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Tea, Flavonoids, and Nitric Oxide-Mediated Vascular Reactivity[1,2]

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Abstract

Epidemiological evidence supports the concept that diets rich in fruits and vegetables promote health and attenuate or delay the onset of cardiovascular disease (CVD). Although a variety of factors contribute to the beneficial effects of plant foods, much attention has been addressed to plant polyphenols. In this regard, in the daily Western diet, both black and green teas contribute to a relevant proportion of total phenol intake. The more abundant class of flavonoids that is present in teas is represented by flavanols, i.e., catechin, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate. Studies using animal models of atherosclerosis indicate that dietary flavonoid consumption delays atherosclerotic plaque development. Accordingly, an inverse association between tea intake and CVD has been demonstrated. Further, flavonoids can reduce endothelial dysfunction, i.e., the key step in the development of atherosclerosis. Concordantly, human data suggest that tea may reduce blood pressure levels. Despite this, although they often show that tea may have cardiovascular protective effects, results from epidemiological studies exploring the association between tea and health are controversial. Conflicting results may be caused by disparate study designs and flavonoid contents in different kinds of tea. Thus, because tea is a popular beverage worldwide, and several studies have shown that it is protective against CVD, further studies are needed to determine the role of tea in primary and secondary cardiovascular prevention. J. Nutr. 138: 1554S–1560S, 2008.

Introduction

Epidemiological studies have shown an inverse correlation between diets rich in polyphenols and reduced risk of cardiovascular disease (CVD)[5] (1–6), cancer, and other chronic diseases (7,8). In this regard, polyphenols are widely distributed in the Mediterranean diet, mainly in plant-derived foods and beverages, and include >8000 phenolic structures. Flavonoids are the main polyphenolic constituent of this group, presenting with a common flavan core formed with 15 carbon atoms arranged in 3 rings (C_6-C_3-C_6) consisting of 2 aromatic ones linked through 3 carbons, usually forming an oxygenated heterocycle nucleus, the flavan nucleus (9). The different patterns of this nucleus permit the classification of flavonoids into several subgroups, i.e., flavanols (catechin, epicatechin), flavonols (quercetin, myricetin, kaempferol), anthocyanidins (cyanidin, delphinidin), flavones (apigenin, diosmin), and flavanones (naringenin, hesperetin) (9).

In this context, tea products account for a significant proportion of total polyphenol intake in different Western countries (10,11). Both green and black teas are made from the leaves of the plant *Camellia sinensis*. Green tea is produced by steaming fresh leaves for 1 min to inactivate polyphenol oxidase, followed by drying (12,13). In contrast, black tea undergoes a fermentation procedure in which the leaves are kept at room temperature for 16–24 h and then cut and dried (13). Green tea is a rich source of flavonoids, the predominant being catechins (particularly epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate) (13,14). These catechins comprise 30–50% of the solids in green tea (15) and 90% of total flavonoids

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[5] Abbreviations used: ACE, angiotensin-converting enzyme; CVD, cardiovascular disease; CHD, coronary heart disease; FMD, flow-mediated dilation; HUVEC, human umbilical vein endothelial cells; NO, nitric oxide; NOS, nitric oxide synthase; $\cdot O_2^-$, superoxide anion; $ONOO^-$, peroxynitrite; RR, relative risk.

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(16). The fermentation process used to produce black tea results in the conversion of catechins to theaflavins (including theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, and theaflavin-3,3′-digallate) and thearubigin polymers (12–17). The major fraction of black tea polyphenols is composed of thearubigins, which account for >20% of the solids (17) and ~47% of the total flavonoids (13,16). Increasing attention is currently being given to flavanols to define their cardiovascular effects and to clarify the specific link between tea ingestion and suggested lower incidence of cardiovascular events (11,13,17,18). The majority of epidemiological studies suggests that tea consumption might protect against CVD (3,4,11,13,15–18), although both in vitro and in vivo studies suggest that flavanols might reduce cardiovascular risk mainly by increasing nitric oxide (NO) bioavailability and then restoring endothelial function (13,15,16). Therefore, in this article we will focus on the endothelial effects of flavanols from tea that are likely to be associated with a decreased cardiovascular risk and on the evidence from either epidemiological or experimental studies supporting protective effects of tea against CVD.

