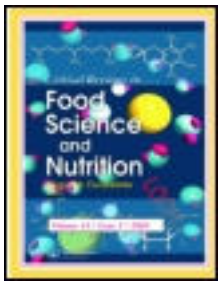

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Tea Catechins and Polyphenols: Health Effects, Metabolism, and Antioxidant Functions

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ABSTRACT: Increasing interest in the health benefits of tea has led to the inclusion of tea extracts in dietary supplements and functional foods. However, epidemiologic evidence regarding the effects of tea consumption on cancer and cardiovascular disease risk is conflicting. While tea contains a number of bioactive chemicals, it is particularly rich in catechins, of which epigallocatechin gallate (EGCG) is the most abundant. Catechins and their derivatives are thought to contribute to the beneficial effects ascribed to tea. Tea catechins and polyphenols are effective scavengers of reactive oxygen species *in vitro* and may also function indirectly as antioxidants through their effects on transcription factors and enzyme activities. The fact that catechins are rapidly and extensively metabolized emphasizes the importance of demonstrating their antioxidant activity *in vivo*. In humans, modest transient increases in plasma antioxidant capacity have been demonstrated following the consumption of tea and green tea catechins. The effects of tea and green tea catechins on biomarkers of oxidative stress, especially oxidative DNA damage, appear very promising in animal models, but data on biomarkers of *in vivo* oxidative stress in humans are limited. Larger human studies examining the effects of tea and tea catechin intake on biomarkers of oxidative damage to lipids, proteins, and DNA are needed.

KEY WORDS: flavanol, theaflavin, thearubigin, cancer, cardiovascular disease, osteoporosis, epidemiology, LDL oxidation, plasma antioxidant capacity, TEAC, FRAP, ORAC, F_2-isoprostanes, 8-hydroxydeoxyguanosine, 8-OHdG.

I. INTRODUCTION

Tea is an infusion of the leaves of the *Camellia sinensis* plant. First discovered in China, tea is grown in over 30 countries and is the most widely consumed beverage in the world, aside from water.[1] Recently, tea has attracted attention for its health benefits, particularly with respect to its potential for preventing and treating cancer and cardiovascular diseases.[2] Increasing scientific and consumer interest in the health benefits of tea has led to the inclusion of tea extracts in oral nutritional supplements, and topical preparations, whose potential for decreasing the risk of skin cancer is under investigation.[3,4] While tea contains a number of bioactive chemicals, it is particularly rich in flavonoids, including catechins, and their derivatives. These polyphenolic compounds, the most abundant of which is epigallocatechin gallate (EGCG), are thought to contribute to the beneficial effects ascribed to tea. Although abundant evidence suggests that catechins and their derivatives are effective antioxidants *in vitro*, the evaluation of their efficacy as antioxidants *in vivo* is more complex.[5] In the following review, we have assessed the available evidence that tea consumption confers significant health benefits to humans, as well as the evidence that tea catechins and polyphenols mediate the proposed health benefits of tea consumption by functioning as effective antioxidants *in vivo*.

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II. HEALTH BENEFITS ASSOCIATED WITH TEA CONSUMPTION

Oxidative damage to biomolecules has been implicated in the pathology of a number of chronic diseases, including cardiovascular diseases, cancers, and neurodegenerative diseases. The known *in vitro* antioxidant properties of catechins and other polyphenolic compounds in tea have led to considerable interest in the potential health benefits of tea consumption. Numerous epidemiologic studies have addressed the relationships between tea consumption and the incidence of cardiovascular diseases and cancer in humans. Many of the earlier epidemiologic studies presented below were designed to examine the effect of coffee, caffeine, or other lifestyle factors on chronic disease endpoints, and therefore are limited in the information they can provide on tea consumption and chronic disease risk.

A. Epidemiologic Studies of Tea Consumption and Cardiovascular Diseases

Six out of nine cohort studies failed to find significant relationships between tea consumption and coronary heart disease (CHD) mortality,[6-11] while two found inverse associations,[12,13] and one found a positive association (Table 1).[14] The only cohort study to assess the effects of green tea followed 8522 Japanese men and women for a period of 12 years. Compared with men who drank $\leq$ 3 cups (450 ml) of green tea daily, men who consumed $\geq$ 10 cups (1500 ml) daily had only 58% the risk of death from CHD.[13] In the Zutphen Elderly Study, 43 out of 805 elderly Dutch men died of CHD during a 5-year follow-up period.[12] Compared with men who drank $\leq$ 250 ml of black tea daily, men who drank more than 250 ml daily had only a 38% to 45% risk of death from CHD. In contrast, a study of 1900 Welsh men followed for 14 years found that men who drank $\geq$ 900 ml of black tea daily had more than twice the risk of death from ischemic heart disease (IHD) than men who drank $\leq$ 300 ml daily.[14] Although the reasons for this unique finding are not clear, the authors noted that the majority of subjects in this population add milk to their tea, which might adversely affect flavanol absorption. Additionally, smoking is highly correlated with heavy tea consumption in the U.K. and may have affected the outcome, despite statistical adjustment for smoking variables.

The association of tea consumption with the severity of aortic atherosclerosis was examined in 3454 men and women who were free of cardiovascular disease at the beginning of the Rotterdam Study.[15] Calcified plaques of the aorta were detected radiographically after 2 to 3 years of follow up. The risk of aortic atheroslcerosis for black tea drinkers compared with nondrinkers was 54% for those who drank 1 to 2 cups/day ($\leq$ 250 ml/day), 47% for those who drank 3 to 4 cups/day (> 250 to $\leq$ 500 ml/day), and 31% for those who drank more than 4 cups/day (> 500 ml/day).

Two cohort studies have demonstrated an inverse relationship between tea consumption and the incidence of stroke. One study followed 5910 Japanese women, who neither smoked nor drank alcohol for 4 years.[16] The incidence of stroke was significantly lower in women who consumed at least 3 to 4 cups of green tea/day. In a study of 552 Dutch men followed for 15 years, the risk of stroke for men who drank more than 4.7 cups/day of black tea was only 31% that of men who drank less than 2.6 cups/day.[17] Two other cohort studies failed to find a significant association between black tea consumption and stroke incidence[6] or mortality,[7] but tea consumption was relatively low in both cohorts.

The findings of case control studies of tea consumption and cardiovascular diseases have been similar to those of cohort studies. Out of six case control studies that examined relationships between the risk of myocardial infarction (MI) and black tea consumption, only one study of 340 cases of MI and 340 community-matched controls found a significant inverse association.[18] The risk of MI in those who consumed at least one cup of black tea daily was only 56% the risk of those who did not drink tea. The other five studies did not observe a significant association between tea consumption and MI risk.[19-23] In an observational study of Japanese men and women undergoing coronary angiography, green tea consumption was inversely related to coronary artery disease, de-

Table 1: Prospective cohort studies of tea and flavonoid consumption and cardiovascular disease risk

Reference	Country (tea)	Subjects/ Events (Follow up period)	Outcome: Association	RR (95% CI)
Tea				
Sato et al. 1989 [16]	Japan (Green tea)	5910 non-smoking, non-drinking women 174 cases of stroke (4 y)	Stroke incidence: Inverse	Incidence of stroke (% of cohort) 0 cups/day: 2.26% 3-4 cups/day: 0.40% (P < 0.01) ≥ 5 cups/day: 0.41% (P < 0.01)
Stensvold et al. 1992 [9]	Norway (Black tea)	9856 men 141 CHD deaths 10,233 women 18 CHD deaths (12 y)	CHD mortality: Non-significant	Men ≥ 1 cup/d vs < 1 cup/d: RR = 0.64 (0.38-1.07) Women Too few deaths to calculate RR
Klatsky et al. 1993 [7]	U.S. (Black tea)	125,356 men + women 539 CHD deaths 433 MI deaths 275 stroke deaths (8 y)	CHD mortality, MI mortality, and stroke mortality: Non-significant	Risk (per cup/d) CHD mortality: RR = 0.99 (NS) MI mortality: RR = 0.97 (NS) Stroke mortality: RR = 0.94 (NS)
Hertog et al. 1993 [12]	Netherlands (Black tea)	805 men 43 CHD deaths (5 y)	CHD mortality: Inverse	251-500 ml/d vs ≤ 250 ml/d: RR = 0.38 (0.19-0.82) > 500 ml/d vs ≤ 250 ml/d: RR = 0.45 (0.22-0.93)
Rimm et al. 1996 [8]	U.S. (Black tea)	34,789 men 44 CHD deaths (2 y)	CHD mortality Non-significant	≥ 2 cups/d vs 0 cups/d: RR = 1.59 (0.98-2.28)
Keli et al 1996 [17]	Netherlands (Black tea)	552 men 42 first or non-fatal stroke cases (15 y)	Stroke incidence: Inverse	Tea consumption from 1960-1970 ≥ 587 g/day vs < 330 g/d: RR = 0.31 (0.12-0.84)
Hertog et al. 1997 [14]	U.K./Wales (Black tea)	1900 men 186 IHD cases 131 IHD deaths (14 y)	IHD incidence: Non-significant IHD mortality: Positive	IHD incidence: P (trend) = 0.67 IHD mortality: 900-1200 ml/d vs ≤ 300 ml/d: RR = 2.1 (1.0-4.1) > 1200 ml/day vs < 300 ml/d: RR = 2.3 (1.0-5.1)
Woodward & Tunstall-Pedoe 1999 [10]	U.K./ Scotland (Black tea)	11,567 206 CHD deaths (8 y)	CHD mortality: Men: Non-significant Women: Non-significant	Men 5+ cups/d vs. 0 cups/d: RR = 2.19 (NS) Women 5+ cups/d vs. 0 cups/d: RR = 2.77 (NS)

Table 1 (continued)

Reference	Country (tea)	Subjects/ Events (Follow up period)	Outcome: Association	RR (95% CI)
Tea (continued)				
Yochum et al. 1999 [11]	U.S. (Black tea)	34,492 women 483 CHD deaths (10 y)	CHD mortality: Non-significant	5-42 times/wk vs 0 times/wk: RR = 0.89 (0.67-1.17)
Geleijnse, et al. 1999 [15]	Netherlands (Black tea)	3454 men and women, 55% of whom had some degree of aortic atherosclerosis on X-ray (2-3 y)	Aortic atherosclerosis: Inverse	Compared to non-drinkers ≤ 250 ml/day: OR = 0.54 (0.32-0.92) 251-500 ml/day: OR = 0.47 (0.27-0.81) ≥ 500 ml/day: OR = 0.31 (0.16-0.59)
Nakachi et al. 2000 [13]	Japan (Green tea)	8522 men and women 274 CHD deaths (13 y)	CHD mortality: Inverse for men Non-significant for women	Men ≥ 10 cups/d vs ≤ 3 cups/d: RR = 0.58 (0.34-0.99) Women ≥ 10 cups/d vs ≤ 3 cups/d: RR = 0.90 (0.60-1.37)
Hirvonen et al. 2000 [6]	Finland (Black tea)	26,415 male smokers 736 cerebral infarction cases 83 subarachnoid hemorrhage cases 95 intracerebral hemorrhage cases (6 y)	Stroke incidence: Non-significant for all 3 subtypes	≥ 1 cup/d vs < 1 cup/d: Cerebral infarction: RR = 0.90 (0.74-1.09) Subarachnoid hemorrhage: RR = 0.71 (0.38-1.35) Intracerebral hemorrhage: RR = 0.98 (0.57-1.68)
Hirvonen et al. 2001 [26]	Finland (Black tea)	25,372 male smokers 1,122 non-fatal MI 815 CHD deaths (6 y)	Non-fatal MI incidence and CHD mortality: Non-significant	Non-fatal MI ≥ 1 cup (170 ml)/d vs < 1 cup/ RR = 0.94 (0.81-1.11) CHD mortality ≥ 1 cup/d vs < 1 cup/d: RR = 1.09 (0.91-1.30)
Flavonoids				
Knekt et al. 1996 [27]	Finland (Flavonoids; no data on tea)	2748 men and 2,385 women 473 CHD deaths (26 y)	CHD mortality: Non-significant	Men > 4.8 mg/d vs < 2.1 mg/d: RR = 0.67 (0.44-1.00) Women >5.5 mg/d vs < 2.4 mg/d: RR =0.73 (0.41-1.32)

Table 1 (continued)

Reference	Country	Subjects/ Events (Follow up period)	Outcome: Association	RR (95% CI)
Flavonoids (continued)				
Rimm et al. 1996 [8]	U.S. (Flavonols and flavones)	Primary analysis: 34,789 men 486 non-fatal MI cases (6 y) Secondary analysis: 4814 men with prevalent CHD 140 CHD deaths (2 y)	Non-fatal MI: Non-significant CHD mortality: Non-significant	Non fatal MI 40.0 mg/d vs. 7.1 mg/d: RR = 1.08 (0.81-1.43) CHD mortality 40.0 mg/d vs 7.1 mg/d: RR = 0.63 (0.33-1.20)
Keli et al. 1996 [17]	Netherlands (Flavonoids)	552 men 42 stroke cases (15 y)	Stroke incidence: Inverse	< 18.3 mg/day: 1.00 18.3-28.5 mg/d vs < 18.3 mg/d: RR = 0.46 (0.24-0.90) ≥ 28.6 mg/d vs. 18.3 mg/d: RR = 0.27 (0.11-0.70) P (trend) = 0.004
Hertog et al. 1997 [28]	Netherlands (Flavonoids)	804 men 90 deaths from CHD 92 episodes of first MI (10 y)	CHD mortality: Inverse First MI: Non-significant	CHD mortality 19.1-29.9 mg/d vs ≤ 19 mg/d: RR = 0.58 (0.35-0.95) > 29.9 mg/d vs ≤ 19 mg/d: RR = 0.47 (0.27-0.82) First MI > 29.9 mg/d vs ≤ 19 mg/d: RR = 0.62: (0.24-1.05)
Hertog et al. 1997 [14]	U.K./Wales (Flavonols)	1900 men 186 IHD cases 131 IHD deaths (14 y)	IHD incidence: Non-significant IHD mortality: Non-significant	IHD incidence > 34 mg/d vs < 19 mg/d: RR = 1.1 (0.6-1.6) IHD mortality > 34 mg/d vs < 19 mg/d: RR = 1.6 (0.9-2.9)
Hirvonen et al. 2000 [6]	Finland (Flavones and flavonols)	26,415 male smokers 736 cerebral infarctions 83 subarachnoid hemorrhages 95 intracerebral hemorrhages (6 y)	Stroke incidence: Non-significant for all 3 subtypes	16.4 mg/d vs 4.2 mg/d: Cerebral infarction: RR = 0.98 (0.80-1.21) Subarachnoid hemorrhage: RR = 0.75 (0.40-1.41) Intracerebral hemorrhage: RR = 0.88 (0.59-1.57)

Table 1 (continued)

Reference	Country (tea)	Subjects/ Events (Follow up period)	Outcome: Association	RR (95% CI)
Flavonoids (continued)				
Hirvonen et al. 2001 [26]	Finland (Flavones and flavonols)	25,372 male smokers 1122 non-fatal MI 815 CHD deaths (6 y)	Non-fatal MI: Inverse	Non-fatal MI 10.8 mg/d vs 3.9 mg/d: RR = 0.77 (0.64-0.93) 17.8 mg/d vs 3.9 mg/d: RR = 0.77 (0.64-0.93)
			CHD mortality: Non-significant	CHD mortality 17.8 mg/d vs 3.9 mg/d: RR = 0.89 (0.71-1.11)
Arts, et al. 2001 [29]	Netherlands (Catechins)	806 men 90 deaths from CHD 90 cases of MI 47 deaths from stroke 88 cases of stroke (10 y)	CHD mortality: Inverse	CHD mortality: 86-355 mg/d vs ≤ 49 mg/d: RR = 0.49 (0.27-0.88)
			MI incidence: Non-significant	MI incidence: 86-355 mg/d vs ≤ 49 mg/d: RR = 0.70 (0.39-1.59)
			Stroke mortality: Non-significant	Stroke mortality: 86-355 mg/d vs ≤ 49 mg/d: RR = 0.81 (0.36-1.83)
			Stroke incidence: Non-significant	Stroke incidence 86-355 mg/d vs ≤ 49 mg/d: RR = 0.92 (0.51-1.68)

fined as significant stenosis of at least one coronary vessel, in men only when those who were taking medication for diabetes were excluded from the sample.[24] Green tea consumption was not significantly related to coronary artery disease in women.

Because flavonoids are thought to represent the cardioprotective components of tea, a number of investigators have reexamined the relationships between tea consumption and cardiovascular disease in cohort studies by including estimates of flavonoid consumption (Table 1).[25] The sources of dietary flavonoids are highly variable between studies. In Finland, tea consumption is very low, and the contribution of tea to dietary flavonoid intake is negligible. In a cohort of more than 25,000 male Finnish smokers followed for 6 years, flavonoid intake was inversely associated with nonfatal MI, but not CHD mortality or stroke incidence.[6,26] Flavonoid intake was not significantly associated with CHD mortality in another Finnish cohort of 5133 men and women followed for 26 years.[27] Nonfatal MI and CHD mortality were not significantly associated with flavonoid intake in a prospective study of 34,789 male health professionals in the U.S., where black tea intake contributed 25% of the total dietary flavonoid intake.[8] In several European studies, black tea was the source of 60% to 80% of total dietary flavonoids. While stroke incidence[17] and CHD mortality[28] were inversely related to flavonoid intake in Dutch men, CHD incidence and mortality were not significantly related to flavonoid intake in a cohort of Welsh men.[14] In an attempt to explain the inverse relationship between tea consumption and CHD in the Zutphen Elderly Study, dietary catechin intake was evaluated recently in this Dutch cohort.[29] After 10 years of follow up, catechin intake was significantly and inversely related to CHD mortality, but not to MI incidence, stroke incidence, or stroke mortality. Tea was the source of 87% of dietary catechins.

