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Review

The role of tea and tea flavonoids in cardiovascular health

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Consumption of green or black tea has been inversely associated with the development and progression of cardiovascular diseases. In this review, the current knowledge about protective effects of tea and tea constituents, particularly flavonoids, on the cardiovascular system is summarized. Underlying mechanisms for the beneficial effects of tea include vasculoprotective, antioxidative, antithrombogenic, anti-inflammatory, and lipid-lowering properties of tea flavonoids. Although promising experimental data on beneficial effects of tea in various cardiovascular diseases are available, results of clinical studies in humans are not uniform. A number of factors are discussed which may contribute to inconsistent data in humans. Overall, tea represents a promising tool for the prevention and treatment of cardiovascular disorders.

Keywords: Atherosclerosis / Cardiovascular / Endothelial function / Flavonoids / Tea

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1 Introduction

Tea in its various processed forms – *i.e.* non-fermented green tea; partly-fermented oolong tea; and fermented black tea – represents, after water, the most widely consumed beverage in the world. Tea contains large amounts of polyphenolic compounds with important biological activities. These polyphenolic substances (flavonols) exert a great variety of physiological actions and are held partly responsible for the favorable health properties of tea, which include the reduced risk of cardiovascular diseases with high intake of tea. An increasing number of epidemiological and experimental studies have established a positive correlation between the consumption of green and black tea and protection against atherosclerosis and cardiovascular diseases. Despite the established positive health effects of tea, however, little is known about the molecular mechanisms responsible for the protective effects of tea in the process of atherogenesis. There are, nevertheless, strong indications that antioxidative, antithrombogenic, and anti-inflammatory properties of catechins – the most prominent biologically active compounds in green tea – are involved.

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Abbreviations: CAD, coronary artery disease; **EC**, epicatechin; **EGC**, epigallocatechin; **ECG**, epicatechin gallate; **EGCG**, epigallocatechin gallate; **eNOS**, endothelial nitric oxide synthase; **LDL**, low-density lipoprotein; **NO**, nitric oxide; **VSMC**, vascular smooth muscle cells

2 Main constituents of tea

Tea leaves originating from *Camellia sinensis* contain a large amount (30% of the dry substance) of polyphenols, mainly flavonoids, which are characterized as containing two or more aromatic rings, each bearing at least one aromatic hydroxyl connected with a carbon bridge [1]. In both black and green tea the major class of flavonoids are flavanols, which include catechin, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG). Quercetin, kaempferol, and several other polyphenols are also components of tea [2]. Content and composition of the constituents, including the catechins, vary substantially among the various teas, depending on the degree of fermentation (green, black, and oolong tea) and on the individual mode of preparation. Although the total content of polyphenols in green and black tea is comparable, the compositions of the individual compounds differ. The manufacturing process is designed to either prevent or allow tea polyphenols to be oxidized by naturally occurring polyphenol oxidase enzymes in the leaves. The object

in the production of green tea is to avoid the oxidation of polyphenols. In contrast, black tea is produced by promoting enzymatic oxidation of tea polyphenols. During this process, catechins are oxidized to complex theaflavins. The flavor of black tea results from fermentation. The partly fermented oolong tea represents an intermediate between black and green tea.

In green tea, catechins constitute about 80–90%, and flavanols about 10% of total flavonoids [3]. EGCG represents, with 48–55%, the most abundant catechin in green tea. EGCG and the other catechins EC (5–7%), EGC (9–12%), and ECG (9–12%) predominantly account for the biological effects of green tea [4]. During the oxidative process that occurs during the production of black and oolong tea, flavanols are converted primarily into thearubigins and, to a lesser extent, into theaflavins, which are complex condensation products of tea polyphenols. Whereas these theaflavins and thearubigins account for 10% and 50–60% of total flavonoids in black tea, respectively, catechin content is only 20–30% [3]. The content of catechins in black tea is around 30% of that in green tea. A cup of green tea contains between 20 and 100 mg of EGCG.