Epidemiological evidence

Disparate health benefits have been attributed to tea consumption since its inception in China (18). More recently, epidemiological studies have associated tea drinking with reduced cardiovascular and cancer risks (18). The 5-y follow-up of a cohort of 805 men aged 65–84 y from the Zutphen Elderly Study revealed flavonoid intake was inversely associated with mortality from coronary heart disease (CHD) ($P = 0.015$) and showed a trend toward an inverse relation with the incidence of myocardial infarction ($P = 0.08$) (3). In particular, a marked reduction in the relative risk (RR) of CHD mortality was found in the tertile of subjects with the highest flavonoid consumption compared with individuals in the lowest tertile (RR = 0.42, after adjustment for age, BMI, smoking, total- and HDL-cholesterol, blood pressure, physical activity, coffee consumption, and intake of energy, vitamin C, vitamin E, beta-carotene, and dietary fibers. RR = 0.32) (3). In keeping with this, an inverse correlation between flavonoid intake and CHD mortality was also found after the 25-y follow-up of 12,763 men from the 16 cohorts of the Seven Countries Study and explained ~25% of the variance in CHD among cohorts (7).

Although the above studies investigated total daily dietary flavonoid intake, black tea is known to represent 1 of the main contributors to the total amount of daily flavonoid ingestion in different European countries (3,7,18). Accordingly, the major source (61%) of flavonoid intake in the Zutphen Elderly Study was represented by black tea (3). Thus, it is conceivable that tea ingestion significantly contributed to the observed cardiovascular protection exerted by a high flavonoid intake. Consistent with this, in the case-control Boston Area Health Study, men and women who consumed 1 cup (237 mL each)[6] or more a day of tea had a 44% lower risk of myocardial infarction than those who drank no tea (19). Of note, the protective effects of tea were independent of other established coronary risk factors (19). In the study of a cohort of 8552 Japanese men and women, a significant decrease in the RR of death from CVD (RR = 0.58 for men, 0.82 for women, and 0.72 for both) was observed in individuals consuming >10 cups/d of green tea compared with those consuming <3 cups/d (20). In addition, Keli et al. (21) observed a 0.27 RR of a first-ever stroke in the highest vs. the lowest quartile of flavonoid intake (≥28.6 mg/d vs. <18.3 mg/d). Of note, black tea accounted for ~70% of total flavonoid intake (21), whereas the RR of a first-ever stroke for a daily consumption ≥4.7 cups of tea vs. <2.6 cups of tea was 0.31. Mukamal et al. (5) prospectively examined tea consumption in 1900 patients [1019 consuming no tea (nondrinkers), 615 consuming <14 cups/wk (moderate tea drinkers), and 266 consuming ≥14 cups/wk (heavy tea drinkers)] presenting with myocardial infarction to community hospitals in the United States. After a median follow-up of 3.8 y, age- and sex-adjusted mortality was lower among moderate tea drinkers (hazard ratio = 0.69) and heavy tea drinkers (hazard ratio = 0.61) compared with nondrinkers. Of particular relevance, the association of tea and mortality was similar for total and cardiovascular mortality (5), which indicated that tea can also reduce vascular events in secondary prevention.

In the Ohsaki National Health Insurance Cohort Study (22), green tea consumption was inversely associated with all-cause and cardiovascular mortality, the inverse association with all-cause mortality being stronger in women than in men ($P = 0.03$). Similarly, in men the multivariate hazard ratios of all-cause mortality associated with different green tea consumption frequencies were 1.00 (reference) for <1 cup/d (1 cup ≈ 100 mL), 0.93 for 1 to 2 cups/d, 0.95 for 3 to 4 cups/d, and 0.88 for 5 or more cups/d, respectively ($P = 0.03$). The corresponding data for women were 1.00, 0.98, 0.82, and 0.77, respectively ($P < 0.001$), and the inverse association with CVD mortality was stronger than that with all-cause mortality. In women, the multivariate hazard ratios of CVD mortality across increasing green tea consumption categories were 1.00, 0.84, 0.69, and 0.69, respectively ($P = 0.004$), with the strongest inverse association observed for stroke mortality (22). In the Rotterdam population-based follow-up study, incidence of myocardial infarction was lower in drinkers of black tea (RR = 0.57) than in nondrinkers (4). Further, tea drinkers showed reduced radiologically evident aortic atherosclerotic lesions (the odds ratio decreased from 0.54 in individuals drinking from 125 to 250 mL of tea, i.e., 1–2 cups/d, to 0.31 in individuals drinking >500 mL of tea, i.e., 4 cups/d) (23). In contrast, the Caerphilly Study showed no association between tea ingestion and ischemic heart disease incidence in 1900 Welsh men aged 45–59 y followed up for 14 y (24). Further, the Scottish Heart Health Study reported a slightly positive association between an increased tea consumption and all-cause mortality and coronary morbidity (25).