The authors of a recent meta-analysis, based on ten cohort and seven case control studies, concluded that an increase in tea consumption of three cups (711 ml)/day decreased the risk of MI by 11% (relative risk estimate = 0.89, 95% confidence interval: 0.79, 1.01).[30] However, they also

urged caution in interpreting their results due to evidence of bias toward publication of smaller studies that suggested protective effects. Overall, epidemiologic studies do not provide conclusive evidence for a protective effect of tea consumption on the risk of cardiovascular diseases, although several studies have demonstrated significant risk reduction in consumers of black and green tea.

The findings of two recent clinical trials suggest that black tea consumption reverses endothelial dysfunction in individuals with CHD[31] and hyperlipidemia.[32] Endothelial dysfunction is associated with atherosclerosis, and increasing evidence suggests that it is particularly germane to the clinical expression of cardiovascular diseases, that is, angina pectoris, MI, and stroke.[33] Brachial artery flow-mediated dilation, a measure of endothelial function, is impaired in patients with CHD, but significantly improved 2 h after consumption of 450 ml of black tea or 900 ml/day of black tea for 4 weeks, compared with consumption of equal quantities of water by the same patients.[31] Brachial artery flow-mediated dilation was not affected 2 h after 200 mg of caffeine, a dose equivalent to that in 450 ml of black tea, suggesting that tea polyphenols may be responsible for the effect. The consumption of 1250 ml/day of black tea for 4 weeks also improved brachial artery flow-mediated dilation in patients with mild to moderate hyperlipidemia.[32] It is not clear whether the beneficial effect of tea on endothelial function is a result of the antioxidant properties of tea polyphenols. The antioxidant, vitamin C, has also been found to improve endothelial function.[34] However, vitamin C appears to increase endothelial nitric oxide synthase (eNOS) activity by maintaining its cofactor tetrahydrobiopterin in the reduced, and thus active, form.[35]

B. Epidemiologic Studies of Tea Consumption and Cancer

1. Tea Consumption and Total Cancer

Of three cohort studies that examined the relationship between black tea consumption and total cancer risk (Table 2), two found no significant association,[7,36] whereas one study in the U.K. found a positive association with heavy tea consumption ($\geq$ 7 cups/day).[37] This positive association between black tea consumption and total cancer deaths has been questioned because there was no adjustment for cancer risk factors, including cigarette smoking, which is known to be prevalent in heavy tea drinkers in the U.K.[38] No significant association between dietary flavonoid intake and total cancer risk was observed in another cohort study in which black tea provided 61% of total dietary flavonoid intake.[39] Although there is little evidence of a protective effect of black tea consumption on total cancer risk, one Japanese cohort study found a significant inverse association between total cancer risk and green tea consumption in women, but not men, who drank $\geq$ 10 cups/day.[40]

2. Esophageal Cancer

In case control studies, the consumption of tea at scalding hot temperatures has been positively associated with esophageal cancers, likely due to thermal irritation of the esophagus.[38] When the consumption of very hot tea is excluded from the analyses, most case control studies find no significant association between tea consumption and esophageal cancer. Three studies observed positive associations between the consumption of tea that was not scalding hot and esophageal cancer risk. Black South African men with esophageal cancer were significantly more likely to drink black tea with milk daily than hospital controls, but the analysis was not adjusted for other risk factors, such as smoking.[41] When compared with population-based controls, but not hospital controls, Indian men who drank more than 2 cups/day of black tea were 2.4 times more likely to have esophageal cancer than those who drank 2 cups/day or less.[42] In China, men and women who drank strong green tea or consumed more than 1500 g/year had significantly higher risks of esophageal cancer.[43] Interestingly, two of the largest case control studies found inverse relationships between tea consumption and esophageal cancer. Chinese women who consumed at least 150 g/month of green tea were 66% less likely to

Table 2. Prospective cohort studies of tea consumption and cancer risk

Reference	Country (tea)	Subjects/ Events (Follow up period)	Association	RR (95% CI)
All cancers				
Kinlen et al. 1988 [37]	UK (Black tea)	14,085 men 1652 cancer deaths (19 y)	Positive	Observed deaths/expected 0-3 cups/d: 0.7 4-6 cups/d: 0.8 7-9 cups/d: 1.1 ≥ 10 cups/d: 1.2 P (trend) < 0.0001
Klatsky et al. 1993 [7]	U.S. (Black tea)	128,934 men and women 1424 cancer deaths (10 y)	Non-significant	Tea as a continuous variable RR = 0.99 (per cup/day)
Hertog et al. 1994 [39]	Netherlands (Flavonoids)	738 men 75 cancer cases (5 y)	Non-significant	> 29.9 mg/d vs ≤ 19 mg/d: RR = 1.21 (0.66-2.21)
Zheng et al. 1996 [36]	U.S. (Non-herbal tea)	35,369 postmenopausal women 2,936 non-skin cancer cases (8 y)	Non-significant	Never/monthly: RR = 1.00 ≥ 2 cups/d: RR = 0.90 (0.76-1.07)
Imai et al. 1997 [40]	Japan (Green tea)	8522 men and women 384 cancer cases (9 y)	Inverse Significant for women only	Men ≥ 10 cups/d vs ≤ 3 cups/d: RR = 0.68 (0.39-1.21) Women ≥ 10 cups/d vs < 3 cups/d: RR = 0.57 (0.33-0.98)
Gastric cancer				
Heilbrun et al. 1986 [48]	U.S. Hawaii (Black tea)	7833 men 136 deaths (20 y)	Non-significant	Age adjusted proportion of frequent black tea consumption (almost daily vs > daily): Stomach cancer deaths: 14.6% Controls: 15.3% P = 0.82
Kinlen et al. 1988 [37]	UK (Black tea)	14,085 men 172 deaths (19 y)	Positive	Observed deaths/expected 0-3 cups/d: 0.58 4-6 cups/d: 0.76 7-9 cups/d: 1.20 ≥ 10 cups/d: 1.44 P (trend) < 0.0005
Goldbohm et al. 1996 [47]	Netherlands (Black tea)	58,279 men and 62,573 women 160 cases in men 40 cases in women (4.3 y)	Non-significant	≥ 5 cups/d vs 0 cups/d: RR = 0.94 (0.51-1.75)

Table 2 (continued)

Reference	Country (tea)	Subjects/ Events (Follow up period)	Association	RR (95% CI)
Gastric cancer (continued)				
Galanis et al. 1998 [46]	U.S./Hawaii (Green tea and Black Tea)	5,233 men 6,297 women 64 cases in men 44 cases in women (14.8 y)	Green tea: Non-significant Black tea: Non-significant	Green tea ≥ 2 cups/d vs 0 cups/d: RR = 1.5 (0.9-2.3) Black tea ≥ 1 cups/d vs 0 cups/d: RR = 0.8 (0.5-1.4)
Tsubono et al. 2001 [49]	Japan (Green tea)	11,902 men 14,409 women 296 cases in men 123 cases in women (8 y)	Non-significant	≥ 5 cups/d vs < 1 cup/d: RR = 1.2 (0.9-1.6)
Colorectal cancer				
Heilbrun et al. 1986 [48]	U.S. Hawaii (Black tea)	7833 men 152 colon cancer deaths 76 rectal cancer deaths (20 y)	Colon cancer: Non-significant Rectal cancer: Positive	Age adjusted proportion of frequent black tea consumption (almost daily vs > daily): Controls: 15.3% Colon cancer deaths: 14.6% Rectal cancer deaths: 26.9% Rectal cancer Almost daily vs almost never: RR = 2.1 (P < 0.05) > once daily vs almost never: RR = 4.2 (P < 0.05)
Kinlen et al. 1988 [37]	UK (Black tea)	14,085 men 153 colon cancer deaths 154 rectal cancer deaths (19 y)	Colon cancer: Non-significant Rectal cancer Non-significant	Observed deaths/expected Colon cancer 0-3 cups/d: 1.0 4-6 cups/d: 0.83 7-9 cups/d: 0.45 ≥ 10 cups/d: 0.67 P (trend) = 0.066 Rectal cancer 0-3 cups/d: 0.46 4-6 cups/d: 0.90 7-9 cups/d: 0.76 ≥ 10 cups/d: 0.50 P (trend) = 0.94
Goldbohm et al. 1996 [47]	Netherlands (Black tea)	58,279 men 62,573 women 650 colorectal cancer cases (4.3 y)	Colorectal cancer: Non-significant	≥ 5 cups/d vs 0 cups/d: RR = 0.94 (0.66-1.34)

Table 2 (continued)

Reference	Country (tea)	Subjects/ Events (Follow up period)	Association	RR (95% CI)
Colorectal cancer (continued)				
Zheng et al. 1996 [36]	U.S. (Non-herbal tea)	35,369 postmenopausal women 350 colon cancer cases 124 rectal cancer cases (8 y)	Colon cancer: Non-significant Rectal cancer: Non-significant	Colon cancer ≥ 2 cups/d vs never/monthly: RR = 0.71 (0.45-1.11) Rectal cancer ≥ 2 cups/d vs never/monthly: RR = 0.70 (0.34-1.46)
Hartman et al. 1998 [68]	Finland (Black tea)	29,133 male smokers 111 colon cancer cases 83 rectal cancer cases (8 y)	Colon cancer: Positive Rectal cancer: Non-significant	Colon cancer < 1 cup/d vs 0 cups/d: RR = 1.40 (0.84-2.33) ≥ 1 cup/d vs 0 cups/d: RR = 2.09 (1.34-3.26) Rectal cancer ≥ 1 cup/d vs 0 cups/d: RR = 0.87 (0.47-1.60)
Pancreatic cancer				
Whittemore et al. 1983 [76]	U.S. (Black tea)	630 Harvard graduates 126 deaths (16-50 y)	Inverse	Tea drinkers vs non-drinkers: RR = 0.5 (0.3-0.9)
Heilbrun et al. 1986 [48]	U.S. Hawaii (Black tea)	7833 men 30 cases (20 y)	Non-significant	Age adjusted proportion of frequent black tea consumption (almost daily vs > daily): Lung cancer deaths: 17.4% Controls: 15.3% P (trend) = 0.75
Kinlen et al. 1988 [37]	UK (Black tea)	14,085 men 70 cancer deaths (19 y)	Non-significant	Observed deaths/expected 0-3 cups/day: 0.64 4-6 cups/day: 0.83 7-9 cups/day: 1.10 ≥ 10 cups/day: 0.90 P (trend) = 0.28
Hiatt et al. 1988 [77]	U.S. (Black tea)	11,504 men and women 36 cases (6 y)	Non-significant	Average daily tea consumption Cases: 0.32 cups/day Controls: 0.62 cups/day P = 0.10
Shibata et al. 1994 [75]	U.S. (Black tea)	13,979 men and women 65 cases (9 y)	Inverse	1 cup/d vs < 1 cup/d: RR = 0.65 (0.31-1.37) ≥ 2 cups/d vs < 1 cup/d: RR = 0.37 (0.12-1.19) P (trend) < 0.05

Table 2 (continued)

Reference	Country (tea)	Subjects/ Events (Follow up period)	Association	RR (95% CI)
Pancreatic cancer (continued)				
Harnack et al. 1997 [78]	U.S. (Non-herbal tea)	33,976 postmenopausal women 66 cases (9 y)	Non-significant	> 1 cup/wk vs 0 cups/wk: RR = 0.92 (0.52-1.63)
Michaud et al. 2001 [79]	U.S. (Black tea)	47,794 men 130 cases (12 y) 88,799 women 158 cases (16 y)	Non-significant for men, women, and pooled sample	Men > 1 cup/d vs none: RR = 1.17 (0.61-2.22) Women > 1 cup/d vs none: RR = 0.98 (0.60-1.60) Pooled > 1 cup/d vs none: RR = 1.04 (0.71-1.54)
Lung cancer				
Heilbrun et al. 1986 [48]	U.S. Hawaii (Black tea)	7833 men 151 deaths (20 y)	Non-significant	Age adjusted proportion of frequent black tea consumption (almost daily vs > daily): Lung cancer deaths: 14.3% Controls: 15.3% P = 0.74
Kinlen et al. 1988 [37]	UK (Black tea)	14,085 men 718 deaths (19 y)	Positive	Observed deaths/expected 0-3 cups/day: 0.61 4-6 cups/day: 0.80 7-9 cups/day: 1.13 ≥ 10 cups/day: 1.41 P (trend) = 0.0001
Goldbohm et al. 1996 [47]	Netherlands (Black tea)	58,279 men and 62,573 women 764 cases (4.3 y)	Non-significant	≥ 5 cups/d vs 0 cups/d: RR = 1.07 (0.73-1.57)
Zheng et al. 1996 [36]	U.S. (Non-herbal tea)	35,369 postmenopausal women 312 cases (8 y)	Non-significant	≥ 2 cups/d vs never/monthly: RR = 1.05 (0.71-1.55)
Knekt et al. 1997 [90]	Finland (Flavonoids)	9959 men and women 151 cases (143 men, 8 women) (20 y)	Inverse (Tea was not a significant source of flavonoids)	Quartiles of flavonoid intake 1 (lowest); RR = 1.0 2: RR = 0.76 (0.50-1.16) 3: RR = 0.50 (0.29-0.85) 4 (highest): RR = 0.53 (0.29-0.97)

Table 2 (continued)

Reference	Country (tea)	Subjects/ Events (Follow up period)	Association	RR (95% CI)
Lung cancer (continued)				
Arts et al. 2001 [91]	Netherlands (Catechins)	728 elderly men 42 lung cancer cases (10 y)	Non-significant for catechins and catechins from tea	Tertile of total catechin intake Low: RR = 1.0 Medium: RR = 0.72 (0.33-1.56) High: RR = 0.92 (0.41-2.07)
Bladder cancer				
Heilbrun et al. 1986 [48]	U.S. Hawaii (Black tea)	7,833 men 57 deaths (20 y)	Non-significant	Age adjusted proportion of frequent black tea consumption (almost daily vs > daily): Bladder cancer deaths: 10.7% Controls: 15.3%
Kinlen et al. 1988 [87]	UK (Black tea)	14,085 men 188 deaths (19 y)	Non-significant	Observed deaths/expected 0-3 cups/d: 1.02 4-6 cups/d: 0.67 7-9 cups/d: 1.22 ≥ 10 cups/d: 1.41 P (trend) = 0.13
Zheng et al. 1996 [36]	U.S. (Non-herbal tea)	35,369 postmenopausal women 43 cases (8 y)	Non-significant	≥ 2 cups/d vs never/monthly: RR = 0.33 (0.08-1.35)
Michaud et al. 1999 [99]	U.S. (Black tea)	47,909 men 252 cases (10 y)	Non-significant P (trend) = 0.08	≥ 2 cups/d vs < 1 cup/mo: RR = 0.69 (0.40-1.19)
Nagano et al. 2000 [100]	Japan (Green tea and Black tea)	38,450 atomic bomb survivors 114 cases (12-14 y)	Green tea: Non-significant Black tea: Non-significant	Green tea 5+ cups/d vs 0-1 cup/d: RR = 1.07 (0.58-2.08) Black tea 2+ cups/wk vs 0 cups/wk: RR = 0.81 (0.43-1.44)

Table 2. Prospective cohort studies of tea consumption and cancer risk (continued)

Reference	Country (tea)	Subjects/ Events (Follow up period)	Association	RR (95% CI)
Bladder cancer (continued)				
Zeegers et al. 2001 [101]	Netherlands (Black tea)	3123 men and women 569 cases (6 y)	Inverse	No tea vs 2-< 3 cups/d: RR = 1.30 (0.96-1.78) < 2 cups/d vs 2-<3 cups/d: RR = 0.95 (0.67-1.34) 3-< 4 cups/d vs 2-<3 cups/d: RR = 0.81 (0.58-1.13) 4-< 5 cups/d vs 2-<3 cups/d: RR = 0.81 (0.59-1.12) ≥ 5 cups/d vs 2-<3cups/d: RR = 0.93 (0.66-1.30) P (trend) <0.01
Prostate cancer				
Heilbrun et al. 1986 [48]	U.S./Hawaii (Black tea)	7833 men 149 deaths (20 y)	Inverse	Age adjusted proportion of frequent black tea consumption (almost daily vs > daily): Prostate cancer: 10.8% Controls: 15.3%
Kinlen et al. 1988 [37]	UK (Black tea)	14,085 men 185 cases (19 y)	Non-significant	Observed deaths/expected Almost never: RR = 1.0 < 2 times/wk: RR = 0.8 2-4 times/wk: RR = 0.4 > 4 times/wk: RR = 0.6 P (trend) = 0.02
Ellison et al. 2000 [122]	Canada (Black tea)	3400 men 145 cases (20 y)	Non-significant	0-3 cups/d: 0.60 4-6 cups/d: 0.81 7-9 cups/d: 1.00 ≥ 10 cups/d: 0.82 P (trend) = 0.3
Breast cancer				
Goldbohm et al. 1996 [47]	Netherland (Black tea)	62,573 women 507 cases (4.3 y)	Non-significant	>750 ml/d vs 0 ml/d: RR = 1.13 (0.72-1.76)
Zheng et al. 1996 [36]	U.S. (Black tea)	35,369 postmenopausal women 1,015 cases (8 y)	Non-significant P (trend) = 0.28	4 cups/d vs non-drinker: RR = 1.31 (0.86-1.99) ≥ 2 cups/d vs never/monthly: R = 1.14 (0.92-1.41)

have esophageal cancer than women who did not drink tea.[44] The same study did not observe a significant relationship between green tea consumption and esophageal cancer risk in men. In South America, men and women who consumed more than 500 ml/day of tea were 38% less likely to have esophageal cancer than those who did not drink tea.[45] Although consumption of tea at very high temperatures may increase the risk of esophageal cancer, most studies do not find an association between the consumption of tea that is not scalding hot and esophageal cancer when analyses are adjusted for other risk factors.