3 Atherosclerosis/coronary artery disease (CAD)

3.1 Epidemiological data

There is considerable epidemiological evidence that tea consumption reduces the risk of cardiovascular diseases and total mortality [5–8]. In the Zutphen Elderly Study, 5-year mortality was reduced by 50% in elderly tea drinkers in the Netherlands [6, 9]. Data from the Onset Study, a multicenter prospective cohort study of early survivors of acute myocardial infarction, revealed that self-reported tea consumption during the year before infarction was associated with lower subsequent mortality after myocardial infarction [10]. Likewise, an inverse association between flavanol intake and coronary heart disease and mortality was found after a 25-year follow-up of 12 763 men from the Seven Country Study [8]. Consistent with these observations, the Oppland County Study and the Boston Area Health Study both indicated an inverse correlation between black tea consumption and the risk of coronary heart disease [11, 12]. In addition, the prospective Rotterdam study reported that tea consumption was inversely associated not only with the incidence but also with the severity of atherosclerosis. This risk reduction was more pronounced in women than in men [13]. Nakachi *et al.* [5] investigated a cohort of 8552 Japanese and found a more than 40% reduction in cardiovascular mortality in men, and a beneficial trend in women. For green tea, there is some evidence that higher tea intake lowers the incidence of CAD [14].

However, data are not uniform: other studies have failed to show beneficial effects of tea [15–17]. Thus, in a population of 17 228 college alumni, tea intake – most likely consumed as black tea – was not strongly associated with a reduced risk of cardiovascular disease [18]. Similarly, Hertog *et al.* [16], monitoring Welsh population (334 men, 45–59 years of age) throughout 14 years, reported no association of tea intake and incidence of CAD. In this study, as well as in the Scottish Heart Health Study, a rather positive association of tea consumption and all-cause mortality became apparent [16, 17].

A meta-analysis of 17 studies (10 cohort and 7 case-control studies) by Peters *et al.* [19] investigated the association between tea intake in relation to stroke, myocardial infarction, and coronary heart disease. The authors reported that the study-specific effect estimates for stroke and coronary heart disease were too heterogeneous to be summarized. Only the relative risk estimates for myocardial infarction (seven studies) were reasonably homogeneous: the incidence rate of myocardial infarction was estimated to decrease by 11% with increase in tea consumption by three cups *per* day. The authors presumed that the geographic regions, in which the studies have been conducted, may explain much of the heterogeneity of the study results. Thus, with increasing tea consumption, the risk of coronary heart disease in the United Kingdom and for stroke in Australia increased, whereas the risk in other regions, particularly in Continental Europe, decreased [19]. In addition, interactions with lifestyle factors have to be considered as underlying reasons for these discrepant results. It is conceivable that regular tea drinkers differ in other lifestyle aspects that affect CAD risk: *e.g.*, nutritional habits and smoking. Thus, in Welsh and Scottish studies tea consumption was positively associated with a lower social class and a higher prevalence of risk factors [16, 17]. In contrast, tea drinkers from the Netherlands belonged to higher social classes and conducted a healthier lifestyle [6, 9].

Although the kind of tea used in the studies is frequently not reported, it can be presumed that results from East Asian cohorts are derived predominantly from consumption of green tea, whereas the results from European and American cohorts originate more likely from black tea.