Many potential confounding factors might explain the above discrepancies: socioeconomic status and lifestyle pattern as well as baseline tea intake in the different national cohorts and the eventual different kinds and doses of teas. In awareness of these factors, the recent meta-analysis by Peters et al. (11) was based on 10 cohort and 7 case-control studies and reported an overall reduction of 11% in the incidence rate of myocardial infarction with an increase in tea consumption of 3 cups/d (1 cup = 237 mL) (fixed-effects RR estimate = 0.89). Thus, although data are not unequivocal, the possibility that either green or black teas might protect against CVD is supported by epidemiological evidence (3,4,5,7,19–30) (**Table 1**).

Tea, flavonoids, and endothelial function

The vascular endothelium is probably the most extensive tissue in the body, and its continuous smooth and nonthrombogenic surface forms a highly selective impermeable barrier (31–33). A single layer of endothelial cells lines the entire vascular system, and normality of both endothelial cell structure and functions are of great importance in the maintenance of vessel wall

[6] When not otherwise defined, 1 cup = 250 mL.

TABLE 1 Epidemiological evidence on the relation between tea and flavonoid intake and CVD[1]

Reference	Tea and/or flavonoids considered	Study design and population	Evidence	Relation[2]
Stensvold et al. 1992 (26)	Tea intake	Follow-up study (12 y; 9856 men and 10,233 women aged 35–49 y without CVD or diabetes)	Inverse association between tea intake and CHD and all-cause mortality	+
Brown et al. 1993 (27)	Tea intake	Cross-sectional follow-up study (2 y; 10,359 subjects aged 40–59 y)	Inverse dose-response effect on CHD (removed after adjustment for various risk factors)	−
Hertog et al. 1993 (3)	Flavonoid intake	Follow-up study (5 y; 805 men aged 65–84 y)	Inverse association with CHD mortality and MI incidence	+
Hertog et al. 1995 (7)	Flavonoid intake	Cross-cultural cohort follow-up study (25 y; 16 cohorts)	Inverse association with CHD mortality	+
Knekt et al. 1996 (28)	Flavonoid intake	Cohort follow-up study (25 y; 5133 patients aged 30–69 y without CHD)	Inverse gradient with total and CHD mortality	+
Keli et al. 1996 (21)	Flavonoid intake	Cohort follow-up study (15 y; 552 men aged 50–69 y)	Inverse association with stroke incidence after adjustment for potential confounders	+
Rimm et al. 1996 (29)	Flavonol and flavon intake	Prospective cohort study (6 y; 34,789 men aged 40–75 y)	Modest but non significant inverse association with CHD mortality	±
Hertog et al. 1997 (24)	Flavonol intake	Follow-up study (14 y; 1900 men aged 45–59 y)	Not inverse association with CHD risk	−
Yochum et al. 1999 (30)	Flavonoid intake	Prospective follow-up study (10 y; 34,492 postmenopausal women)	Inverse association with a decreased risk of CHD death but no association with stroke mortality	±
Sesso et al. 1999 (19)	Tea intake	Case-control study (340 subjects aged <76 y and controls)	Lower risk of MI	+
Woodward and Tunstall-Pedoe 1999 (25)	Tea intake	Cohort follow-up study (mean 7.7 y; >11,000 subjects aged 40–59 y)	Increasing tea consumption associated with detrimental effects on mortality and coronary morbidity.	−
Nakachi et al. 2000 (20)	Tea intake	Prospective cohort follow-up study (8552 subjects)	Decreased RR of CVD death	+
Geleijnse et al. 2002 (4)	Tea intake	Population-based follow-up study (mean 5.6 y; 4807 subjects aged ≥55 y without history of MI)	Inverse association with AMI (stronger for fatal than nonfatal events)	+
Mukamal et al. 2002 (5)	Tea intake	Prospective cohort follow-up study (median 3.8 y; 1900 patients with a confirmed AMI)	Inverse association with total and CVD mortality	+
Kuriyama et al. 2006 (22)	Tea intake	Prospective cohort follow-up study (mean 11 y; 40,530 subjects aged 40–79 y without CVD)	Inverse association with all cause and CVD mortality (the strongest for stroke)	+