3. Gastric Cancer

Four out of five cohort studies did not observe a significant association between tea consumption and gastric cancer risk (Table 2).[46-49] One cohort study conducted in the U.K. found a positive association between black tea consumption and gastric cancer risk.[37] However, it did not adjust for smoking, a gastric cancer risk factor known to be prevalent in heavy tea drinkers in the U.K. Two of the cohort studies, one in Hawaii[46] and one in Japan,[49] evaluated green tea consumption, but neither observed a significant association with gastric cancer risk. Out of 18 case control studies, 7 found significant inverse associations between tea consumption and gastric cancer,[50-56] while 11 found no significant associations.[57-67] Of those case control studies that found inverse relationships between tea and gastric cancer risk, four observed them in green tea drinkers,[50-53] while three observed them in black tea drinkers.[54-56]

4. Colorectal Cancer

Out of five cohort studies that examined the relationship between black tea consumption and the risk of colorectal cancer (Table 2), one found a positive association with colon cancer risk,[68] another found a positive association with rectal cancer risk,[48] while three did not observe significant associations between black tea consumption and the risk of colon and/or rectal cancer.[36,37,47] No cohort studies examining the relationship between green tea consumption and colorectal cancer risk were identified. Out of nine case control studies,[57,58,67,69-74] three found positive associations between black tea consumption and colon cancer risk,[67,69,73] while one found an inverse association between black tea consumption and rectal cancer risk.[71] Of the four case control studies that examined green tea consumption, one found green tea consumption to be inversely related to colon cancer risk,[69] while another found green tea consumption to be inversely related to rectal cancer risk.[72]

5. Pancreatic Cancer

Out of seven cohort studies that examined only black tea consumption, two found a significant inverse association between tea consumption and pancreatic cancer risk,[75,76] while five found no significant association (Table 2).[37,48,77-79] Among the cohort studies that did not observe a significant association between black tea consumption and pancreatic cancer was a pooled analysis of data from two very large studies in the U.S., the Health Professionals Follow-up Study and the Nurses Health Study.[79] Results from case control studies are mixed. Although 7 out of 12 case control studies did not observe significant associations between black tea consumption and the risk of pancreatic cancer,[62,80-85] three case control studies found a positive association,[86-88] while one found an inverse association.[89] Of the case control studies that examined green tea consumption, two found an inverse association with pancreatic cancer risk,[72,86] while one found a positive association.[84] At least two of the case control studies that found positive associations between tea and pancreatic cancer did not adjust for other risk factors, such as smoking.[87,88]

6. Lung Cancer

Three out of four cohort studies found no significant relationship between black tea consumption and lung cancer risk (Table 2).[36,47,48] One cohort study conducted in the U.K. observed a positive association between tea consumption

and lung cancer, but these results are likely to be related to a positive association between cigarette smoking and heavy tea consumption.[37] Flavonoid intake in a Finnish cohort was inversely related to lung cancer risk, but tea consumption was so low in this population that it was not even recorded.[90] Catechin intake, 87% of which came from black tea, was not significantly associated with lung cancer risk in a cohort of Dutch men.[91] None of the cohort studies examined green tea consumption. Three out of four case control studies found no significant associations between black tea consumption and lung cancer risk,[92-94] while two out of three found no significant association between green tea consumption and lung cancer risk.[92,95] One study in Hong Kong found a positive association between green tea consumption and lung cancer risk in women,[94] but this finding did not persist when smokers were eliminated from the sample.[96] The consumption of Okinawan tea, a partially fermented tea, was inversely related to lung cancer risk in Okinawan women, but not Okinawan men,[97] while increased consumption of black tea in Uruguay was inversely associated with lung cancer risk in men and women.[98]

7. Bladder Cancer

Five out of six cohort studies did not observe a significant association between bladder cancer and tea consumption (Table 2).[36,37,48,99,100] Only one of those studies followed green tea drinkers.[100] Recently, an inverse association between black tea consumption and bladder cancer risk in men and women was observed after 6 years of follow up in the Netherlands Cohort Study.[101] Fifteen out of 20 case control studies found no significant association between tea consumption and bladder cancer risk.[102-116] Three case control studies identified a positive association between black tea consumption and bladder cancer risk,[117-119] while another small case control study found a positive association between oolong tea consumption and bladder cancer risk in Taiwan.[120] One case control study in France found an inverse association between black tea consumption and bladder cancer in women who smoked cigarettes, but not in nonsmoking women or men.[112] A recent meta-analysis, including 20 studies that evaluated tea consumption and urinary tract cancer risk, calculated a summary odds ratio of 1.01 (95% confidence interval: 0.92 to 1.10) for tea drinkers compared with nondrinkers.[121] While the majority of studies evaluated only black tea consumption, the single cohort study and the two case control studies that evaluated green tea consumption did not find significant associations between green tea consumption and bladder cancer risk.[100,107,115]

8. Prostate Cancer

A cohort study of Hawaiian men of Japanese descent found a significant inverse association between black tea consumption and prostate cancer risk (Table 2).[48] However, two other cohort studies found no significant association between black tea consumption and prostate cancer risk.[37,122] Similarly, one out of three case control studies demonstrated an inverse association between black tea consumption and prostate cancer risk,[123] while the other two found no significant associations.[62,124] Epidemiologic studies on green tea consumption and prostate cancer risk are lacking.

9. Breast Cancer

Two published cohort studies did not find a significant association between black tea intake and breast cancer risk (Table 2).[36,47] An inverse association between black tea consumption and breast cancer risk in the Nurses Health Study was reported in an abstract in 1992,[125] but the full report has not been published. One out of five case control studies found an inverse association between black tea consumption and breast cancer risk,[22] while the other four studies did not find significant associations.[126-129] Recently, a case control study of breast cancer in men observed a positive association with tea consumption, although the authors concluded that dietary factors were unlikely to be strong determinants of breast cancer risk in men.[130] Studies on green tea and breast cancer incidence are lacking. However,

two recent studies in Japanese women diagnosed with breast cancer have observed increased green tea consumption to be inversely associated with breast cancer recurrence, especially in the early stages of breast cancer.[131,132]

10. Tea Consumption and Cancer Risk: Summary

Overall, the epidemiologic studies on tea consumption and cancer to date do not provide support for the idea that increased tea consumption is protective against cancer. There is some evidence that green tea at high levels of intake may provide some benefit in preventing cancers of the digestive tract, especially gastric cancer. Green tea contains more catechins, especially EGCG, which has been found to inhibit carcinogenesis of the skin, lung, esophagus, stomach, liver, small intestine, colon, bladder, prostate, and mammary glands in animal models.[133] Most of the epidemiologic studies reviewed were not designed specifically to assess the effect of tea consumption on cancer risk. Future studies should be designed with the goal of examining green and black tea consumption in more detail. For example, a recent population-based case control study found a significant inverse relationship between tea consumption frequency and the risk of squamous cell carcinoma of the skin only after adjusting for brewing time.[134]

C. Epidemiologic Studies of Tea Consumption and Other Health Conditions

1. Neurodegenerative Diseases

Although oxidative stress is thought to play a role in the pathology of neurodegenerative diseases, few epidemiologic studies have examined the association of tea consumption with the incidence of neurodegenerative diseases. A case control study of 215 Parkinson's disease patients and 312 population controls in Taiwan found a regular tea drinking habit to be protective against the disease,[135] while a study of 140 Parkinson's disease patients and 240 hospital controls in France found tea consumption to increase the risk of Parkinson's disease by 90%.[136] An earlier population-based case control study in Spain did not find a significant association between tea drinking and Parkinson's disease risk.[137] Two cohort studies have examined the relationship between flavonoid intake and the risk of dementia. No significant relationship between flavonoid consumption and cognitive decline was observed in elderly Dutch men, in which black tea provided 61% of flavonoid intake.[138] However, flavonoid intake was inversely related to the risk of dementia in a French cohort, in which tea provided only 16% of the total flavonoid intake.[139]

2. Osteoporosis

A cross-sectional study of 1276 older women (65 to 76 years) in the U.K. found that tea drinkers had significantly higher bone mineral density (BMD) at the lumbar spine and hip than nondrinkers.[139b] These findings were independent of other factors known to affect BMD (e.g., smoking and hormone replacement therapy), and whether milk was added to the tea. However, an earlier study designed to examine the effect of caffeine on BMD found tea consumption to be associated with slightly decreased BMD in 281 perimenopausal women (50 to 60 years).[140] Two large case control studies in Mediterranean countries found low tea consumption to be significantly and independently associated with an increased risk of hip fractures in men and women over 50 years of age.[141,142] In the prospective Nurses' Health Study, tea consumption was inversely related to the risk of hip fractures over a 6-year period, but the relationship was not statistically significant.[143] The mechanisms for a beneficial effect of tea consumption on bone mineral density are not clear. Although tea is a relatively good source of fluoride, an element known to increase bone density in pharmacologic doses, there is little evidence that the amount of fluoride supplied by tea would significantly affect BMD.[144] The oxidative stress-responsive transcription factor, NF-κB has been found recently to play a role in bone resorption, and increased levels of urinary 8-iso-$PGF_{2\alpha}$, a biomarker for oxidative stress, were significantly associated with decreased lumbar spine

and total body BMD in a cross-sectional study of 101 men and women.[145] Tea polyphenols could potentially inhibit bone resorption by decreasing oxidative stress or inhibiting NF-κB activation (Section V).

3. Dental Caries

Fluoride concentrations in tea are comparable to those recommended for U.S. water supplies in order to prevent dental caries,[146] and green, black, and oolong tea extracts have been found to inhibit bacterial growth and cariogenic activity.[147,148] Although tea extracts have been found to prevent or decrease dental caries in animal models, relatively few published studies have examined the effect of tea consumption on dental caries in humans. A cross-sectional study of 6014 14-year-old children in the U.K. found that those who drank tea had significantly fewer dental caries than nondrinkers, regardless of whether they added sugar to their tea.[149]

4. Kidney Stones

Two large prospective studies found tea consumption to be significantly inversely associated with the risk of kidney stones, which decreased by 8% in women[150] and 14% in men[151] for each 240 ml (8 oz) cup of tea consumed daily. The implications of these findings for individuals with a previous history of calcium oxalate stone formation are unclear. High fluid intake, including tea intake, is generally considered the most effective and economical means of preventing kidney stones.[152] However, tea consumption has been found to increase urinary oxalate levels in healthy individuals,[153] and some experts continue to advise calcium oxalate stone formers to limit tea consumption.[154]

III. TEA CATECHINS AND POLYPHENOLS

Many of the biologic activities of tea appear to be related to its flavonoid content. Catechins, which are flavanols, are the major group of flavonoids found in tea.[155] The principal catechins in fresh tea (*Camellia sinensis*) leaves are (–)-epicatechin (EC), (–)-epigallocatechin (EGC), (–)-epicatechin gallate (ECG), and (–)-epigallocatechin gallate (EGCG) (Figure 1). EC has an *ortho*-dihydroxyl group in the B-ring at carbons 3' and 4' and a hydroxyl group at carbon 3 on the C ring (Figure 1). EGC differs from EC in that it has a trihydroxyl group at carbons 3', 4', and 5' on the B ring. ECG differs from EC in that it has a gallate moiety esterified at carbon 3 of the C ring, while EGCG has both a trihydroxyl group at carbons 3', 4', and 5' on the B ring and a gallate moiety esterified at carbon 3 on the C ring. EGCG is the most abundant catechin in tea leaves and in most green, oolong, and black teas.[1] Green and oolong teas typically contain 30 to 130 mg of EGCG per cup (237 ml), while black teas may contain 0 to 70 mg of EGCG per cup.[155]

The type of processing applied to the fresh tea leaves determines the types and amounts of flavonoids present in green, oolong, and black teas. Polyphenol oxidase enzymes and catechins exist in separate layers of the tea leaf. The rolling process disrupts the leaf, allowing enzymatic oxidation of catechins to occur. To produce black tea, the fresh leaves are withered and then rolled to allow for oxidation of catechins, resulting in the formation of dimers and polymers, such as theaflavins and thearubigins (Figure 2). Thearubigins are a heterogeneous group of compounds that may comprise more than 70% of the total flavonoids in black tea, while theaflavins comprise close to 10% of total flavonoids.[156] During the production of oolong tea, the oxidation period is shortened, resulting in a tea that is only partially oxidized, containing more catechins and fewer theaflavins and thearubigins than black tea. In order to preserve its catechins, green tea is typically steamed or pan-fired to inactivate polyphenol oxidase. Consequently, 60 to 80% of the total flavonoids in green tea are catechin monomers (Figure 3). Because some oxidation occurs during the withering process, 20 to 30% of total flavonoids in green tea may be oxidized catechin polymers such as those found in black and oolong teas.[1,157]

Glycosides of the flavonols, quercetin, kaempferol, and myricetin, are also present in tea.

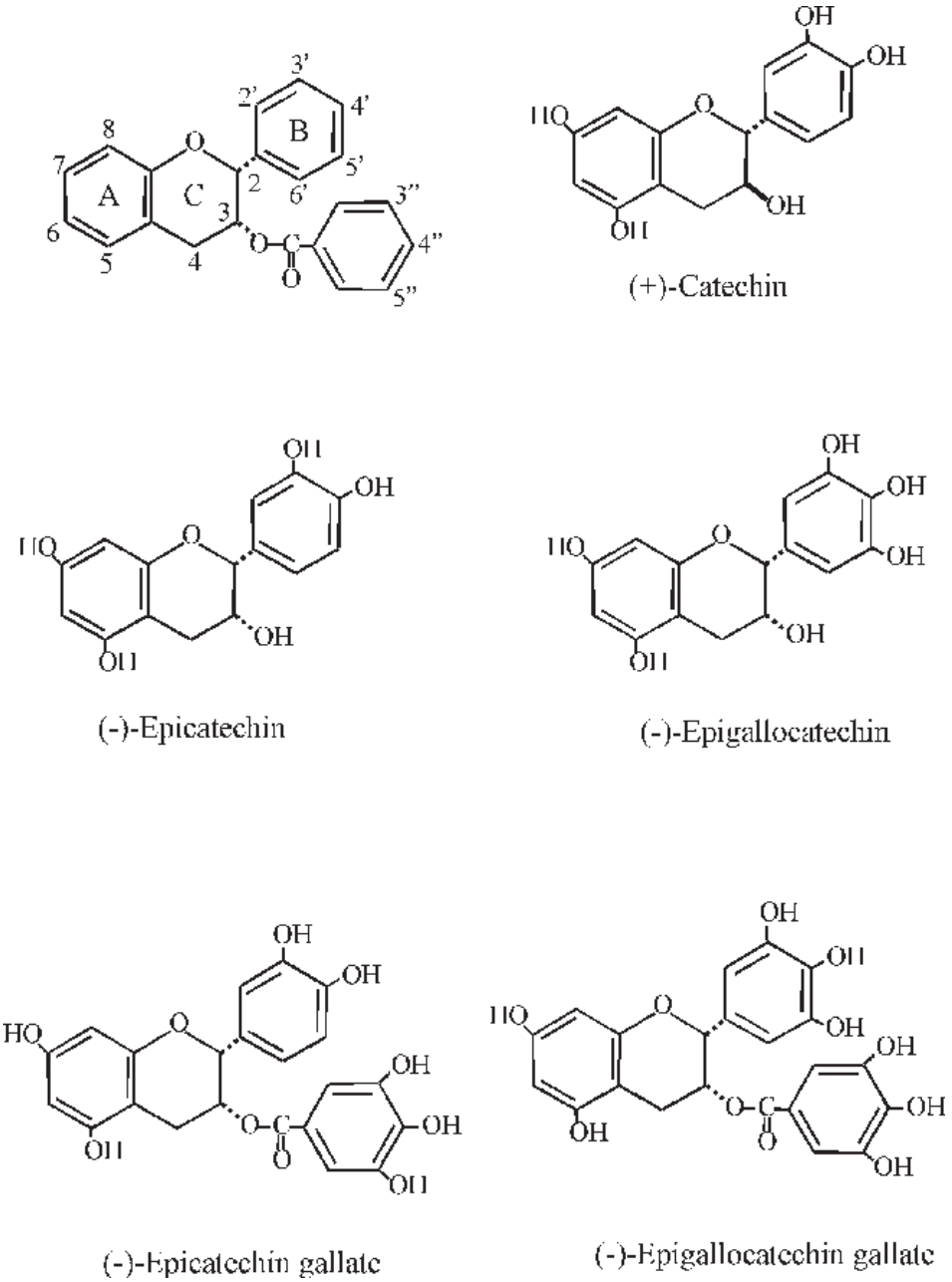


FIGURE 1. Structure and nomenclature of the principal catechins found in tea.