3.2 Experimental models of atherosclerosis

Tea consumption has been inversely associated with the development and progression of atherosclerosis in various experimental settings. In cholesterol-fed rabbits supplementation of green tea through drinking water achieved a slight, nonstatistically significant reduction in atherosclerotic plaque formation; black tea at the same dose was without effect [20]. Chronic ingestion of tea extract (mainly catechins) prevented the accumulation of aortic cholesterol and triglycer-

ides as well as atheroma formation in the aorta of apoE-deficient mice fed an atherogenic diet, without changing plasma lipid concentrations [21]. Whereas, in this study, the dose of catechins applied to mice was equivalent to 50–60 cups of tea/day taken in a Japanese population, a recent investigation of long-term supplementation with green or black tea in a hamster model of atherosclerosis applied human equivalent doses. Both green and black tea were equally effective in inhibiting atherosclerosis in this model and likewise reduced risk factors in control animals [22]. Chyu *et al.* [23] showed recently that EGCG (intraperitoneal injection) effectively reduced the progression of accelerated atherosclerotic carotid plaque formation induced by cuff injury in apoE-deficient mice, whereas it had no effect on advanced aortic plaques from the same animals. In this study, EGCG enhanced systemic and local antioxidative capacities. The authors concluded that EGCG therapy would be effective only when initiated during a critical window in the temporal evolution of atherosclerotic plaques.

3.3 Antioxidative mechanisms

In general, mechanisms that have been suggested for being involved in the prevention of coronary heart disease by tea consumption primarily entail the powerful radical-scavenging and antioxidative properties of flavonoids from green and black tea. Tea polyphenols are antioxidants by virtue of the number and arrangement of their phenolic hydroxyl groups [24]. *In vitro*, they have been shown to scavenge reactive oxygen and nitrogen species including superoxide, peroxyl radicals, singlet oxygen, peroxynitrite, and hypochlorous acid in a structure-dependent manner [24, 25]. In addition, ability of tea flavonoids to chelate metal ions, to prevent the activation of redox-sensitive transcription factors (nuclear-factor-κB, activator protein-1), and to inhibit prooxidant enzymes may contribute to their antioxidative capacity [25]. In general, green tea has been found superior to black tea in terms of antioxidative activity, owing to the higher content of (–) EGCG. Lee *et al.* [26] measured the total phenol content and antioxidative capacity of commercial tea products. They reported that the antioxidative activity of tea catechins differs (EGCG $\cong$ ECG > EGC > EC) and that the antioxidative capacity *per* serving of green tea (436 mg of vitamin C equivalents) is much higher than that of black tea. For extracted tea constituents, Leung *et al.* [27] showed that theaflavins present in black tea possess at least the same antioxidant potency as catechins present in green tea.

The strong antioxidant property of tea may be one explanation for its protective effect during the development of atherosclerosis. Oxidative modification of low-density lipoprotein (LDL) is one of the critical steps for the development of atherosclerosis. Tea flavonoids have been shown to inhibit LDL oxidation – possibly by reducing macrophage superoxide production [28] – thereby preventing the formation of foam cells in atherosclerotic lesions [29, 30]. Polyphenols from green tea may prevent endothelial cell-mediated LDL lipid peroxidation and may accordingly inhibit heme oxygenase, which has been linked with the transformation of monocytes to resident macrophages [31, 32].

In contrast to the evident effects of tea flavonoids against LDL oxidation *in vitro*, the effects of green or black tea ingestion on LDL oxidation in animal and human studies are less clear. On the one hand, tea intake has been shown to decrease the susceptibility of LDL oxidation in animal models of atherosclerosis usually by prolonging the lag phase of copper-mediated lipid peroxidation [25, 33]. On the other, no effects of tea components on plasma lipid and antioxidant levels as well as on LDL oxidation have been found in a number of other animal studies [20, 25, 34]. The same applies for studies in humans [35]. The antioxidant activity of tea *in vivo* has been extensively studied; however, results obtained from dietary intervention studies are controversial. One cup of green or black tea has been shown to increase plasma antioxidant potential by 40–50% [36]. The effects of two cups of green tea (containing approximately 250 mg of total catechins) consumed within the context of a balanced, controlled diet to improve the antioxidative status in healthy volunteers (*i.e.*, increase in plasma total antioxidant activity, decrease in plasma peroxide level, induction of DNA damage in lymphocytes, decrease in LDL-cholesterol) [37]. Ingestion of four cups of green tea daily for 4 wk decreased plasma concentrations of oxidized LDL in human volunteers [38]. Other studies found no or only slight increase in antioxidant potential after tea consumption [39–43].

