Nutr. 2001;131:27–32.
47. Negishi H, Xu JW, Ikeda K, Njelekela M, Nara Y, Yamori Y. Black and green tea polyphenols attenuate blood pressure increases in stroke-prone spontaneously hypertensive rats. J Nutr. 2004;134:38–42.
48. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet. 2006;368:647–658.
49. Cao G, Sofic E, Prior R. Antioxidant capacity of tea and common vegetables. J Agric Food Chem. 1996; 44:3426–3431.
50. Princen HMG, Duyvenvoorde van W, Buytenhek R, et al. No effect of consumption of green and black tea on plasma lipid and antioxidant levels and on LDL oxidation in smokers. Arterioscler Thromb Vasc Biol. 1998;18:833–841.
51. Klaunig JE, Xu Y, Han C, et al. The effect of tea consumption on oxidative stress in smokers and nonsmokers. Proc Soc Exp Biol Med. 1999;220: 249–254.
52. Nagaya N, Yamamoto H, Uematsu M, et al. Green tea reverses endothelial dysfunction in healthy smokers. Heart. 2004;90:1485–1486.
53. Lee W, Min WK, Chun S, et al. Long-term effects of green tea ingestion on atherosclerotic biological markers in smokers. Clin Biochem. 2005;38:84–87.
54. Kim W, Jeong MH, Cho SH, et al. Effect of green tea consumption on endothelial function and circulating endothelial progenitor cells in chronic smokers. Circ J. 2006;70:1052–1057.
55. Benzie IF, Szeto YT, Strain JJ, Tomlinson B. Consumption of green tea causes rapid increase in plasma antioxidant power in humans. Nutr Cancer. 1999;34:83–87.
56. Nakagawa K, Ninomiya M, Okubo T, et al. Tea catechin supplementation increases antioxidant capacity and prevents phospholipid hydroperoxidation in plasma of humans. J Agric Food Chem. 1999;47:3967–3973.
57. Serafini M, Laranjinha JA, Almeida LM, Maiani G. Inhibition of human LDL lipid peroxidation by phenol-rich beverages and their impact on plasma total antioxidant capacity in humans. J Nutr Biochem. 2000;11:585–590.
58. Freese R, Basu S, Hietanen E, et al. Green tea extract decreases plasma malondialdehyde concentration but does not affect other indicators of oxidative stress, nitric oxide production, or hemostatic factors during a high-linoleic acid diet in healthy females. Eur J Nutr. 1999;38:149–157.
59. Wagner KH, Tomasch R, Elmadfa I. Impact of diets containing corn oil or olive/sunflower oil mixture on the human plasma and lipoprotein lipid metabolism. Eur J Nutr. 2001;40:161–167.
60. Erba D, Riso P, Bordoni A, Foti P, et al. Effectiveness of moderate green tea consumption on antioxidative status and plasma lipid profile in humans. J Nutr Biochem. 2005;16:144–149
61. Hirano-Ohmori R, Takahashi R, Momiyama Y, et al. Green tea consumption and serum malondialdehyde-modified LDL concentrations in healthy subjects. J Am Coll Nutr. 2005;24:342–346.
62. Wu CH, Lu FH, Chang CS, Chang TC, Wang RH, Chang CJ. Relationship among habitual tea consumption, percent body fat, and body fat distribution. Obesity Res. 2003;11:1088–1095.
63. Wolfram S, Wang Y, Thielecke F. Anti-obesity effects of green tea: from bedside to bench. Mol Nutr Food Res. 2006;50:176–187.
64. Chantre P, Lairon D. Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. Phytomedicine. 2002;9:3–8.
65. Kovacs EMR, Lejeune MPGM, Nijs I, Westerterp-Plantenga MS. Effects of green tea on weight maintenance after body-weight loss. Br J Nutr. 2004;91: 431–437.
66. Westerterp-Plantenga MS, Lejeune MPGM, Kovacs EMR. Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. Obesity Res. 2005;13:1195–1204.
67. Nagao T, Komine Y, Soga S, Meguro S, Hase T, Tanaka Y, Tokimitsu I. Ingestion of a tea rich in catechins leads to a reduction in body fat and malondialdehyde-modified LDL in men. Am J Clin Nutr. 2005;81:122–129.
68. Hase TKY, TKY, Meguro S, Takeda Y, et al. Antiobesity effects of tea catechins in humans. J Oleo Sci. 2001;50:599–605.