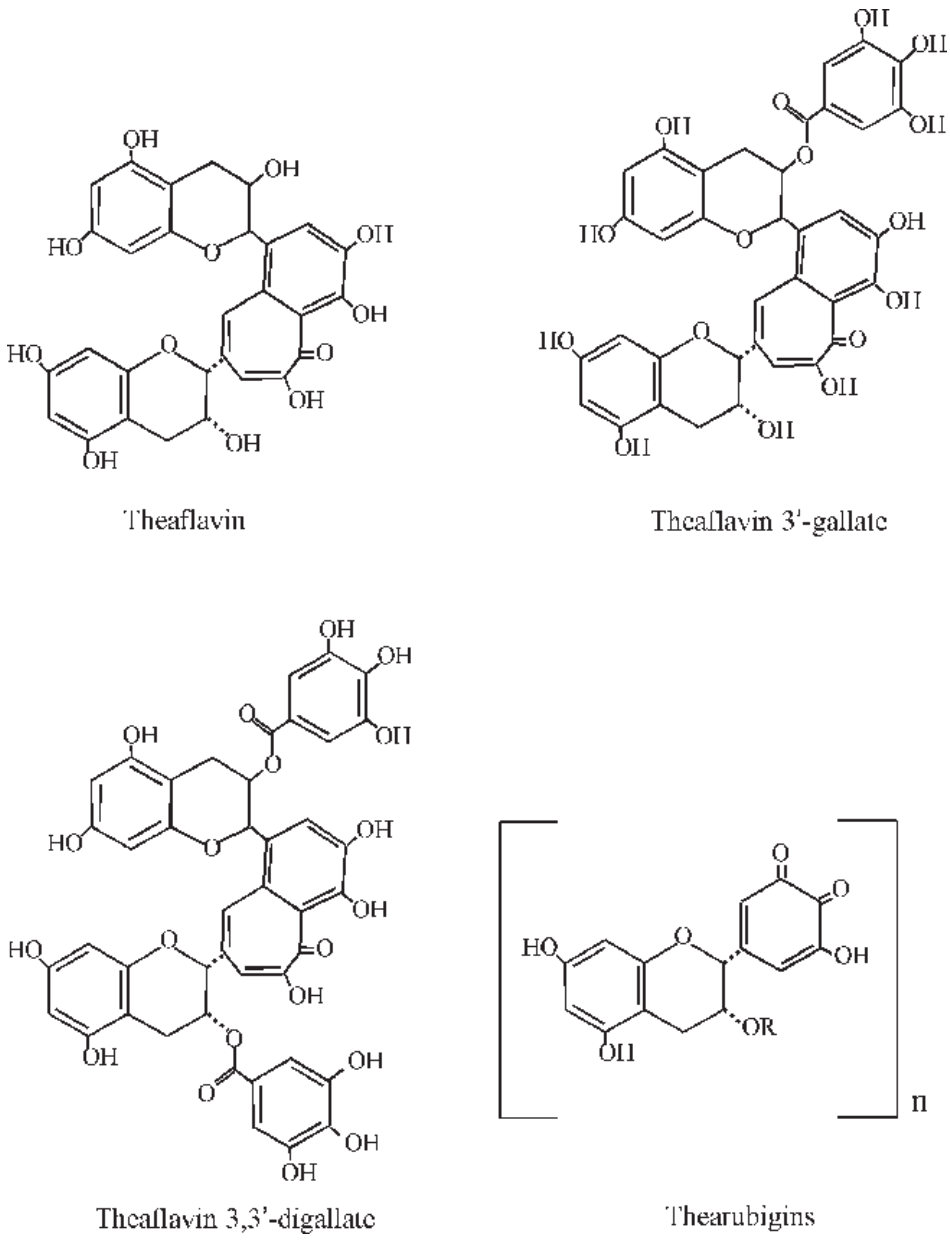
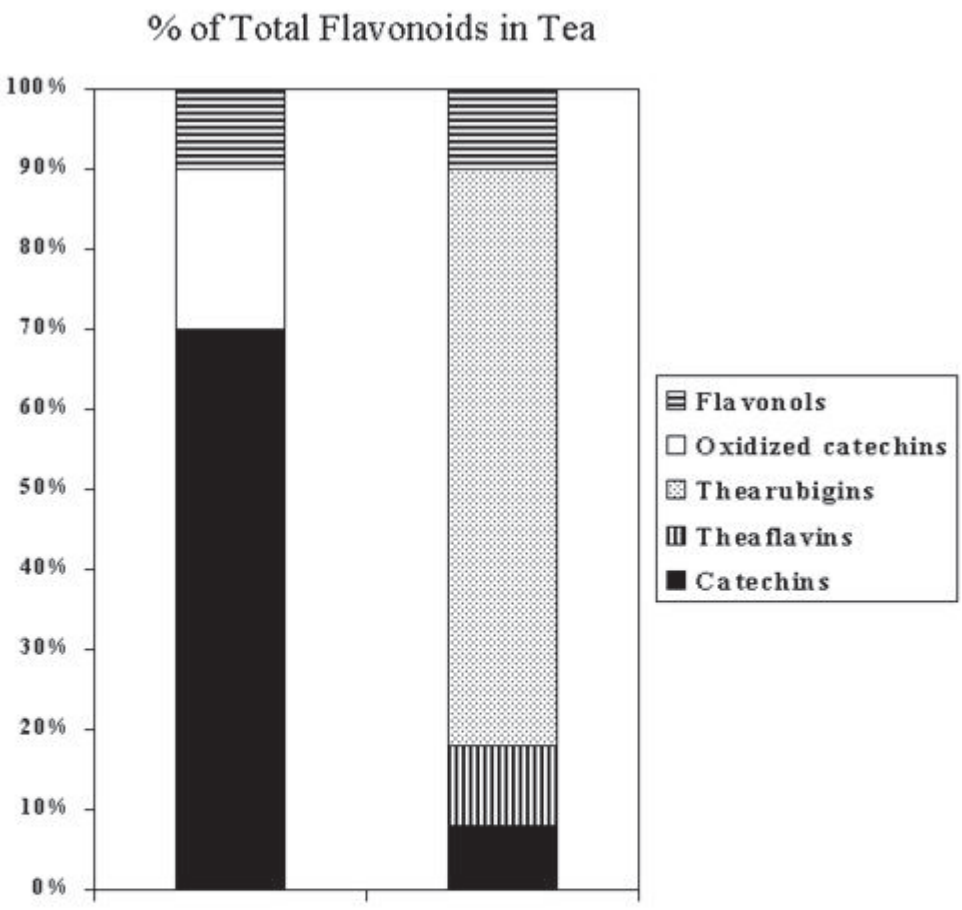


FIGURE 2. The theaflavins and thearubigins.



Flavonols	7-9%	7-9%
Oxidized catechins	20-30%	
Thearubigins		63-74%
Theaflavins		5-12%
Catechins	60-80%	6-24%

FIGURE 3. Flavonoid content of green and black tea

Flavonol content is less affected by processing, and flavonols are present in comparable quantities in green, oolong, and black teas.[155]

IV. METABOLISM AND BIOAVAILABILITY

A. Absorption and Relative Bioavailability of Catechins

Following oral administration of tea catechins to rats, the four principal catechins (EC, ECG, EGC, and EGCG) have been identified in the portal vein, indicating that tea catechins are absorbed intestinally.[158] In rats given 0.6% green tea polyphenols (GTP) in their drinking water over a period of 28 days, plasma concentrations of EGCG were much lower than those of EGC or EC, even though the ratio of EGCG to EGC was 5:1 in the GTP solution. Plasma catechin levels reached their peak values on day 14 but declined to day 1 levels by day 28. When the same GTP preparation was given to mice, plasma levels of EGCG were much higher than those of EGC and EC, suggesting species differences in the bioavailability of EGCG. Plasma catechin levels in mice peaked on day 4 and then decreased to day 1 levels, indicating an adaptive response of plasma catechin levels to catechin ingestion over time in mice and rats.[159]

Catechin levels in human plasma reach their peak 2 to 4 h after ingestion.[160-162] After a single dose of green tea or green tea extract, the highest concentrations of individual catechins measured in human plasma were slightly greater than 1 μ*M*.[160] A recent study in humans compared the pharmacokinetics of equimolar doses of pure EGC, ECG, and EGCG in 10 healthy volunteers.[163] Average peak plasma concentrations (conjugated plus unconjugated) after a single dose of 1.5 mmol were 5.0 μmol/l for EGC, 3.1 μmol/l for ECG, and 1.3 μmol/l for EGCG. After 24 h, plasma EGC and EGCG returned to baseline, but plasma ECG remained elevated. Another study found peak plasma levels to average 0.96 μmol/l after a single dose of 1.75 mmol (800 mg) of EGCG compared with 0.82 μmol/l after a single dose of a green tea catechin mixture containing the same amount of EGCG.[162] In humans, ECG has been found to be more highly methylated than EGC and EGCG,[163] and EGCG has been found to be less conjugated than EGC and EC.[162] In summary, there appear to be species differences in the bioavailability of EGCG relative to other tea catechins. In humans, EGCG may be less bioavailable than other tea catechins, but the metabolism of individual tea catechins and the pharmacokinetics of their metabolites require further clarification.

B. Tissue Distribution

When rats were given 0.6% GTP in their drinking water over a period of 28 days, substantial amounts of EGC and EC were found in the esophagus, large intestine, kidney, bladder, lung, and prostate. EGC and EC concentrations were relatively low in liver, spleen, heart, and thyroid.[159] EGCG levels were higher in the esophagus and large intestine, but lower in other organs, likely due to poor systemic absorption of EGCG. Unlike rats, mice given 0.6% GTP in their drinking water for 28 days had higher lung concentrations of EGCG than EGC and comparable liver concentrations of EGCG and EGC, suggesting relatively higher bioavailability of EGCG in mice than rats. Little published data are available on tissue distribution of catechins in humans after tea consumption. Citing unpublished data, Yang et al. reported that substantial amounts of catechins were detected in colon mucosa and prostate surgical samples from patients who consumed tea 12 h prior to surgery.[133]

C. Elimination

Studies in rats indicate that EGCG is mainly excreted through the bile, while EGC and EC are excreted through urine and bile,[164] which is consistent with the observation that EGC and EC, but not EGCG are recovered from human urine samples.[165] However, EGCG may be metabolized into simpler compounds by colonic bacteria, absorbed, and ultimately excreted in the urine.[166,167]

D. Metabolism

Catechins are rapidly and extensively metabolized. A study that examined salivary levels of tea catechins in humans found that holding an

EGCG solution in the mouth resulted in EGCG and EGC in the saliva and EGC in the urine.[168] Additionally, saliva was found to have catechin esterase activity, suggesting that EGCG may be degalloylated in the mouth and esophagus. Although phase I transformation reactions for catechins have not been well defined, phase II reactions, including glucuronidation, sulfation, and *O*-methylation, have been reported in rodents and humans after oral, i.v., and i.p. administration.[169] Enzymes involved in polyphenol metabolism include catechol-*O*-methyltransferase (COMT), UDP-glucuronosyltransferases (UGT), and phenolsulfotransferases (SULT) (Figure 4).

A study of the activity of conjugative enzymes in rat tissues found the highest UGT activity in the mucosa of the small and large intestine, the highest PST activity in the liver, and the highest COMT activity in the liver and kidney.[170] Based on serial measurements of rat plasma levels of EC and its methylated, sulfated, and glucuronidated metabolites after an oral dose of 10 mg of EC, Piskula and Terao proposed that catechins were glucuronidated extensively in the intestinal mucosa, sulfated in the liver and methylated in the liver and kidney. However, COMT activity has also been reported in the jejunum, and a recent study of isolated segments of rat small intestine found that (+)-catechin and EC were extensively glucuronidated and *O*-methylated in the jejunum during transfer from the lumen to the serosal surface.[171] While the major metabolites detected were glucuronidated, *O*-methylated metabolites and an *O*-methylated glucuronide were also detected in the serosal fluid. In contrast, the majority of the catechin and EC that appeared on the serosal side of isolated ileum segments were unmetabolized. *O*-Methylated and both *O*-methylated and glucuronidated catechin metabolites have been observed in human plasma.[172]

Higher doses of catechins may change the profile of conjugated metabolites by saturating specific metabolic pathways, such as intestinal glucuronidation and *O*-methylation. In a human

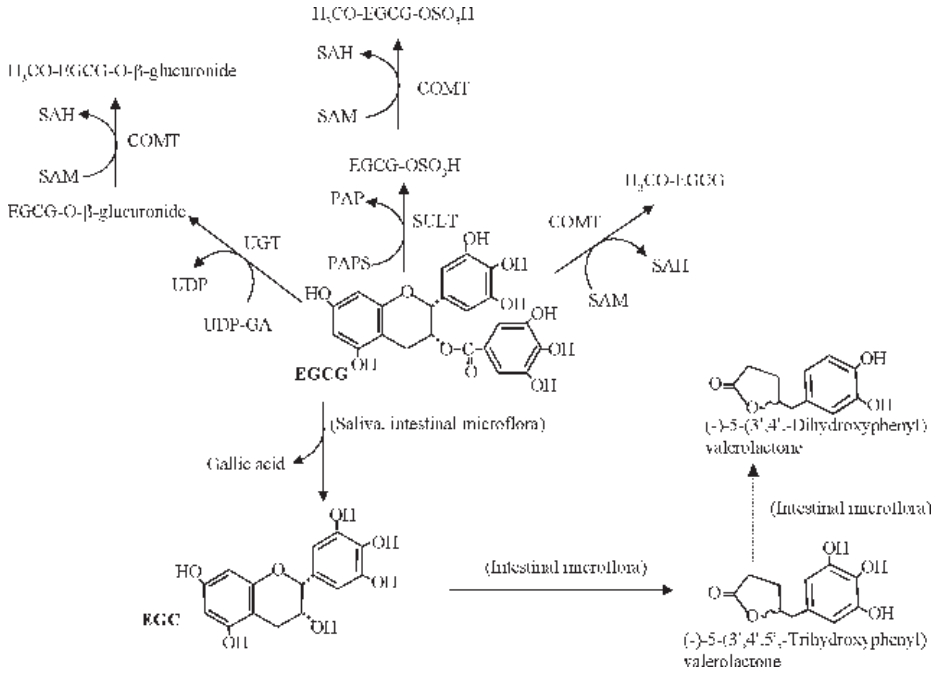


FIGURE 4. Potential biotransformation pathways for epigallocatechin gallate (EGCG) and its metabolites. Adapted from Yang et al.[133] Abbreviations: COMT; Catechol-*O*-methyl transferase, PAP; Adenosine 3',5'-bisphosphate, PAPS; 3'-Phosphoadenosine 5'-phosphosulfate, SAH; *S*-Adenosyl-*L*-homocysteine, SAM; *S*-Adenosyl-*L*-methionine, SULT; Sulfotransferase, UDP; Uridine diphosphate, UDP-GA; UDP-glucuronic acid, UGT; UDP-glucuronosyl transferase.

pharmacokinetic study of acute oral administration of 200, 400, 600, and 800 mg of EGCG, the AUC for unconjugated EGCG rose disproportionately at 800 mg, indicating saturation of the conjugation pathways.[162]

Catechins that are not absorbed in the small intestine, as well as conjugated catechins excreted in the bile, reach the large intestine where they may be metabolized by colonic bacteria and absorbed. In the colon, bacterial enzymes may deconjugate or break down catechins into more simple compounds. A study that compared the metabolic fate of orally administered EGCG in rats pretreated with antibiotics to suppress the metabolic activity of their intestinal bacteria to that of rats that were not treated with antibiotics indicated that a significant portion of ingested EGCG was metabolized by intestinal bacteria before being absorbed, distributed, and excreted.[166] Two catechin metabolites recently identified in human urine, (-)-5-(3', 4', 5'-trihydroxyphenyl)-γ-valerolactone and (-)-5-(3',4'-dihydroxyphenyl)-γ-valerolactone, are metabolites of EGC and EC, respectively, and are likely formed in the colon, absorbed, and excreted in the urine.[167]

E. Variability Among Individuals

A functional polymorphism resulting in a 3- to 4-fold difference in activity has been described for COMT, and glucuronidation may be modified by dietary, environmental, and behavioral factors (e.g., alcohol use and smoking).[173] Individual variations in the activity of these enzymes may explain the large interindividual variations found in pharmacokinetic studies that have measured plasma levels of unconjugated and conjugated catechins.[162]