In conclusion, *in vitro* data and results of animal studies favor the assumption that tea flavonoids act as natural antioxidants with possible relevance as antiatherogenic agents. Human studies, however, are controversial and do not allow reliable conclusions on possible beneficial antioxidant effects. Discrepant results may be explained by the inability to achieve sufficiently high concentrations of the effective compounds *in vivo*. Thus, interindividual variations may be relevant in the bioavailability of polyphenols, owing to differences in intestinal absorption or metabolizing enzymes. Moreover, confounding factors such as lifestyle could be important. It is essential to remember that interpretation of data from experimental models and transfer to the clinical setting require a good deal of caution, since most of these studies in animal models were done with rather high doses.

3.4 Endothelial function

As a major regulator of vascular homeostasis, the endothelium is associated with a number of protective effects, such as vasodilation, inhibition of proliferation and migration of

smooth muscle cells, as well as prevention of inflammatory responses. Most of these effects are mediated by nitric oxide (NO). Reduced production or bioavailability of NO leads to endothelial dysfunction. There is accumulating evidence that endothelial dysfunction is one of the initial steps in atherogenesis, even before structural changes in the vessel wall become apparent. In addition, the existence of endothelial dysfunction has been linked to future cardiovascular events. Substances, able to prevent damage to endothelial cells or to restore endothelial function (such as has been shown for statins) may have important clinical implications. Experimental and clinical data suggest that tea constituents significantly ameliorate endothelial function, thereby providing a plausible mechanism for the beneficial effects of tea in patients with cardiovascular diseases [44, 45]. Duffy *et al.* [45] showed in a randomized crossover trial that black tea consumption reverses endothelial dysfunction in patients with documented CAD. Both acute (2 h) and chronic (4 wk) tea consumption ameliorated flow-mediated dilation in association with increased catechin concentrations. In participants with a history of CAD, drinking three cups of black tea in conjunction with a meal increased flow-mediated dilation after 4 h [46]. *In vitro*, purified catechins from tea evoked endothelium-dependent vasorelaxation in precontracted rat aortic rings *via* NO release from the endothelium [44, 47]. We have recently provided insights into possible molecular mechanisms involved in these vasculoprotective effects. We showed that endothelium-dependent vasorelaxation induced by the tea-derived catechin EGCG occurs in response to significant, dose-dependent activation of the endothelial nitric oxide synthase (eNOS) in endothelial cells. EGCG-induced endothelium-dependent vasodilation was primarily caused by rapid phosphorylation and activation of eNOS through a phosphatidylinositol 3-kinase-, PKA-, and Akt-dependent pathway, independently of an altered eNOS protein content [47] (Fig. 1). Subsequently, it was shown by another group that the polyphenolic fraction of black tea phosphorylated and activated eNOS *via* a p38 MAPK-estrogen receptor-alpha-dependent pathway in endothelial cells [48]. Accordingly, EGCG and black tea polyphenols act as a natural activator of eNOS in endothelial cells by enhancing its protein phosphorylation.

Despite the experimental evidence of protective vascular effects of catechins, results on vasorelaxation in isolated aortic rings are not consistent. Both, no effects on vasoreactivity and opposite effects in terms of vasoconstriction have been described [49–51]. Although these *ex vivo* data with isolated rings are in some way not uniform, human studies suggest that tea polyphenols may improve endothelial function in men.