[1] AMI, acute myocardial infarction; MI, myocardial infarction.
[2] +, positive relation between tea and/or flavonoid intake and decreased mortality; −, negative or no evident relation between tea and/or flavonoid intake and decreased mortality; ±, no complete relation between tea intake and/or flavonoid intake and decreased mortality.

integrity (31–33). In this regard, endothelial cells actively regulate vascular reactivity by responding to mechanical forces and neurohormonal mediators with the release of a variety of relaxing and contracting factors (31–34). The most important endothelium-derived vasodilator is represented by NO, an endogenous gas that is synthesized by NO synthase (NOS) starting from L-arginine. After diffusion from endothelial to vascular smooth muscle cells, NO increases intracellular cyclic guanosine monophosphate concentrations and then leads to vascular relaxation (32–34). NO is released from endothelial cells in response to shear stress, acetylcholine, and other stimuli and can profoundly affect both function and structure of the underlying vascular smooth muscle cells (31–36). Indeed, continuous production of NO by constitutive NOS maintains the vasculature in a state of vasodilation, whereas its phasic generation by inducible NOS can acutely dilate an artery in response to either physiological and pathological stimuli (31–36). However, NO is a reactive nitrogen compound and can be rapidly transformed into peroxynitrite ($ONOO^-$) by superoxide anion ($\cdot O_2^-$). In addition, $\cdot O_2^-$ and other endogenous oxidants

are able to favor NOS encoupling (31,33,37). In turn, encoupled NOS induces $\cdot O_2^-$ generation and then further decreases NO bioavailability and increases $ONOO^-$ formation (32,33,35,37). Finally, augmented $ONOO^-$ concentration decreases tetrahydrobiopterin, a fundamental cofactor in NO generation/activity, thereby further reducing NO bioavailability (37). Thus, an increased oxidative stress may result in a complete derangement of the NO system, with decreased NO bioavailability and a paradoxical NOS-related increment in oxidant generation. Because of the antiatherogenic, antithrombotic properties of NO (32–39) and the proatherogenic prothrombotic actions of endogenous oxidants (33,37,39), a decreased NO bioavailability with increased oxidative and nitrosative stress will result not only in impaired endothelium-dependent vasorelaxation and blood pressure regulation but also in the acceleration of atherogenesis and onset of acute atherothrombotic events (33–39) (**Fig. 1**). Thus, improved NOS activity and NO bioavailability and decreased oxidant generation, particularly of $\cdot O_2^-$ and $ONOO^-$, are both expected to protect the vessel wall and favor blood pressure homeostasis (33–39).

A number of studies have evaluated the effects of flavonoids on endothelial function. Polyphenols have been demonstrated to increase NOS activity in vascular endothelial cells (40). After the pioneering studies performed in rat aortic rings with various grape products (2,41), similar conclusions were reported from studies conducted in various animal and human isolated vessels using plant polyphenols from various sources, i.e., wine, cocoa, tea, and maritime pine bark (37). In all of these studies, plant polyphenols significantly increased endothelium-dependent vasodilation. We observed a dose-dependent vasorelaxing effect of epigallocatechin-3-gallate in rat isolated aortic rings precontracted by phenylephrine (**Fig. 2**). With respect to tea, Anter et al. (42) showed that black tea and black tea polyphenols promoted both endothelial NOS catalytic activity and NO bioavailability in cultured vascular endothelial cells. Recently, Jochmann et al. (43) also reported that both green and black teas significantly increased endothelial NOS activity in bovine aortic endothelial cells. Similar findings were described in rat aortic rings (43). In vivo, both teas increased endothelium-dependent vasodilation in healthy women (43). Indeed, ingestion of green and black teas led to significant increments in brachial artery flow-mediated, i.e., NO-mediated, dilation (FMD) (from baseline 5.4 ± 2.3% to 10.2 ± 3% 2 h after green tea consumption and from baseline 5 ± 2.6% to 9.1 ± 3.6% 2 h after black tea consumption, $P < 0.001$), respectively. The observed increments in FMD were not significantly different between the black and green tea preparations (43).