69. Tsuchida T, Itakura H, Nakamura H. Reduction of body fat in humans by long-term ingestion of catechins. Prog Med. 2002;22:2189–2203.
70. Dulloo AG, Duret C, Rohrer D, et al. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. Am J Clin Nutr. 1999;70: 1040–1045.
71. Komatsu T, Nakamori M, Komatsu K, et al. Oolong tea increases energy metabolism in Japanese females. J Med Invest. 2003;50:170–175.
72. Maron DJ, Lu GP, Cai NS, et al. Cholesterol-lowering effect of a theaflavin-enriched green tea extract.

A randomized controlled trial. Arch Intern Med. 2003;163:1448–1453.
73. Unno T, Tago M, Suzuki Y, et al. Effect of tea catechins on postprandial plasma lipid responses in human subjects. Br J Nutr. 2005;93:543–547.
74. Fukino Y, Shimbo M, Aoki N, Okubo T, Iso H. Randomized controlled trial for an effect of green tea consumption on insulin resistance and inflammation markers. J Nutr Sci Vitaminol. 2005;51:335–342.
75. Ryu OH, Lee J, Lee KW, et al. Effects of green tea consumption on inflammation, insulin resistance and pulse wave velocity in type 2 diabetes patients. Diabetes Res Clin Pract. 2006;71:356–358.
76. Peters U, Poole C, Arab L. Does tea affect cardiovascular disease? A meta-analysis. Am J Epidemiol. 2001;154:495–503.
77. Kuriyama S, Shimazu T, Ohmori K, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan. The Ohsaki Study. JAMA. 2006;296:1255–1265.
78. Kono S, Shinchi K, Ikeda N, Yanai F, Imanishi K. Green tea consumption and serum lipid profiles: a cross-sectional study in northern Kyushu, Japan. Prev Med. 1992;21:526–531.
79. Imai K, Nakachi K. Cross-sectional study of effects of drinking green tea on cardiovascular and liver diseases. BMJ. 1995;310;693–696.
80. Tsubono Y, Tsugane S. Green tea intake in relation to serum lipid levels in middle-aged Japanese men and women. Ann Epidemiol. 1997;7:280–284.
81. Yang YC, Lu FH, Wu JS, Wu CH, Chang CJ. The protective effect of habitual tea consumption on hypertension. Arch Intern Med. 2004;164:1534–1540.
82. Hertog M, Kromhout D, Aravanis C, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. Arch Intern Med. 1995;155:381–386.
83. Sesso H, Gaziano J, Buring J, Hennekens C. Coffee and tea intake and the risk of myocardial infarction. Am J Epidemiol. 1999;149:162–169.
84. Sasazuki S, Kodama H, Yoshimasu K, et al. Relation between green tea consumption and the severity of coronary atherosclerosis among Japanese men and women. Ann Epidemiol. 2000;10:401–408.
85. Hirano R, Momiyama Y, Takahashi R, et al. Comparison of green tea intake in Japanese patients with and without angiographic coronary artery disease. Am J Cardiol. 2002;90:1150–1153.
86. Ohmori R, Momiyama Y, Takahashi R, et al. Inverse association of green tea intake with myocardial infarction (MI) and its genetic variation. Atheroscler Suppl. 2003;4:21.
87. Sano J, Inami S, Seimiya K, et al. Effects of green tea intake on the development of coronary artery disease. Circ J. 2004;68:665–670.
88. Iso H, Date C, Wakai K, Fukui M, Tamakoshi A; the JACC Study Group. The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med. 2006;144:554–562.
89. Lahoz-Rallo B, Blanco-Gonzalez M, Casas-Ciria I, et al. Cardiovascular disease risk in subjects with type 2 diabetes mellitus in a population in southern Spain. Diabetes Res Clin Pract. 2007;76:434–444.
90. van het Hof KH, de Boer HS, Wiseman SA, Lien N, Westrate JA, Tijburg LB. Consumption of green or black tea does not increase resistance of low-density lipoprotein to oxidation in humans. Am J Clin Nutr. 1997;66:1125–1132.
91. Hodgson JM, Puddey IB, Croft KD, Burke V, Mori TA, Caccetta RA, Beilin LJ. Acute effects of ingestion of black and green tea on lipoprotein oxidation. Am J Clin Nutr. 2000;71:1103–1107.
92. Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). Ann Intern Med. 2006;144:68–71.