F. Biological Activity of Catechin Metabolites

Evidence that catechins are metabolized extensively by the time they are distributed to tissues brings into question the relevance of much of the *in vitro* data on the biological activities of unconjugated catechins and raises questions regarding the biological activities of catechin metabolites. There is evidence that at least some catechin metabolites retain comparable antioxidant capacities to their parent compounds. Plasma obtained from rats 6 h after intragastric administration of 10 mg of EC was more resistant to oxidation by the radical generator, 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH), than that of control rats, despite the fact that only conjugated forms of EC were detected in this plasma.[174] Similarly, in humans who drank green tea containing approximately 400 mg of catechins, measures of free catechins in the plasma were found to account for only 20% of its increased total radical-trapping parameter (TRAP), suggesting that catechin conjugates and metabolites may have contributed to the measured TRAP increase.[175] In the TEAC assay, an assay designed to measure the capacity of antioxidants to scavenge the $ABTS^{\cdot+}$ radical cation [2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)], urinary catechin metabolites were found to have lower TEAC values than EGCG, but higher than vitamin E, suggesting they may contribute to increases in plasma antioxidant capacity measured after tea consumption in humans.[176]

The presence of an *ortho*-dihydroxyl group in the B-ring has been shown to be important to the radical scavenging abilities of tea catechins. The addition of a gallate moiety at the 3 position of the C-ring increases the radical scavenging effectiveness of catechins in a number of systems.[177] In rats, the major metabolites of EC and (+)-catechin identified in plasma after oral administration were (–)-epicatechin-5-*O*-β-glucuronide and (+)-catechin-5-*O*-β-glucuronide, respectively.[178] These glucuronide conjugates exhibited comparable superoxide scavenging abilities to the parent compounds as measured by electron spin resonance (ESR) spectrometry. Conjugation at the 5-*O*-position in the A ring did not disrupt the *ortho*-dihydroxyl group at the 3'- and 4'-positions on the B-ring. In contrast, the major metabolites recovered in bile, 3'-*O*-methyl-(-)-epicatechin-5-*O*-β-glucuronide and 3'-*O*-methyl-(+)-catechin-5-*O*-β-glucuronide, were methylated at the 3'-position on the B ring and, not surprisingly, had very low superoxide scavenging activity. Recently, six biliary metabolites of EGCG were isolated from rats. At least five out of the six metabolites iso-

lated are expected to exert similar antioxidative effects to unconjugated EGCG because of the presence of a trihydroxyl group or an *ortho*-dihydroxyl group in the B ring or the gallate moiety in the C ring.[179] Similarly, the structures of two catechin metabolites isolated from human urine, (-)-5-(3',4',5'-trihydroxyphenyl)-γ valerolactone and (-)-5-(3',4'-dihydroxyphenyl)-γ-valerolactone are predictive of antioxidant activity.[167]

A limited amount of evidence indicates that some catechin metabolites have different biological activities than their parent compounds. Koga and Meydani administered (+)-catechin to rats and extracted the catechin metabolites from their plasma.[180] An analysis of the plasma preparation showed it contained sulfate or glucuronide conjugates or both, as well as methylated forms. They found that pretreatment of human aortic endothelial cells with catechin metabolites inhibited monocyte adhesion to endothelial cells that were stimulated with the cytokine interleukin-1β (IL-1β), but pretreatment with unconjugated (+)-catechin had no effect. Generation of reactive oxygen species (ROS) in hydrogen peroxide (H_2O_2)-stimulated aortic endothelial cells was inhibited by unconjugated (+)-catechin and catechin metabolites, while generation of ROS in IL-1β-stimulated aortic endothelial cells was inhibited only by catechin metabolites.

A series of studies comparing the effects of EC metabolites on oxidative stress-induced cell death in fibroblasts and striatal neurons also indicates that the biological activities of EC metabolites differ from those of unconjugated EC. EC and 3'-*O*-methyl (–)-epicatechin were equally effective in protecting fibroblasts from H_2O_2-induced cell death[181] and striatal neurons from oxidized low-density lipoprotein (LDL)-induced apoptosis,[182] despite the fact that methylation at the 3' position on the B ring significantly diminished the antioxidant activity of 3'-*O*-methyl (-)-epicatechin as measured by the TEAC assay. Surprisingly, glucuronidated EC metabolites, (-)-epicatechin-7- and (-)-epicatechin-5-*O*-β-D-glucuronide, failed to protect fibroblasts and neurons from oxidative-stress induced cell death, despite the fact that the *ortho*-dihydroxyl group in the B-ring was intact.[183]

V. MECHANISMS FOR THE ANTIOXIDANT EFFECTS OF TEA AND TEA CATECHINS

A. Scavenging of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)

Tea catechins and polyphenols have been found to be efficient scavengers of free radicals in a number of *in vitro* systems.[184] The ability of a compound to act as a free radical scavenger is partly related to its one-electron reduction potential, a measure of reactivity of antioxidants as hydrogen or electron donors.[185] A lower reduction potential indicates that lower energy is required for hydrogen or electron donation and is one factor in determining antioxidant activity. EGCG and EGC have lower reduction potentials than vitamin E (Table 3), suggesting they are superior electron donors to vitamin E.[186] However, vitamin C has a significantly lower reduction potential (Table 3), indicating it is superior to all tea polyphenols measured.

In addition to hydrogen or electron donating activity, the effectiveness of an antioxidant is also determined by the rate of its reaction with free radicals in a given system (scavenging rate constant) and the stability of the resulting antioxidant radical. Based on a series of pulse radiolysis studies that compared the reactivities of a number of flavonoids with hydroxyl radicals (·OH), superoxide anions ($O_2^{\cdot -}$), and azide radicals ($\cdot N_3$), Bors and Michel[187] concluded that catechins were superior radical scavenging agents compared with monomeric flavonols and flavones. Based on these findings, they concluded that catechins, rather than flavonols and flavones, represented the antioxidative principle in red wine and tea.

The radical scavenging activities of tea catechins have been examined in a number of *in vitro* systems. Studies measuring radical scavenging activities of catechins using (ESR) spectrometry have found them to be efficient scavengers of singlet oxygen ($^1O_2$), $O_2^{\cdot -}$, ·OH, and peroxyl radicals (·OOH).[177,188,189] In the majority of the systems examined, EGCG was a more efficient radical scavenger than ECG, EGC, or EC, suggesting that the trihydroxyl group on the B ring and the

Table 3. Reduction potentials [186, 288, 289] and relative antioxidant activities of tea polyphenols [190] and other antioxidants [185].

Antioxidant	Reduction potential (V)[a]	Antioxidant activity (mM)[b]
(-)-Epicatechin	0.57	2.4 ± 0.02
(-)-Epigallocatechin	0.43	3.8 ± 0.06
(-)-Epicatechin gallate	0.55	4.9 ± 0.02
(-)-Epigallocatechin gallate	0.43	4.8 ± 0.06
Theaflavin	0.51	2.9 ± 0.08
Theaflavin digallate	0.54	6.2 ± 0.43
Green tea (1,000 ppm)	-	3.8 ± 0.03
Black tea (1,000 ppm)	-	3.5 ± 0.03
Vitamin E	0.48	1.0 ± 0.03
Vitamin C	0.28	1.0 ± 0.02

[a] Reduction potential at pH 7, 20° C.
[b] TEAC (Trolox equivalent antioxidant activity)

gallate moiety at the 3 position in the C ring (Figure 1) increase the antioxidant activity of catechins in a number of systems.

Stable radicals such as the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and the $ATBS^{\cdot+}$ radical cation have also been used to evaluate the antioxidant activities of flavonoids *in vitro*. Using the TEAC assay, catechins and theaflavins were found to be more effective in reducing the $ATBS^{\cdot+}$ radical cation than vitamin E and vitamin C on a molar basis.[190] Relative antioxidant activities among the catechins determined by the TEAC assay has been found to be EGCG ≈ ECG > EGC > EC (Table 3). Catechins have also been found to be more efficient scavengers of the DPPH radical than vitamin E or vitamin C.[191] Relative activities of catechins in scavenging DPPH radicals have been found to be EGCG ≈ ECG > EGC > EC.[177,188]

Overproduction of nitric oxide (·NO) and peroxynitrite ($ONOO^-$), the product of a rapid reaction between $O_2^{\cdot-}$ and ·NO, has been associated with chronic inflammation and may be associated with the etiology and pathology of a number of chronic diseases. Flavonoids, including catechins, have been found to efficiently scavenge ·NO *in vitro*.[192] Green tea and black tea have been found to scavenge ·NO *in vitro*, although green tea was about five times more potent than black tea.[193] Inhibition of the nitration of tyrosine has been investigated as a measure of $ONOO^-$ scavenging activity of flavonoids. In this assay, tea catechins were found to be more effective than the water-soluble vitamin E analog Trolox.[194] EGCG, ECG, and gallic acid were equally effective in inhibiting tyrosine nitration and more effective than EGC and EC, suggesting that the gallate moiety was an important structure for interaction with $ONOO^-$. Additionally, EGCG was found to inhibit the $ONOO^-$ -mediated formation of 8-OHdG in calf thymus DNA more potently than vitamin C or glutathione.[195]

The exact mechanisms for the radical scavenging activity of catechins are not known, but several structures appear to be important in conferring this activity. All catechins have at least an *ortho*-dihydroxyl group (*o*-3'4'-OH) in the B ring, which participates in electron delocalization and stabilizes the radical form [196]. The gallocatechins (EGC and EGCG) have a trihydroxyl group in the B ring (3'4'5'-OH), while the catechin gallates (ECG and EGCG) have a gallate moiety esterified at the 3 position in the C ring, adding three more hydroxyl groups. Both the presence of the 3'4'5'-OH

group and the gallate moiety have been associated with increased antioxidant activity.[177] Recent studies examining oxidation products of gallocatechins with peroxyl radicals indicate that the 3'4'5'-OH group in the B ring is the principal site of antioxidant reaction in EGC and EGCG.[197,198] Additionally, a study of the oxidation products of gallocatechins with H_2O_2 indicated that the A ring may also be an antioxidant site for EGC and EGCG.[199]

The oxidizing environment should also be taken into consideration when evaluating the antioxidant activity of catechins. Although the tea catechins are all water soluble, they have been found effective in inhibiting *in vitro* lipid peroxidation in liposomes[200] and LDL,[201] with the exception of EGC. The partition coefficient of EGC, as measured in octanol/water mixtures, is 0.12 compared with 1.2, 1.14, and 11.8 for EC, EGCG, and ECG, respectively, suggesting that the lower efficacy of EGC in inhibiting lipid peroxidation may be related to its higher solubility in the aqueous phase than other catechins.[184]

B. Metal Chelation

The ability of flavonoids in general, and catechins in particular, to chelate metal ions, such as iron and copper, may contribute to their antioxidant activity by inhibiting transition metal-catalyzed free radical formation.[190] A likely metal binding site for catechins is the *o*-3'4'-OH group on the B ring.[202] However, the results of a recent study examining the effects of pH and metal ions on the antioxidant activities of catechins suggested that the gallate moiety of the gallocatechins also binds metals.[203] The same study found that binding Cu^{2+} increased the antioxidant activity of EGCG during 2,2'-azobis(2,4-dimethylvaleronitrile) (AMVN)-initiated lipid peroxidation, while binding Fe^{2+} inhibited its antioxidant activity. The ability of catechins to inhibit copper-mediated LDL oxidation and other metal-catalyzed oxidations *in vitro* is likely related to their ability to chelate metals, as well as their radical scavenging activities.[204] However, it is not clear whether metal chelation is a physiologically relevant antioxidant activity, because most transition metal ions are bound to proteins *in vivo* where they cannot participate in metal-catalyzed free radical formation.

C. Inhibition of Transcription Factor Activation

1. Nuclear Factor-κB (NF-κB)

NF-κB is a transcription factor, that is, a complex of proteins that binds to DNA and activates gene transcription. In unstimulated cells, NF-κB is present in the cytoplasm bound to an inhibitory protein called IκB. A wide variety of stimuli, for example, ultraviolet (UV) light, inflammatory cytokines, and endotoxins, may result in the phosphorylation of IκB by IκB kinase, which results in the ubiquitination and degradation of IκB by the proteosome complex. Released NF-κB is able to translocate to the nucleus where it binds DNA and activates the transcription of multiple inflammatory and other genes. Many of the stimuli that activate NF-κB also induce oxidative stress, and there is some evidence that NF-κB activation is stimulated by ROS and inhibited by antioxidants.[185] Both green tea catechins and black tea theaflavins have been found to inhibit the activation of NF-κB in cultured cell lines. In activated macrophages and epidermal cells treated with the tumor promoter, 12-*O*-tetradecanoylphorbol-13 acetate (TPA), EGCG and black tea theaflavins were found to inhibit phosphorylation of IκB, preventing NF-κB from translocating to the nucleus and binding to DNA. [205,206] In cultured intestinal epithelial cells, EGCG was found to be the most potent inhibitor of IκB kinase activity among green tea catechins, with an IC_{50} (concentration required for 50% inhibition) of approximately 18 μ*M*.[207] Recently, EGCG treatment (1 to 10 μ*M*) was found to inhibit proteosome activity of cultured tumor cells, resulting in increased cytosolic accumulation of the IκB-α subunit, which would be expected to decrease NF-κB activation.[208]

2. Activator Protein-1 (AP-1)

AP-1 is another transcription factor that is affected by the intracellular redox environment and can be affected by both ROS and certain antioxidants.[185] AP-1 exists as a family of jun/fos dimers that include different jun proteins (c-jun,

junB, and junD) and fos proteins (c-fos, fosB, fra-1, fra-2, and fosB2). AP-1 activation occurs through three mitogen-activated protein kinase (MAPK) pathways, including extracellular signal-related protein kinases (Erk1 and Erk2), c-jun NH_2-terminal kinases (JNK1 and JNK2), and p38 kinases.[209] AP-1 activation is of interest to cancer researchers because high AP-1 activity appears to play a role in tumor promotion in breast, skin, and lung cancer.[210] UV light exposure results in increased oxidative stress in skin and increased risk of skin cancer.[3] In epidermal cell lines, green tea catechins, especially EGCG, and black tea theaflavins (1 to 80 μ*M*) have been found to inhibit AP-1 activity induced by UV light, the tumor promoter, TPA, and a mutant H-*ras* gene.[209-211] Topical EGCG has also been found to inhibit UV-induced AP-1 activation *in vivo* in a transgenic mouse model.[212] In skin cells, catechins and theaflavins appear to inhibit AP-1 activity by inhibiting kinases, for example, JNK and Erks, in the MAPK cell-signaling pathways.[213]

D. Enzyme Inhibition

The inhibition of enzymes whose activity may increase oxidative stress represents a potential indirect antioxidant effect of tea catechins.

1. Inducible Nitric Oxide Synthase (iNOS)

Nitric oxide (·NO) is a short-lived free radical that functions as a signaling molecule with both physiological and pathological functions. It is synthesized from L-arginine through the action of nitric oxide synthase (NOS). Three isoforms of NOS have been identified. The isoforms found in the endothelium of blood vessels and in neurons are constitutively expressed and calmodulin dependent, synthesizing small amounts of ·NO in response to agonists that increase intracellular calcium. An inducible form of NOS (iNOS) is found in some cell types, including macrophages. Stimulation of these cells by endotoxins or cytokines results in the expression of iNOS and the production of large amounts of ·NO, which can react rapidly with $O_2^{\cdot-}$ *in vivo* to form $OONO^-$ and other ·NO-derived oxidants, capable of damaging DNA and proteins.[214] Green tea and black tea, as well as individual catechins and theaflavins, have been found to inhibit LPS-induced iNOS gene expression and iNOS enzyme activity in cultured macrophages.[193,215-218] Among the catechins, EGCG was the most potent inhibitor of LPS-induced iNOS expression, with concentrations of 5 to 10 μ*M,* resulting in 40 to 50% inhibition of iNOS expression.[215,216] The finding that theaflavin-3,3'-digallate (TFdiG) was a more potent inhibitor of LPS-activated iNOS expression than EGCG, while other theaflavins and thearubigins were somewhat less effective than EGCG, suggests that the gallate moiety is important to the effect.[217] The induction of iNOS has been shown to depend on two transcription factors, IFN regulatory factor and NFκB.[214] Both EGCG and TFdiG were found to inhibit NF-κB DNA binding activity and phosphorylation of IκB, the inhibitory binding protein of NFκB.[216,217]

2. Lipoxygenases and Cyclooxygenases

Lipoxygenases and cyclooxygenases catalyze the synthesis of leukotrienes and prostaglandins from long-chain polyunsaturated fatty acids like arachidonic acid. Through their peroxidase activity, lipoxygenases and cyclooxygenases are capable of cooxidizing other molecules, with the potential for increasing oxidative stress or damage in some tissues.[219] Flavonoids and phenolic antioxidants have been found to inhibit lipoxygenase and cyclooxygenase activity *in vitro*.[220] EC inhibited 15-lipoxygenase-mediated LDL oxidation more effectively than ascorbic acid or α-tocopherol at similar concentrations.[221] The expression of 15-lipoxygenase has been found to be increased in human colorectal cancer cells compared with adjacent normal epithelial cells.[222] Overexpression of cyclooxygenase-2 (COX-2), the inducible form of cyclooxygenase, has been observed in a number of human cancers, including colon cancer. [214] Recently, green and black tea polyphenols were found to inhibit COX-2 and 5-, 12-, and 15-lipoxygenase activities in human colon mucosa cells and human colon cancer cells.[223] *In vivo*, topical black or green

tea polyphenols were found to decrease cyclooxygenase and lipoxygenase activities in the skin of mice treated with the tumor promoter, TPA.[224,225] Feeding green tea polyphenols inhibited cyclooxygenase activity in the skin of mice exposed to UV light.[226] Precancerous colon lesions (aberrant crypts) and COX-2 activity were decreased in azoxymethane-treated rats given 2% green tea extract in their drinking water compared with controls.[227] The mechanisms for lipoxygenase and cyclooxygenase inhibition by tea polyphenols are not yet known. NF-κB has been shown to be a positive regulator of COX-2 expression in LPS-stimulated J774 macrophages and human colon adenocarcinoma cell lines,[214] and recent findings that tea polyphenols inhibit NF-κB activation through the inhibition of IκB phosphorylation may partially explain the effect on COX-2.