In support of this, we have observed a significant dose-dependent increment of brachial artery FMD in healthy volunteers who drank an extract of commercial black tea (Lipton Yellow Label) for a short period of time in a placebo-controlled double-blind study (data not shown). Accordingly, Duffy et al. (44) also found that both acute and prolonged black tea ingestion—i.e., either 450 mL of black tea given as a single dose or 900 mL/d of black tea given over a period of 4 wk—significantly improved FMD in patients with coronary artery disease. Of particular relevance, the positive effects of tea on FMD were clearly related to significant increments in plasma flavonoid concentration, thereby strongly supporting the conclusion that black tea consumption markedly improved NO bioavailability in vivo because of its high flavonoid content. In a randomized controlled parallel study, Hodgson et al. (45) showed a significant and consistent increase in endothelium-dependent vasodilation after regular consumption of 5 cups/d (250 mL each) of black tea, given over a period of 4 wk in mildly dyslipidemic subjects.

Of interest, Widlansky et al. (46) also examined the effects of dietary supplementation with epigallocatechin gallate on endothelial function in patients with coronary artery disease and observed an acute increase in FMD (from 7.1 ± 4.1% to 8.6 ± 4.7% after the administration of 300 mg epigallocatechin gallate, $P = 0.01$). In agreement, Ardalan et al. (47) observed that short-term consumption of black tea significantly increased FMD ($P < 0.05$) in renal transplant recipients. Therefore, although the study conditions were different, Hodgson et al. (48) showed no significant acute effects of black tea on endothelial function. The majority of available data support the evidence that teas and flavonoids from tea are able to improve NO bioavailability and thereby increase endothelium-dependent vasorelaxation in healthy subjects as well as in various pathological conditions (43–48). In addition to the vascular benefits from tea, a number of clinical supplementation studies with flavonoid-rich foods demonstrate that high intake of flavonoids can have a favorable impact on endothelial function, showing that flavonoids can improve endothelium-dependent vasodilation. More specifically, this effect has also been documented with

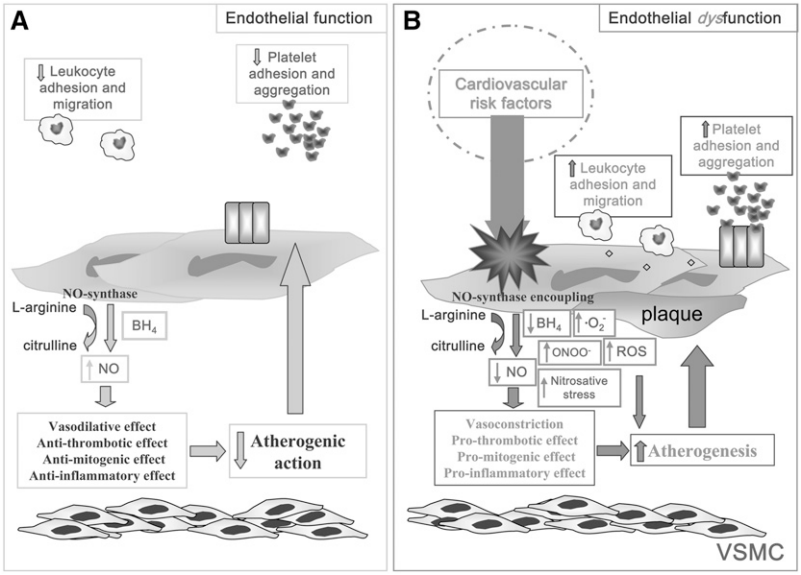

FIGURE 1 Endothelial cells have a major role in the regulation of vascular tone through production of several vasoactive mediators. Constitutive production of NO by the endothelial cells maintains the vasculature in a state of vasodilation and inhibits the recruitment and adhesion of inflammatory cells as well as platelet adhesion and aggregation (*A*). In the presence of cardiovascular risk factors, NO bioavailability is reduced, thus favoring the onset of atherosclerotic lesions (*B*). ROS, reactive oxygen species; VSMC, vascular smooth muscle cells.