3.5 Anti-inflammatory and antiproliferative effects

Another hypothesis has been proposed to explain the beneficial effects of tea beverages in CAD, namely that anti-inflammatory properties of tea constituents might be involved in protective antiatherogenic effects. Inflammation plays a key role in CAD and other manifestations of atherosclerosis. Immune cells dominate in early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. Green tea has been shown to have preventive effects in chronic inflammatory diseases [52, 53]. Sueoka *et al.* [53] treated TNF-alpha transgenic mice, which overexpress TNF-alpha only in their lungs, with green tea (in drinking water) and found that expression of TNF-alpha and IL-6 was inhibited in the lungs of these mice after treatment with green tea for 4 months. Since TNF-alpha is known to be a central mediator in inflamma-

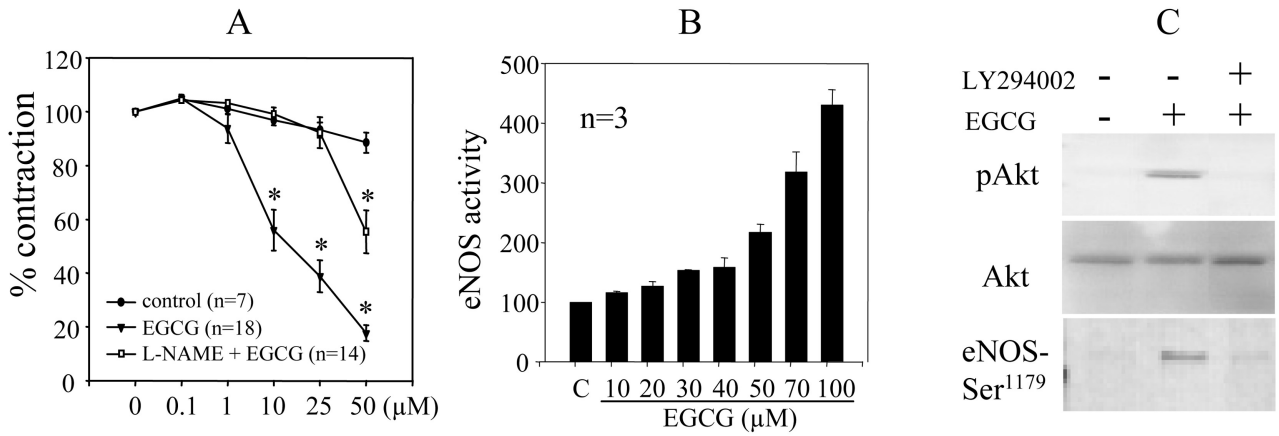

Figure 1. Cumulative doses of EGCG lead to NO-dependent vasorelaxation in rat aortic rings (A), and a dose-dependent increase in eNOS activity in endothelial cells (B). Increase in eNOS activity is caused by a PI3 kinase-, Akt-dependent phosphorylation of eNOS (C). *$p < 0.05$ by Mann–Whitney test; *N*(omega)-nitro-L-arginine methyl ester (L-NAME), nitric oxide synthase inhibitor; LY294002, PI3 kinase inhibitor (reproduced from Lorenz *et al.* [47]).

tory disorders, such as in atherosclerosis, the authors hypothesized that green tea may represent a preventive agent for chronic inflammatory diseases.

Inflammation of the vessel wall, activation of the vascular endothelium, increased adhesion of mononuclear cells to the injured endothelial layer, and their subsequent extravasation into the vessel wall are initial events in atherogenesis. Catechins have been shown to suppress neutrophil infiltration by a direct action on neutrophils including the suppression of chemokine production at the inflammatory site [54]. Furthermore, catechins interfere with endothelial leukocyte interaction *in vitro*. Thus, EGCG at physiological concentrations inhibited neutrophil migration through cultured human endothelial monolayers [55]. Metabolites of (+)-catechin reduced U937 cell adhesion to human aortic endothelial cells [56]. We have recently shown that EGCG, the major flavonoid in green tea, selectively prevents cytokine-induced VCAM-1 expression and reduces monocyte adhesion to endothelial cells independently of NF-κB activation. EGCG prevented induction of VCAM-1 expression in a concentration-dependent manner after stimulation with two different cytokines. ECG proved less effective than EGCG, whereas the two other catechins, EC and EGC, were without effect [57]. It has been suggested that the gallate group plays an important role in modulating adhesion molecule expression in endothelial cells [58]. The results of our study support the hypothesis that only tea extracts containing a gallate group significantly reduce adhesion molecule expression. Since VCAM-1 is one of the key molecules involved in the early atherogenic process, our data call attention to an additional mechanism by which tea catechins may exert antiatherogenic effects. In line with the above data, daily drinking of four cups of green tea in human volunteers for 4 wk reduced plasma levels of soluble P-selectin, another endothelial adhesion molecule implicated in the process of atherogenesis [38].