3. Xanthine Oxidase

Tea polyphenols may also inhibit the formation of ROS by inhibiting the enzyme xanthine oxidase. Xanthine oxidase catalyzes the oxidation of both hypoxanthine and xanthine to uric acid, while reducing O_2 to $O_2^{\cdot-}$ and H_2O_2. Tea catechins have been found to significantly inhibit the activity of xanthine oxidase *in vitro*, with EGCG having the most potent effect.[228] In cultured human leukemia (HL-60) cells, EGCG and theaflavin gallates inhibited xanthine oxidase activity and TPA-stimulated $O_2^{\cdot-}$ formation.[229] TFdiG and theaflavin-3-gallate (TFG) were more potent inhibitors of xanthine oxidase activity than EGCG; IC_{50} values were 4.5 μ*M*, 7.5 μ*M*, and 12.5 μ*M* for TFdiG, TFG, and EGCG, respectively.

E. Enzyme Induction

1. Phase II Enzymes

Phase II detoxifying enzymes promote the excretion of potentially toxic or carcinogenic chemicals. Glutathione *S*-transferases (GST) are a family of phase II enzymes that catalyze the conjugation of glutathione to electrophiles, generally reducing their ability to react with nucleic acids and proteins.[219] Black tea extract (300 mg/kg body weight) by gavage did not affect urethane-induced GST inhibition in mice.[230] However, supplying 0.2% green tea polyphenols in the drinking water of mice for up to 30 days significantly increased GST activity in liver and small intestine.[231] Feeding rats green tea leaves (2.5%) for 63 weeks also significantly increased liver GST activity.[232] Injecting EGCG into the portal vein of rats dose dependently increased total GST activity and specifically induced expression of the GSTM2 subunit.[233] Most phase II enzymes contain cis-acting regulatory elements called antioxidant response elements (ARE), which have been found in some rat GST genes and rat and human quinone reductase genes.[234] Green tea polyphenol extract significantly increased ARE-mediated reporter gene activity in transiently transfected HepG2 cells, which was correlated with stimulation of the MAPK pathway.[235] More recently, EGCG and ECG were also found to induce ARE reporter gene activity in stably transfected HepG2 cells.[236] EGCG was the most potent inducer of ARE reporter gene activity, with induction observed at a concentration of 25 μ*M*. Additionally, EGCG showed potent activation of all three MAPKs (ERK, JNK, and p38) at concentrations of 25 to 50 μ*M*.

2. Antioxidant Enzymes

Increasing the activity of antioxidant enzymes, such as glutathione peroxidase (GPX), catalase, and superoxide dismutase (SOD), also represents a potential indirect antioxidant effect of tea catechins and polyphenols. Hairless mice given 0.2% green tea polyphenols in their drinking water for 30 days had significantly increased GPX and catalase activity in small intestine, liver, and lung, as well as increased liver glutathione reductase activity compared with controls.[231] Furthermore, providing hairless mice with 0.2% green tea polyphenols in their drinking water prior to a single exposure to UVB radiation resulted in a significant inhibition of UVB-induced decreases in epidermal catalase and glutathione reductase activity 12 and 24 h after exposure.[226] Rats fed a diet

containing 2.5% green tea leaves for 63 weeks had significantly increased serum SOD activity and liver catalase activity compared with those on a control diet.[232] Muscle GPX and SOD activities after electrical stimulation that elicited oxidative damage to muscle proteins was not different in rats given a diet containing 0.1% EGCG compared with those given a control diet.[237] In humans, topical application of EGCG (1 mg/cm^2 skin) inhibited UV-induced decreases in epidermal GPX activity and glutathione content compared with control skin.[238] However, in humans drinking 900 ml of green or black tea daily for 4 weeks, whole blood GPX, SOD, and catalase activities were not different from those who drank 900 ml of mineral water daily.[239] Taking 3 g/day of green tea extract for 4 weeks also did not change whole blood levels of reduced or oxidized glutathione compared to a placebo.[240]

VI. ANTIOXIDANT FUNCTIONS OF TEA CATECHINS

A. Effects on Plasma Antioxidant Capacity

Several assays of total antioxidant capacity have been applied to plasma in an attempt to measure the contribution of tea catechins and polyphenols. Each assay differs somewhat in its measurement of the individual contributions of plasma antioxidants due to the differences in the nature of the radical generating system and the conditions of the assay. The FRAP (ferric reducing ability of plasma) assay is based on the reduction of Fe^{3+} ions to Fe^{2+} ions. The TEAC (trolox-equivalent antioxidant capacity) assay is based on the formation and scavenging of the $ATBS^{\cdot+}$ radical cation. TRAP assays measure total peroxyl radical trapping capacity. The ORAC (oxygen radical absorbance capacity) assay is a commonly used TRAP assay that measures the decrease in fluorescence of phycoerythrin in the presence of AAPH, an azo-initiator that generates aqueous peroxyl radicals at a constant rate.[241]

A number of studies have examined the effect of tea or tea extract consumption on plasma antioxidant capacity in humans (Table 4). Two studies from the same laboratory using the ORAC assay observed increases in plasma antioxidant capacity of more than 40% 50 min after consuming 300 ml of green or black tea,[242,243] while another study using the FRAP assay observed increases of over 60% 1 h after consuming 200 ml of black tea every hour for 6 h.[244] In a pharmacokinetic study of pure green tea catechins, a single dose of 1.5 mmol of EGC or ECG significantly increased plasma antioxidant activity measured by the FRAP assay 2 h after ingestion.[163] Plasma antioxidant activity also increased 2 h after ingestion of 1.5 mmol of EGCG, but the increase was not significantly different from controls.

Most studies using FRAP, ORAC, or TEAC assays observed an acute increase in plasma antioxidant activity ranging from only 4% to 15% 1 to 3 h after green or black tea consumption.[175,245-249] Two studies using chemiluminescence assays found no significant change in plasma antioxidant activity.[250,251] The three studies that examined chronic green and black tea consumption (1 to 4 weeks) found either little or no increase in plasma antioxidant activity from fasting plasma samples.[31,239,251] Overall, most increases in plasma antioxidant capacity as a result of tea or green tea extract consumption have been modest and short-lived, possibly due to limited absorption and rapid metabolism and excretion of tea catechins.

In a number of countries, tea is commonly consumed with milk. Two studies found that the addition of milk decreased[244] or eliminated[242] increases in plasma antioxidant capacity induced by tea consumption, while another found no effect.[249] Interactions of tea catechins and polyphenols with proteins present in milk and human plasma have been found to diminish their antioxidant capacity when measured *in vitro*, but the effects of these interactions *in vivo* are not known.[252]

B. Effects on Resistance of Plasma to *Ex Vivo* Oxidation

While adding tea or tea extracts to plasma *in vitro* has been found to increase its resistance to oxidation,[253] studies of *ex vivo* plasma oxidation have not convincingly demonstrated increased resistance to lipid peroxidation after

Table 4. Effects of Tea and Tea Catechins on Plasma Antioxidant Capacity and Plasma Susceptibility to Oxidation

Ex Vivo

Reference	Treatment (N)	Design	Assay	Results
Serafini et al 1996 [242]	300 ml green tea (5) 300 ml black tea (5) 300 ml green tea w/milk (5) 300 ml black tea w/milk (5) 300 ml hot water (5)	Crossover between tea w/o and tea w/ milk. Compared baseline to 30, 50, 80 minutes after ingestion	TRAP (ORAC)	Green tea: 40% increase over baseline ($P < 0.05$) Black tea: 48% increase over baseline ($P < 0.05$) AUC for green tea and black tea > hot water ($P < 0.05$) Milk eliminated increases for green and black tea
Maxwell & Thorpe 1996 [250]	500 ml black tea (10)	Compared baseline to 60, 120, 240 min	Chemi-luminescence	4% non-significant increase from baseline at 120 min
van het Hof et al. 1997 [239]	900 ml green tea/day x 4 wk (14) 900 ml black tea/day x 4 wk (15) 900 ml mineral water/ day x 4 wk (16)	Parallel	TEAC	3.5% increase after green tea compared to control ($P < 0.05$)
Pietta et al. 1998 [175]	300 ml green tea (6)	Compared 1-5 h after ingestion to baseline	TRAP (ORAC)	15% increase over baseline (no P value)
Pietta et al. 1998 [245]	400 mg green tea free catechins (6) 400 mg green tea catechins in phospholipid complex (6)	Parallel; Compared 180 min after ingestion to baseline	TRAP (ORAC)	Free: 16% increase at 4h post-ingestion Phospholipid: 19% increase at 180 min post-ingestion (no P value)
McAnalis et al. 1998 [251]	Acute trial 600 ml black tea (5)	Compared baseline	Chemi-luminescence	Acute trial: No change from baseline
	Chronic trial Black tea: 5 x 300 ml/d x 7d (10) Coffee: 5 x 300 ml/d x 7d (10)	Complete crossover		Chronic trial: No significant difference from coffee
Benzie et al. 1999 [246]	300-400 ml strong green tea (10) 300-400 ml warm water (7)	Crossover (3 did not return for water)	FRAP	Green tea higher than control at 20, 40, 60 min after ingestion ($P < 0.05$) 4% increase over baseline at 40 min

Table 4 (continued)

Reference	Treatment (N)	Design	Assay	Results
Sung et al. 2000 [247]	150 ml green tea (10) 300 ml green tea (10) 450 ml green tea (10)	Complete crossover; Compared baseline to 60, 120 min after ingestion	TEAC	150 ml: no increase over baseline 300 ml: 7% increase at 60 min and 6% increase at 120 min ($P < 0.001$) 450 ml: 12% increase at 60 min and 120 min ($P < 0.001$)
Hodgson et al. 2000 [248]	400 ml green tea (20) 400 ml black tea (20) 400 ml water w/ caffeine (20) 400 ml water (20)	Complete crossover; Compared baseline to 60 min after ingestion	TRAP	Non-significant increases for green (4%) and black tea (3%)
Leenen et al. 2000 [249]	300 ml (2g) green tea (21) 300 ml (2g) black tea (21) 300 ml water (21) 300 ml (2g) green tea w/ milk (21) 300 ml (2g) black tea w/ milk (21) 300 ml water w/ milk (21)	Complete crossover; Compared baseline to 60, 90, 120 min after ingestion	FRAP	Black tea: 2% increase compared to water ($P < 0.001$) Green tea: 3% increase compared to water ($P < 0.001$) Green tea > black at 60, 90, 120 min ($P < 0.05$) Milk in tea did not significantly alter responses to FRAP
Serafini et al. 2000 [243]	300 ml green tea (5) 300 ml black tea (5) 300 ml red wine (5) 300 ml white wine (5) 300 ml water (5)	Complete crossover; Compared baseline to 30, 50, 80 min after ingestion	TRAP (ORAC)	Green tea: 40% increase from baseline at 30 min ($P < 0.01$) 20% increase at 50 min ($P < 0.05$) Black tea: 52% increase at 50 min ($P < 0.01$)
Langley-Evans et al. 2000 [244]	1200 ml black tea: 200 ml every hour from 9 am-2 pm (9) 1200 ml black tea w/ milk: 200 ml every hour from 9 am-2 pm (9) No tea (9)	Complete crossover; Change relative to baseline at 12 noon and 3 pm	FRAP	Black tea: 65% increase at 12 noon and 76% at 3 pm when subjects consumed black tea ($P < 0.05$) Black tea w/ milk: Non-significant 50% increase at 3 pm
Duffy et al. 2001 [31]	900 ml black tea/d x 4 wk (21) 900 ml water/d x 4 wk (21)	Complete crossover	FRAP TRAP (ORAC)	Tended to increase ORAC and FRAP ($P = 0.09$ for both)
Van Amelsvoort et al. 2002 [163]	Single dose of pure catechin: 1.5 mmol ECG (10) 1.5 mmol EGC (10) 1.5 mmol EGCG (10)	Complete crossover	FRAP	FRAP significantly increased 2 hours after ingestion of EGC ($P < 0.001$) and ECG ($P < 0.05$), but not EGCG

Table 4 (continued)

Reference	Treatment (N)	Design	Assay	Results
Cherubini et al. 1999 [253]	500 ml of black tea (8)	Compared plasma oxidation before, 60, 120, and 180 min after ingesting black tea	AAPH-mediated plasma oxidation; CEOOH formation	No significant difference in the resistance of plasma to oxidation 60, 120, and 180 min after black tea consumption
Nakagawa et al. 1999 [254]	1 green tea extract tablet containing EGCG:82 mg, ECG: 38 mg, EC: 33 mg, EGC: 27 mg, GCG: 37 mg (4)	Compared plasma oxidation before and 60 min after ingesting green tea	Cu-mediated plasma oxidation; PCOOH & TBARS formation	PCOOH 69% lower at 45 min oxidation after green tea extract ($P < 0.05$) TBARS 72% lower at 180 min oxidation after green tea extract ($P < 0.05$).
Hodgson et al. 2000 [248]	400 ml black tea (20) 400 ml green tea (20) 400 ml water w/ caffeine (20) 400 ml water (20)	Complete crossover Compared serum oxidation 90 minutes after beverage	Cu-mediated serum oxidation; Conjugated diene formation	Compared with water, black tea increased lag time by 5.4 min ($P = 0.05$) and green tea increased lag time by 4.4 min (NS; $P = 0.17$)

TRAP: Total peroxyl radical trapping assay
ORAC: Oxygen radical absorbance capacity assay
FRAP: Ferric reducing ability of plasma assay
TEAC: Trolox-equivalent antioxidant capacity assay

tea consumption (Table 4). Of three studies that examined *ex vivo* plasma oxidation after tea consumption, only one small, uncontrolled study found a substantial decrease in phosphatidylcholine hydroperoxide (PCOOH) formation during copper-mediated oxidation of plasma drawn from four volunteers 60 minutes after ingesting a green tea extract tablet.[254] A larger crossover study (n = 20) found the average lag time in conjugated diene formation during copper-mediated serum oxidation to be significantly increased by 5.4 min, 1.5 h after consuming 400 ml of black tea, and nonsignificantly increased by 4.4 min after consuming the same amount of green tea.[248] In contrast, the consumption of 500 ml of black tea did not increase plasma resistance to AAPH-induced plasma lipid peroxidation up to 3 h after ingestion as measured by cholesterol ester hydroperoxide (CEOOH) formation, a more specific measure of plasma lipid peroxidation than conjugated diene formation.[253]

C. Effects on Individual Plasma Antioxidants

Although moderate acute increases in plasma antioxidant capacity have been observed after tea consumption, chronic tea consumption does not appear to affect plasma levels of other antioxidants. Plasma vitamin E, vitamin C, β-carotene, and uric acid levels did not change significantly after consuming 900 ml/day of black tea or green tea for 4 weeks compared with 900 ml/day of mineral water,[239] or did they change after taking 600 mg/day of green tea extract for 7 days compared with placebo.[255] Freese et al. found that taking 3 g/day of green tea extract prevented the slight decrease in plasma vitamin E that occurred in the placebo group after 4 weeks on a high-linoleic acid diet.[240] However, Princen et al. observed a slight but significant (3%) decrease in plasma vitamin E in a group of smokers who drank 900 ml/day of green tea compared with those who drank water.[256] Plasma vitamin E con-

centrations did not change significantly in those who drank 900 ml/day of black tea for 4 weeks. Consuming six cups of black tea and 400 g of onions daily for 2 weeks did not change plasma antioxidant levels in stable diabetics compared with a low flavonoid diet.[257]

D. Effects on Resistance of Isolated LDL to *Ex Vivo* Oxidation

1. Animal Studies

The results of studies of *ex vivo* lipoprotein oxidation after tea supplementation in animal models of atherosclerosis have been suggestive of increased oxidative resistance of LDL (Table 5). In New Zealand white rabbits fed an atherogenic diet and given tea in their drinking water for a period of 21 weeks, the lag phase for copper-mediated LDL oxidation was significantly prolonged by 13% in those given green tea and 15% in those given black tea compared with controls.[258] However, the lag phase was prolonged by 63% in rabbits supplemented with vitamin E (200 mg/kg diet). The lag phase for copper-mediated LDL + VLDL oxidation was also significantly prolonged in Syrian golden hamsters given green or black tea in their drinking water for 14 days compared with controls.[259] In Sprague-Dawley rats fed green tea powder (20 g/kg diet) for 3 weeks, the lag phase for copper-mediated LDL + VLDL oxidation was significantly prolonged by 33%, although diets enriched in vitamin E and genistein resulted in more substantial increases in all parameters of LDL + VLDL resistance to oxidation.[260] In contrast, black tea in the drinking water of LDL receptor-deficient mice fed a high-cholesterol diet did not significantly change the lag time for copper-mediated LDL oxidation compared with controls, although antioxidant supplementation resulted in significant prolongation of lag time compared with animals given tea or controls.[261] In animal models, the resistance of lipoproteins to *ex vivo* oxidation appears to be modestly improved by green and black tea consumption, but to a lesser extent than by antioxidant vitamin supplementation.