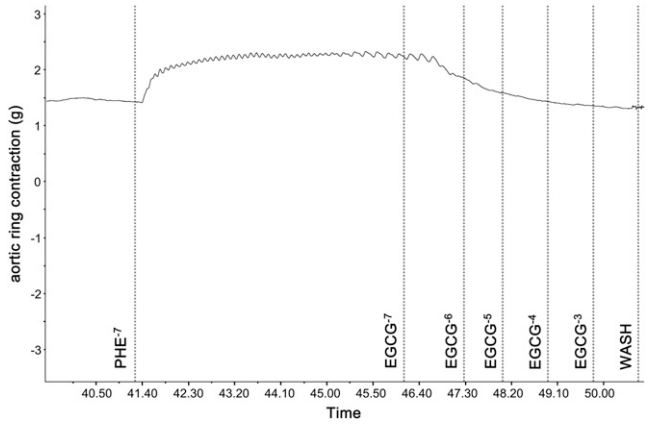

FIGURE 2 Dose-dependent vasorelaxing effect of epigallocatechin-3-gallate (1×10^{-7}, 1×10^{-6}, 1×10^{-5}, 1×10^{-4}, 1×10^{-3} mol/L) in rat isolated aortic rings precontracted by phenylephrine (D. Grassi, A. Aggio, L. Onori, and C. Ferri, unpublished data).

red wine, alcohol-free red wine, polyphenol-rich red wine extracts, purple grape juice, grape seed extract, dark chocolate bars, and an encapsulated fruit and vegetable concentrate derived from freeze-dried juices. In particular, the study using fruit and vegetable concentrate found that presupplementation with this product for 4 wk ameliorated the acute adverse impact of a single high-fat meal on flow-mediated vasodilation in the brachial artery with a parallel increase in serum nitrate plus nitrite concentration by ~40% during supplementation with the active product (49).

Tea, flavonoids, and blood pressure

Oral administration of an alcohol-free grape skin extract significantly decreased systolic, mean, and diastolic blood pressure levels in distinct rodent hypertension models (50). In the rat isolated mesenteric vascular bed precontracted with norepinephrine, bolus injections of grape skin extract markedly increased endothelium-dependent vasodilation that was substantially inhibited by N(G)-nitro-L-arginine methyl ester, a well-established NOS inhibitor (50). Concordant to the apparently NO-dependent decrements of blood pressure described in rats supplemented with grape skin extracts, Negishi et al. (51) reported significant decrements in daytime monitored systolic and diastolic blood pressure levels after the administration of tea polyphenols from both black (3.5 g/L thearubigins, 0.6 g/L theaflavins, 0.5 g/L flavonols, and 0.4 g/L catechins) and green (3.5 g/L catechins, 0.5 g/L flavonols, and 1 g/L polymeric flavonoids) teas in stroke-prone spontaneously hypertensive rats.

In humans, Stensvold et al. (26) indicated that systolic blood pressure levels were inversely related to tea ingestion. Of note, in this study conducted in 9,856 men and 10,233 women without history of CVD or diabetes from the county of Oppland in Norway, deaths from CHD and all-cause mortality rate were both slightly higher among persons drinking no tea or <1 cup/d of tea compared with persons drinking ≥1 cup/d (26). In a community-based study involving 1507 Taiwanese subjects ≥20 y (52) compared with nonhabitual tea drinkers, the risk of developing hypertension decreased by 46% for those who drank 120 to 599 mL/d of tea and was further reduced by 65% for those who drank ≥600 mL/d of tea after careful adjustment for age, sex, socioeconomic status, family history of hypertension, body mass index, waist-to-hip ratio, lifestyle, and dietary factors. According to this, Hodgson et al. (53) investigated the relation between tea intake and urinary 4-O-methylgallic acid excretion, a biomarker of total exposure to tea polyphenols, and blood pressure levels in a cross-sectional study of 218 older women and observed that higher tea intake and 4-O-methylgallic acid excretion were both associated with significantly lower systolic ($P = 0.002$ and $P = 0.040$, respectively) and diastolic ($P = 0.027$ and $P < 0.001$, respectively) blood pressure levels. In particular, a 250 mL/d (1 cup) increase in tea intake was associated with a 2.2 mmHg lower systolic and a 0.9 mmHg lower diastolic blood pressure level. Additionally, a recent meta-analysis (54) of 5 randomized controlled trials of cocoa involving 173 subjects with a median duration of 2 wk showed that pooled mean systolic and diastolic blood pressure levels were decreased after cocoa ingestion by 4.7 mmHg ($P = 0.002$) and 2.8 mmHg ($P = 0.006$), respectively. In contrast, the same meta-analysis also evaluated 5 studies of tea consumption involving a total of 343 subjects with a median duration of 4 wk and showed that tea intake had no effects on blood pressure levels. Indeed, the estimated tea-related pooled blood pressure changes were only +0.04 mmHg ($P = 0.63$) for systolic and −0.6 mmHg ($P = 0.38$) for diastolic levels.

Thus, although different reports seem to support a blood pressure-lowering effect induced either by tea or flavonoids from tea, the pooled meta-analysis of 5 studies contrasts somewhat with the existence of a significant tea-related decrement of blood pressure levels. However, in this case, too, discrepancies could be caused by divergent study design, brief study duration, inhomogeneity in evaluated populations, and disparate kinds of tea preparations. Further, it is evident that 5 studies and only 343 subjects are too few for deriving definite conclusions. Thus, further controlled studies are needed to define the exact role of black and green teas as beverages with blood pressure-lowering effects.

The ability of flavanols to activate endothelial NOS and then improve NO bioavailability is likely to represent the primary mechanism underlying the blood pressure reduction observed in different human studies (50,55–57), and the same mechanism has been strongly implicated as the main process responsible for the blood pressure-lowering effects exerted by either short-term (55,56) or long-term (57) cocoa administration. On the other hand, flavonoids from tea might also act to reduce blood pressure levels by modulating the renin-angiotensin-aldosterone system (58,59). In fact, Actis-Goretta et al. (58) reported that flavanols can inhibit angiotensin-converting enzyme (ACE) activity in homogenized rat kidney (58), and Persson et al. (59) showed a significant and dose-dependent inhibition of ACE activity in cultured human umbilical vein endothelial cells (HUVEC) after incubation with both green and black teas. A dose-dependent inhibition of ACE activity was also observed in HUVEC after incubation with (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechingallate, and (−)-epigallocatechingallate (59) and combined to yield a significant dose-dependent increment in NO production (59). Thus, experimental data from both in vivo and in vitro reports suggest that tea presents with all the biological potential to reduce blood pressure in humans and strongly indicate that further clinical investigation on the matter is needed.

The clinical relevance of the endothelium-dependent effects of plant polyphenols is likely dependent on their systemic availability. Thus, in vitro effects should always be compared with in vivo experiments. The review of epidemiological and mechanistic studies suggests that flavonoids, and particularly tea flavanols, manifest beneficial effects on the cardiovascular system and protect against the risk of CVD. Several lines of clinical

and experimental evidence also indicate that tea flavanols may protect against CVD by improving endothelial function, increasing NO bioavailability, and decreasing blood pressure levels, thereby suggesting fascinating new realms for dietetic cardiovascular prevention. Therefore, although the results from epidemiological and experimental studies are not always consistent, we completely agree with the American College of Cardiology Foundation Task Force (60), which concluded that recommending moderate amounts (1 – 2 cups/d) of tea ingestion in addition to general nutritional advice may well be justified for cardiovascular risk reduction. We also support the new proposed guidance for beverage consumption (61), in which unsweetened tea (the only limitation being in caffeine, which should not exceed 400 mg/d) is the most suggested beverage after water. As we concluded in a recent editorial (62), the Mediterranean diet is the best available diet for correct cardiovascular prevention; over recent decades, however, it has been detrimentally polluted by the addition of commercial snacks, junk food, etc. In contrast, foods and beverages such as cocoa and tea are likely to add positively to the fundamentally beneficial properties of the traditional Mediterranean diet, thereby indicating that a correct diet, and a correct lifestyle, can be neither illegal, nor immoral, nor fattening (63), and can even ameliorate life quality.

Other articles in this supplement include references (64–73).

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