2. Human Studies

When added to isolated human LDL *in vitro*, tea, tea extracts, and individual catechins have been found to significantly inhibit LDL oxidation induced by copper,[262,263] AAPH,[243,264] 15-lipoxygenase,[221] endothelial cells,[265] or macrophages.[262] However, only two out of six studies of *ex vivo* LDL oxidation in humans found significant increases in lag time after the consumption of green tea extract equivalent to 700 ml/day of green tea for 1 week[255] and 750 ml/day of black tea for 4 weeks[262] (Table 6). The lack of a convincing effect of tea consumption on the resistance of isolated LDL to *ex vivo* oxidation is not surprising, because tea catechins are largely water soluble and are not likely to be associated with lipoproteins after their isolation from plasma. Although there is some evidence that green tea catechins may spare or even regenerate α-tocopherol *in vitro* when added to oxidizing LDL[264,266] or plasma,[267] such an effect is not likely to be observed during *ex vivo* oxidation of LDL isolated from the plasma of individuals after tea consumption. *Ex vivo* oxidation of plasma is probably a better model for determining whether tea or tea catechin consumption increases the resistance of plasma lipoproteins to oxidation, because it allows water-soluble catechins and their metabolites present in plasma to interact with oxidizing lipoproteins.

E. Effects on Biomarkers of *In Vivo* Lipid Peroxidation

1. Animal Studies

Most animal studies have used the thiobarbituric acid-reacting substances (TBARS) assay to assess the effect of tea consumption on lipid peroxidation *in vivo* (Table 5). A diet containing 1% tea catechins inhibited increases in plasma TBARS associated with a high polyunsaturated fatty acid diet in Wistar rats.[268] Plasma TBARS were also lower in hamsters given green or black tea in their drinking water[259] and in apolipoprotein E (ApoE)-deficient mice given green tea extract in their drinking wa-

Table 5. Effect of tea on biomarkers of *in vivo* oxidative damage: Animal studies

Reference	Species	Oxidative injury	Treatment (N)	Results
Lipid peroxidation and atherogenesis				
Yamaguchi et al 1991 [290]	Mice	Atherogenic diet x 14 wk	Green tea extract (GTE): 50mg/kg/d 100 mg/kg/d 200 mg/kg/d Control	Atherogenic diet-induced increases in serum lipid peroxides and aortic cholesterol were prevented by GTE in dose-dependent manner
Nanjo et al 1993 [268]	Wistar rats	High saturated fat diet (palm oil) High PUFA diet (perilla oil)	30% palm oil diet (6) 30% perilla oil diet (6) 30% palm oil + 1% tea catechins (6) 30% perilla oil + 1% tea catechins (6)	Tea catechins counteracted perilla oil-associated decreases in plasma and RBC α-tocopherol ($P < 0.01$) and increase in plasma TBARS ($P < 0.05$). No difference in RBC deformability.
Tijburg et al 1997 [258]	New Zealand white rabbits	Atherogenic diet	Green tea in drinking fluid (20) Black tea in drinking fluid (20) Vitamin E in diet (20) β-carotene in diet (20) Control (20)	Lag time for LDL oxidation prolonged 13% by green tea, 15% by black tea ($P < 0.05$), 63% by vitamin E ($P < 0.01$) No differences in plasma TBARS or LOOH in LDL 31% decrease in atherosclerotic plaque only after green tea (NS; $P = 0.11$)
Hayek et a 1997 [272]	ApoE-deficient mice		Red wine (0.5 ml/d) in drinking fluid (10) Quercetin (50 μg/d) in drinking fluid (10) Catechin (50 mg/d) in drinking fluid (10) Placebo (1.1% alcohol) in drinking fluid (10)	Consumption of red wine, quercetin and catechin reduced aortic atherosclerotic lesion area ($P < 0.05$) Basal LOOH levels in LDL and LDL uptake by macrophages were less than placebo ($P < 0.01$). Consumption of red wine and quercetin but not catechin reduced LDL susceptibility to *ex vivo* oxidation.
Vinson & Dabbagh 1998 [259]	Syrian golden hamsters	High cholesterol diet	normal cholesterol (NC) control (6) NC + green tea (6) NC + black tea (6) high cholesterol (HC) control (6) HC + green tea (6) HC + black tea (6)	Plasma TBARS lower for green tea and black tea on both diets. Cu-mediated LDL+VLDL oxidation: lag time longer for green tea on both diets and longer for black tea on NC diet. Fibrinogen lower for green tea and black tea on NC diet ($P < 0.05$ for all)

Table 5 (continued)

Reference	Species	Oxidative injury	Treatment (N)	Results
Lipid peroxidation and atherogenesis (continued)				
Crawford et al 1998 [261]	LDL receptor-deficient mice	High fat, high cholesterol diet	Control (17) Black tea (19) Antioxidant (18)	Lag phase: increased for antioxidant group compared to tea and control ($P < 0.0001$). Lesion area reduced by 60% in antioxidant group compared to tea and control ($P < 0.0001$). NS between tea and control.
Miura et al 2000 [255]	C57BL/6J ApoE-deficient mice	Atherogenic diet	Green tea extract in drinking fluid (16) Control (17)	No differences in plasma TC or TAG. Plasma TBARS lower on green tea ($P < 0.01$). Atheromatous area in aorta smaller on green tea ($P < 0.01$), as were aortic cholesterol and aortic TAG contents ($P < 0.01$).
Osada et al 2001 [291]	Sprague-Dawley rats	*Ex vivo* plasma oxidation	0.5% EGC diet x 5 d (3) 0.5% EGCG diet x 5 d (3) Control diet x 5 d (3)	AAPH mediated plasma oxidation: lag time longer and rate slower in ECG and EGCG groups than control (no P values). Decreases in linoleic acid and increases in total oxidized cholesterol were inhibited in ECG and EGCG groups compared to controls (no P values).
Lipid peroxidation				
Uchida et al 1992 [292]	ICR mice	Whole body X-radiation	EGCG 0.01% in drinking fluid (10) EGCG 0.002% in drinking fluid (10) Control (10)	EGCG decreased liver TBARS in a dose dependent manner ($P < 0.05$) and prolonged life after lethal dose of radiation ($P < 0.01$)
Sano et al 1995 [293]	Wistar rats	*Ex vivo* oxidation of liver and kidney with tert-butyl hydroperoxide (BHP) or bromotrichloro-methane ($BrCCl_3$)	Trial #1 Basal diet (5-6) Basal diet + 3% w/w green tea powder (5-6) Basal diet + 3% w/w black tea powder (5-6) Trial #2 EGCG 50 mg/kg/d (3) Vitamin C 100 mg/kg/d (3) *dl*-α-Tocopherol 100 mg/kg/d (3) Control (6)	#1 In liver, TBARS response to BHP was lower after green tea and black tea. TBARS response to $BrCCl_3$ was lower after black tea. In kidney, TBARS response to BHP was lower after green tea ($P < 0.05$). #2 In liver, TBARS response to BHP was lower after EGCG and α-tocopherol ($P < 0.05$). In kidney, TBARS response to BHP was lower after EGCG ($P < 0.05$).

Table 5 (continued)

Reference	Species	Oxidative injury	Treatment (N)	Results
Lipid peroxidation (continued)				
Lin et al. 1998 [294]	Sprague-Dawley rats	Injection of ferrous citrate (4.2 nmol) into substantia nigra	Trial #1 Intranigral (IN) iron (6-12) IN green tea extract (GTE) (6-12) IN iron + IN GTE (6-12) Control (6-12) Trial #2 IN iron (8) IN iron + oral GTE (8)	Co-infusion of GTE decreased iron-induced increases in intranigral MDA and decreases in striatal dopamine. Oral GTE in drinking fluid had no effect compared to water
Oxidative DNA damage and lipid peroxidation induced by carcinogens				
Xu et a 1992 [277]	A/J mice	Tobacco nitrosamine (NNK) 23 mg/kg i.g. 3 times/wk for 3 wk	2% green tea solution in drinking fluid (10-12) 2% EGCG solution in drinking fluid (10-12) Water (10-12)	NNK increased 8-OHdG levels 2-fold over basal level in lung DNA. Green tea and EGCG suppressed this effect almost completely ($P < 0.05$). No significant increases in liver 8-OHdG with NNK treatment. Decreased lung adenomas in green tea ($P < 0.01$) and EGCG ($P < 0.05$) treated mice.
Inagake et al 1995 [278]	Sprague-Dawley rats	1,2-dimethyl-hydrazine (DMH) 0, 25, 50, or 100 mg i.p.	Green tea extract (0.5%) in drinking fluid 0 mg DMH (8) 25 mg DMH (8) 50 mg DMH (8) 100 mg DMH (8) Water (control) 0 mg DMH (8) 25 mg DMH (8) 50 mg DMH (8) 100 mg DMH (8)	Green tea extract inhibited formation of 8-OHdG in colon DNA at all 3 DMH dose levels ($P < 0.01$). Non-significant decrease in 8-OHdG in liver DNA after green tea extract at the 50 and 100 mg DMH dose levels
Matsumoto et al 1996 [295]	Sprague-Dawley rats	DMH 25, 50, or 100 mg s.c.	0.5% green tea extract in drinking water + DMH (19) Tap water + DMH (19) 0.5% green tea extract + saline (19) Tap water + saline (19)	Intestinal mucosal PCOOH in the tap water groups increased as DMH dose increased. Intestinal mucosa PCOOH was lower in green tea extract groups at DMH 50 and 100 mg doses ($P < 0.05$).
Lodivici et al 2000 [279]	Fisher 344 rats	DMH 20 mg/kg i.g.	Thearubigin (40 mg/kg/d) i.g. (11) Theafulvin (40 mg/kg/d) i.g. (10) Saline i.g. (9)	Pretreatment with thearubigin inhibited DMH-induced increases in 8-OHdG in colon mucosa DNA ($P < 0.05$). A similar but less marked effect was observed with theafulvin ($P < 0.06$).

Table 5 (continued)

Reference	Species	Oxidative Injury	Treatment (N)	Results
Oxidative DNA damage and lipid peroxidation induced by carcinogens (continued)				
Hasegawa et al 1995 [280]	Fisher 344 rats	2-nitropropane (2NP) 100 mg/kg i.p.	2NP (10) 2NP + 2% green tea in drinking fluid (10) 2NP + catechin extract in drinking fluid (10) control (10)	Green tea inhibited 2NP-induced increase in liver 8-OHdG ($P < 0.01$) at 6 h but not 15 h after 2NP 2NP-induced liver TBARS production was inhibited by tea ($P < 0.01$) and by catechin extract ($P < 0.05$) 6 h after 2NP
Sai et al 1998 [281]	Fisher 344 rats	2NP low (L): 60 mg 3 x a wk for 2 wk 2NP high (H): 90 mg x 2 doses, then 120 mg x4 doses 3 x wk for 2 wk i.g.	2NP(L) + green tea 2% in drinking fluid (5) 2NP(H) + green tea 2% in drinking fluid (5) 2NP(L) (5) 2NP(H) (5) Control (5)	The increase in 8-OHdG in the 2NP(L) group was inhibited to the control level ($P < 0.01$) while the increase in the 2NP(H) group was inhibited by 60% in green tea treated animals ($P < 0.05$). Green tea treatment decreased liver TBARS formation in both 2NP dose groups ($P < 0.01$).
Takabayashi et al 1997 [282]	Syrian golden hamsters	N-nitrobis(2-oxopropyl)amine (BOP): single s.c. injection (20 mg/kg bw)	0.1% green tea catechins in drinking fluid (15) Control (15)	Peak pancreatic TBARS (1 h post-injection) and peak pancreatic 8-OHdG (6 h post-injection) were significantly lower in green tea group than control ($P < 0.05$). Liver TBARS and 8-OHdG did not differ significantly.
Kim et al 2001 [270]	Guinea pigs	2 x minimal erythema dose (MED) of UVB radiation	Vehicle control Topical Vitamin E Topical EGCG	Erythema was lower 16, 18, and 24 h after UV exposure in EGCG and vitamin E treated groups ($P < 0.05$). UV-induced TBARS formation was lower in the EGCG and vitamin E treated groups ($P < 0.05$)
Protein oxidation				
Nagasawa et al 2000 [237]	Sprague-Dawley rats	Electrical stimulation to hindlimb every 2nd day x 2 wk. Unstimulated hindlimb served as control	0.1% EGCG w/w in diet (6) Control diet (6)	EGCG feeding prevented electrical stimulation-induced rise in protein carbonyl content in gastrocnemius and soleus muscles ($P < 0.05$). Muscle TBARS was not different between stimulated and unstimulated muscle nor between EGCG and control diets. No changes in SOD, GPX, and GST activity.

Table 5 (continued)

Reference	Species	Oxidative Injury	Treatment (N)	Results
Ischemia-reperfusion injury				
Inanami et al 1998 [296]	Gerbil	Ishemia-reperfusion (IR) 5 min occlusion of common carotid arteries	IR (4) IR + catechin 0.1 mg/ml in drinking fluid (4) IR + catechin 1.0 mg/ml in drinking fluid (4) Sham operated (4)	$O_2^{\cdot}$ scavenging ability of brain and survival of neuronal cells increased in dose dependent manner by catechin. Neuronal cell survival in highest catechin group comparable to sham.
Lee et al 2000 [297]	Gerbil	Ishemia-reperfusion (IR) 3 min occlusion of common carotid arteries EGCG given immediately after ischemia	IR + EGCG 10 mg/kg i.p. (8) IR + EGCG 25 mg/kg i.p. (9) IR + EGCG 50 mg/kg i.p. (15) Vehicle treated i.p. (9) Sham operated (9)	EGCG 25 and 50 mg/kg ($P < 0.001$) but not 10 mg/kg reduced hippocampal neouronal damage. 50 mg/kg provided more neuro-protection than 25 mg/kg ($P < 0.01$)
Hong et al 2000 [298]	Wistar rats	Ishemia-reperfusion (IR): occlusion of middle cerebral arteries for 60 min /24h reperfusion	IR (6) IR + 0.5% green tea extract (GTE) in drinking fluid (6) Sham operated (6)	GTE significantly reduced infarct volume, eicosanoid concentrations, H_2O_2, and apoptotic cell number in the striatum and the cortex. GTE promoted recovery from IR-induced inhibition of active avoidance ($P < 0.05$). No significant difference in 8-OHdG or MDA
Hong et al 2001 [299]	Gerbil	Ishemia-reperfusion (IR) 5 min occlusion of common carotid arteries	IR (6) IR + 0.5% green tea extract (GTE) in drinking fluid (6) IR + 2% GTE in drinking fluid (6) Sham operated (6)	Total and cortex infact volume, number of apoptotic cells, 8-OHdG, IR-induced increases in locomotor activity all reduced dose-dependently by GTE. Striatum infarct volume, MDA+4NE reduced by 2%GTE only

ter[269] compared with controls. However, plasma TBARS were not significantly different in New Zealand white rabbits on an atherogenic diet given green or black tea in their drinking water compared with controls.[258] Topical application of EGCG has also been found to reduce TBARS in the skin of guinea pigs after exposure to UV-B light.[270] Interpretation of the TBARS assay is limited by its lack of specificity for malondialdehyde (MDA) in biological samples and its susceptibility to artifactual oxidation.[271] Basal levels of lipid hydroperoxides in LDL were found to be lower in ApoE-deficient mice given (+)-catechin in their drinking water compared with placebo,[269] but not in New Zealand white rabbits given green or black tea in their drinking water compared with controls.[258] In four studies that examined atherosclerotic plaque formation, two found green tea catechin extracts to reduce atherosclerotic lesion formation,[269,272] while two found no significant effect of black or green tea.[258,261]

2. Human Studies

Studies examining the effect of tea consumption on biomarkers of *in vivo* lipid peroxidation in humans are limited (Table 7). One study found a

Table 6. *Ex vivo* LDL oxidation in humans

Reference	Treatment (N)	Design	Method	Results
Ishikawa et al 1997 [262]	750 ml black tea/d x 4 wk (14) 750 ml water/d x 4 wk (8)	Parallel	Cu-mediated LDL oxidation; monitored conjugated dienes	Lag time increased by 15% (8.2 min) over baseline in tea group ($P < 0.05$) No change in control group
van het Hof et al 1997 [219]	900 ml black tea/d x 4 wk (15) 900 ml green tea/d x 4 wk (14) 900 ml mineral water/d x 4 wk (16)	Parallel	Cu-mediated LDL oxidation; monitored conjugated dienes	No differences in parameters of LDL oxidation before and after treatment among all 3 groups
Princen et al 1998 [256]	900 ml green tea/d x 4 wk (16) 900 ml black tea/d x 4 wk (16) 900 ml mineral water/d x 4 wk (16) 3.6 g green tea extract/d + 900 ml mineral water/d x 4 wk (16)	Parallel; All subjects were smokers (at least 10 cigarettes/d)	Cu-mediated LDL oxidation in hypertonic saline; monitored conjugated dienes; LDL was not dialyzed	No significant change in lag time or propagation rate during LDL oxidation among all 4 groups
McAnalis et al 1998 [251]	Acute trial 600 ml black tea (5) Chronic trial Black tea: 5 x 300 ml/d x 7d (10) Coffee: 5 x 300 ml/d x 7d (10)	Compared baseline Complete crossover	Cu-mediated LDL oxidation; monitored conjugated dienes	Acute trial: Lag times at 30, 60, 90, 120, and 180 min were not different than baseline. Chronic trial: no difference in lag times between tea and coffee
van het Hof et al 1999 [300]	1200 ml green tea/d x 3d (9) 1200 ml black tea/d x 3d (9) 1200 ml black tea w/milk x 3d (9) 1200 ml water/d x 3d (9)	Incomplete crossover; Each subject received 2 out of 4 treatments	Cu-mediated LDL oxidation; monitored conjugated dienes	No differences in parameters of LDL oxidation before and after 3 days of treatment among all 4 groups
Miura et al 2000 [269]	600 mg green tea extract/d (equivalent to 700-800 ml tea/d) x 7 d (11) control (same diet) x 7d (11)	Parallel; 6 smokers in each group	Cu-mediated LDL oxidation; monitored conjugated dienes	Lag time increased 20% (13.7 min) over baseline in green tea extract group ($P < 0.05$) No change in rate

significant 22% decrease in plasma TBARS after the consumption of 3 g/day of green tea extract (equivalent to 10 cups/day of green tea) for 4 weeks compared with a placebo,[240] while no significant changes in plasma TBARS were found in studies where volunteers consumed green tea extract equivalent to two cups of tea acutely[254] or three cups of tea daily for 7 days.[255] In an uncontrolled study, the ingestion of green tea extract equivalent to two cups of tea was associated with a 60% decrease in plasma PCOOH 60 min after ingestion.[254] It is possible that this finding was affected by artifactual lipid peroxidation, because all participants had measurable plasma levels of PCOOH at baseline, an uncommon finding in healthy individuals.

F_2-isoprostanes are a well-established biomarker for *in vivo* oxidative stress and have been shown to correlate with conditions of increased lipid peroxidation in animals and humans.[273] Several studies have examined the effect of increased tea consumption on F_2-isoprostane

Table 7. Effect of tea on biomarkers of *in vivo* oxidative damage: Human studies

Reference	Treatment (N)	Design	Assays	Results
Lipid peroxidation				
Nakagawa et al 1999 [254]	Green tea extract tablet* (18) * equivalent to 2 cups green tea	Compared values prior to ingestion to those taken 60 min after ingestion	Plasma PCOOH by HPLC w/ CL detection Plasma TBARS Plasma EGCG	60% decrease in plasma PCOOH 60 min after green tea extract compared to baseline ($P < 0.05$). Plasma EGCG inversely correlated to PCOOH ($r = 0.52$, $P < 0.05$). No association between plasma TBARS and EGCG
Freese et al 1999 [240]	Green tea extract 3 g/d x 4 wk (10)* placebo capsules x 4 wk (10) * equivalent to 10 cups of green tea/d	Parallel design 2-wk pre-experimental diet: high saturated fat 4-wk experimental diet: high linoleic acid	Plasma TBARS Urine 8-iso-$PGF_{2\alpha}$ by RIA urine NO_2+NO_3	Plasma TBARS decreased from pre-experimental diet by 22% in green tea extract group and increased by 42% in placebo group ($P < 0.05$). No change in urine 8-iso-$PGF_{2\alpha}$ or NO_2+NO_3
Miura et al 2000 [255]	600 mg green tea extract/d* x 1 wk (11) control (11) *equivalent to 700-800 ml of green tea/d	Parallel; 6 smokers in each group	Plasma TBARS	No significant change in plasma TBARS after treatment in either group No difference between smokers and nonsmokers
O'Reilly et al 2001 [275]	High flavonoid diet (HF) Enriched in onions and 300 ml/d black tea (32) Low flavonoid diet (LF) (32)	Randomized Crossover (16 men and 16 women)	Plasma F_2-isoprostanes Antibodies to malondialdehyde (MDA)-modified LDL Plasma quercetin	No difference in plasma F_2-isoprostanes or antibodies to MDA-LDL between HF and LF diet, though plasma quercetin increased after HF diet ($P < 0.05$) In men only, 19% increase in plasma F2-isoprostanes after HF compared to LF diet ($P = 0.04$)
Katiyar et al. 2001 [238]	Skin exposure to UV radiation: 4x minimal erythema dose (MED) with or without application of topical EGCG (6)	UV-exposed skin compared to non-exposed skin. EGCG-treated skin compared with non-treated skin	Epidermal and dermal H_2O_2 and nitrite formation Epidermal TBARS Epidermal GPX and catalase activities Epidermal GSH	Topical EGCG inhibited UV-induced H_2O_2, nitrite, and TBARS formation in skin ($P < 0.05$). EGCG prevented UV-induced decreases in skin GPX activity and GSH levels ($P < 0.05$)

Table 7 (continued)

Reference	Treatment (N)	Design	Assays	Results
Lipid peroxidation (continued)				
Hodgson et al 2002 [274]	Trial #1 (13) 1000 ml/d green tea x 7d 1000 ml/d black tea x 7d 1000 ml/d hot water + caffeine x 7d Trial #2 (22) 1200 ml/d black tea x 4 wk 1200 ml/d hot water + caffeine x 4 wk	Trial #1 Randomized crossover; Pts with hypertension Trial #2 Randomized crossover; Pts with hyperlipidemia	Urine 8-iso-$PGF_{2\alpha}$ by GC/MS (pmol/mmol creatinine)	Trial #1: No significant differences between green tea, black tea or water + caffeine Trial #2: No significant difference between black tea and water + caffeine
DNA damage				
Xue et al 1992 [283]	Tea-drinking smokers (35) Smokers that did not drink tea (35)	Case-control; matched for age, sex, smoking, alcohol intake	Micronucleus formation in peripheral blood lymphocytes	Micronucleus frequency was lower in tea drinkers (1.63%) than non-tea drinkers (2.54%; $P < 0.01$)
Li et al 1999 [284]	Black and green tea flavonoids: 3 g/day orally and 10% ointment topically to oral lesions TID x 6mo (29) Placebo capsules and ointment TID x 6mo (30) Healthy controls (20)	Parallel; 59 oral leukoplakia pts randomly divided into treatment or placebo group.	Micronuclei in buccal mucosal cells and peripheral blood lymphocytes	After tea treatment, micronucleated cell number was significantly lower in oral lesions (48%), normal buccal mucosa (41%), and lymphocytes (32%) compared to baseline and placebo ($P < 0.01$)
Klaunig et al 1999 [285]	~900 ml green tea x 7d (27) ~900 ml placebo x 7d (27)	Crossover; 12 smokers 15 nonsmokers (U.S.)	White blood cell (WBC) 8-OHdG, urine 8-OHdG, plasma and urine MDA by (HPLC)	Decreases in WBC 8-OHdG, urine 8-OHdG, and urine MDA in tea compared to placebo (no P values). No change in plasma MDA for smokers.
Klaunig et al 1999 [285]	300 ml green tea 3 times/d x 7d then smoked 3 cigarettes 1 hr later (20) 300 ml hot water 3 times/d x 7d then smoked 3 cigarettes 1 hr later (20)	Parallel (China)	White blood cell (WBC) 8-OHdG, urine 8-OHdG, plasma and urine MDA by (HPLC)	After 7 d, tea drinkers had 40% decrease in WBC 8-OHdG, 40% decrease in urine 8-OHdG, 50% decrease in urine MDA compared to hot water (no P values). No change plasma MDA

Table 7 (continued)

Reference	Treatment (N)	Design	Assays	Results
DNA damage (continued)				
Lean et al 1999 [257]	High flavonol diet (6 cups of tea/d + 400 g/d onions) x 2 wk (10) Low flavonol diet x 2 wk (10)	Crossover	*Ex vivo* H_2O_2-induced DNA damage in lymphocytes by endonuclease III adaptation of comet assay	Oxidative damage to lymphocyte DNA was 13% lower after high flavonol diet ($p=0.037$)
Katiyar et al. 2000 [286]	Skin exposure to UV radiation (6) 0.5, 1, 2, and 4 x minimal erythema dose (MED) with or without application of topical EGCG (1-4 mg/cm^2 skin)	UV-exposed skin compared to non-exposed skin. EGCG-treated skin compared with non-treated skin	Cyclobutane pyridine dimers by immunostaining epidermal and dermal cells	Topical EGCG dose-dependently inhibited formation of UVB-induced cyclobutane pyridine dimers in dermis and epidermis ($P < 0.05$)

concentrations in humans. In the same study that found a significant decrease in plasma TBARS, urinary levels of 8-iso-$PGF_{2\alpha}$, an F_2-isoprostane, were not different in those who were given 3 g/day of green tea extract for 4 weeks compared with those who received placebo.[240] Similarly, 1000 ml/day of black tea for 7 days and 1200 ml/day of black tea for 4 weeks did not affect urinary 8-iso-$PGF_{2\alpha}$ levels in hypertensive and hypercholesterolemic patients, respectively.[274] In a crossover trial involving 32 men and women, a high flavonoid diet that included onions and 300 ml/day of black tea did not result in any significant change in plasma F_2-isoprostane concentrations in the group as a whole when compared with a low flavonoid diet.[275] However, when men were considered separately, the high-flavonoid diet resulted in a significant 19% increase in F_2-isoprostanes compared with the low-flavonoid diet. Overall, studies examining measures of *in vivo* lipid peroxidation in humans are not as convincing in demonstrating an antioxidant effect of tea consumption as those in animals. Differences in dose and catechin bioavailability among species may explain some of the observed differences.

UVB light exposure has been reported to increase oxidative damage in the skin in animals and humans. Topical EGCG (1 mg/cm^2) was found to significantly reduce epidermal TBARS formation after UV light exposure at four times the minimal erythema dose (MED) compared with controls, in addition to significantly lowering UV light-induced epidermal H_2O_2 and nitrite formation.[238]

F. Effects on Biomarkers of Oxidative DNA Damage

1. Animal Studies

The anticarcinogenic effects of tea and its catechins have been demonstrated in numerous animal studies involving tumors of the lung, digestive tract, prostate, mammary glands, and skin.[276] Animal studies have also been strongly supportive of a role for tea in preventing oxidative DNA damage induced by carcinogens (Table 5). 8-Hydroxydeoxyguanosine (8OHdG) is a product of oxidative DNA damage. In addition to decreasing lung adenomas, green tea and EGCG solutions in the drinking water of mice significantly inhibited increases in lung DNA levels of 8OHdG induced by the tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).[277] In rats, green tea extract in the drinking water[278] and black tea polyphenols by gavage[279] have been found to significantly inhibit increases in 8OHdG in colon mucosa DNA induced by the colon carcinogen 1,2-dimethylhydrazine (DMH).

In addition to inhibiting liver TBARS formation, green tea and catechin extracts in the drinking water of rats inhibited 8OHdG increases in liver nuclear DNA induced by the hepatic carcinogen, 2-nitropropane (2NP).[280,281] Green tea catechins in the drinking water of hamsters significantly inhibited increases in pancreatic TBARS and pancreatic nuclear 8-OHdG induced by the pancreatic carcinogen *N*-nitrobis(2-oxopropyl)amine.[282] Thus, tea and tea polyphenols have consistently been found to inhibit carcinogen-induced increases in a marker of oxidative DNA damage in different species and organs.

2. Human Studies

Few human studies have specifically examined the effects of tea on oxidative DNA damage (Table 7). Micronucleus assays provide information about chromosomal damage in cells, but they are not specific for oxidative DNA damage. An observational study in China found micronucleus frequency in peripheral blood lymphocytes to be significantly lower in smokers that habitually drank tea than in smokers that did not drink tea.[283] An intervention trial in patients with precancerous lesions of the oral mucosa (leukoplakia) who were mostly smokers found that a treatment regimen of green and black tea polyphenols (3 g/day orally and a 10% ointment applied to lesions three times daily) resulted in significantly lower numbers of micronucleated cells from oral lesions, normal oral mucosa, and peripheral blood lymphocytes.[284] Like smokers, diabetic patients are considered to be under increased oxidative stress. In diabetics, a high-flavonoid diet providing six cups of black tea daily for 2 weeks was found to result in decreased oxidative DNA damage when white blood cells were challenged with H_2O_2 *ex vivo*.[257] Oxidized DNA damage was measured by an adaptation of the "comet" assay, designed to detect oxidized DNA bases. Using another measure of oxidative DNA damage *in vivo*, two studies by the same investigators found that drinking 900 ml/day of green tea for 7 days resulted in lower levels of 8OHdG in urine and white blood cell nuclear DNA, especially in smokers.[285] However, no statistical analyses were presented, and high interindividual variability was noted. In the skin, UV light exposure can result in damage to DNA by promoting the formation of cyclobutane pyrimidine dimers (CPD), recognized to play a role in skin carcinogenesis.[3] Topical EGCG treatment (1 to 4 mg/cm^2 skin) 20 min prior to UV light exposure at up to 4.0 MED significantly inhibited the formation of CPD in human skin.[286] Although the evidence from animal studies strongly suggests a role for tea and tea catechins in the prevention of oxidative DNA damage, more research is needed to determine whether tea catechins and polyphenols can also significantly inhibit oxidative DNA damage in humans.

G. Effects on Biomarkers of Oxidative Damage to Proteins

Oxidative damage to proteins may result in chemical modification of amino acids, aggregation or cross-linking of proteins, or fragmentation, ultimately affecting protein function. Measures of protein carbonyl content are indicators of *in vivo* oxidative damage to proteins. Only one animal study has assessed the effect of tea consumption on oxidative damage to proteins (Table 5). Supplementing the diets of rats with 1% EGCG for 2 weeks significantly inhibited increases in muscle protein carbonyl content induced by electrical muscle stimulation compared with controls.[237] Muscle TBARS did not differ between the two groups. No published studies in humans have assessed the effects of tea or tea catechins on oxidative damage to proteins in humans.

VI. CONCLUSION

A great deal of research has evaluated the antioxidant and biological activities of green and black tea as well as their individual catechins and polyphenols *in vitro*. Relatively little of the *in vitro* research has been conducted using physiologically relevant concentrations of catechins. EGCG and other tea catechins are very effective scavengers of ROS and RNS *in vitro*. They may also function indirectly as antioxidants through their effects on transcription factors and enzyme

activities. The fact that catechins are metabolized extensively *in vivo* emphasizes the importance of demonstrating their antioxidant activity *in vivo*. Additional information is needed on the formation, tissue distribution, and elimination of catechin metabolites, as well as the antioxidant and biological activities of the most abundant catechin metabolites.

Epidemiologic evidence that increased tea consumption decreases the risk of cancer appears limited mainly to green tea and cancers of the digestive tract, the tissues that receive the most concentrated exposure to EGCG and other green tea catechins. While epidemiologic studies do not provide conclusive evidence that increased tea consumption offers protection from cardiovascular diseases, several well-designed studies have demonstrated significant risk reduction in consumers of green and black tea. Evidence that tea consumption reduces the risk of other health problems, such as osteoporosis, is limited, but points to the need for well-designed epidemiologic studies that provide more detailed information about tea exposure, such as type, preparation, and timing of intake, in addition to controlling for the potentially confounding effects of socioeconomic and lifestyle factors on chronic disease outcomes.[287]

Research examining more direct measures of oxidative stress offers some support for the idea that tea catechins function as antioxidants *in vivo*. In humans, modest acute increases in plasma antioxidant capacity have been demonstrated consistently with an increased consumption of green tea, black tea, and green tea catechins. Studies in animal models have been more consistent in demonstrating an increase in the resistance of lipoproteins to *ex vivo* oxidation than studies in humans, as have studies of biomarkers of lipid peroxidation *in vivo*. Although a number of studies have examined the effect of high levels of tea or tea polyphenol consumption on the *ex vivo* oxidation of LDL isolated from plasma, few have examined *ex vivo* oxidation of plasma, a setting in which water-soluble green tea catechins may provide more protection from oxidation.

The effects of tea and green tea catechins on biomarkers of oxidative stress, especially oxidative DNA damage, appear very promising in animal models, but data on biomarkers of *in vivo* oxidative stress in humans are very limited. Specifically, larger studies examining the effect of EGCG intake on F_2-isoprostanes, protein carbonyls, and oxidative DNA damage (8OHdG or the Comet assay) in humans are needed, especially in those individuals who may be at increased risk of oxidative damage, for example, smokers, diabetics, and CHD patients. Planned and ongoing cancer chemoprevention trials of EGCG and tea polyphenols should also include the assessment of biomarkers of *in vivo* oxidative damage.

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