Proliferation and migration of vascular smooth muscles cells (VSMC) from the media to the subendothelial space are major events in the development of atherosclerosis, and particularly of restenosis, after balloon angioplasty. Several lines of evidence demonstrate that tea components interfere with processes of proliferation and migration. Thus, EGCG treatment has been shown to reduce VSMC growth and to arrest VSMC in the G1 phase of the cell cycle. PCNA, a marker of cell growth, was also inhibited by EGCG *in vitro* [23]. Green tea polyphenols suppressed SMC DNA synthesis [59] and inhibited advanced glycation end products (AGE)-induced proliferation and p44/42 MAPK expression of rat VSMC [60]. Platelet-derived growth factor, which plays an important role in proliferation, was inhibited by ECG, EGC, and EGCG [61]. In a rat model of restenosis, local delivery of either a mixture of tea catechins or EGCG alone led to a significant reduction in neointimal formation *via* inhibition of VSMC proliferation [62]. Recent data suggest that green tea extracts and catechins also prevent SMC migration most likely by inhibiting matrix metalloproteinase-2 (MMP-2) expression and its activation by direct inhibition of MT1–MMP [63]. In addition, EGCG prevented TNFα-induced expression of matrix metalloproteinase-9 (MMP-9), a critical factor in the progression of atherosclerotic lesions, in VSMC [64]. The ability of tea components to prevent cell invasion and matrix degradation may contribute to their antiatherogenic potential [65].

3.6 Antithrombotic effects

Other putative mechanisms involved in beneficial cardiovascular effects of tea ingredients are potent antithrombotic effects. The interaction between platelets and the vessel wall is important in the development of acute cardiovascular events. In the presence of vascular/endothelial injury, platelet aggregation occurs rapidly to form hemostatic plugs and arterial thrombi. These thrombi may be sources of acute events such as myocardial infarction or stroke.

Antithrombotic mechanisms of tea products are more probably due to antiplatelet effects; coagulation parameters are in all likelihood not changed. Green tea extracts prolonged bleeding time in mouse tails and inhibited ADP-, collagen-, and calcium-ionophore-induced human platelet aggregation *in vivo* in a dose-dependent manner [66]. The inhibitory effects of tea flavonoids on platelet aggregation appear to be partially mediated by inhibition of cytoplasmic calcium release, which leads to inhibition of fibrinogen GPIIb/IIIa binding *via* activation of $Ca(2^+)$ ATPase and inhibition of inositol 1,4,5–triphosphate (IP_3) formation [67]. Flavonoid-induced suppression of cyclooxygenase activity and prevention of arachidonic acid liberation (thereby inhibiting thromboxane A_2 formation) have been proposed as underlying mechanisms [68, 69]. Finally, theaflavin and its galloyl esters in black tea extract and isoprenyl gallates, as well as green tea catechins, have been shown to be potent inhibitors of PAF synthesis and platelet aggregation [70, 71]. These activities may be relevant to the claimed antiplatelet effects of tea beverages.

3.7 Lipid profile

Hyperlipidemia is a major risk factor for the development of cardiovascular disease and considerable evidence suggests that drugs with the ability to lower LDL-cholesterol also reduce the probability of cardiovascular death. Numerous experimental investigations have suggested that tea is associated with beneficial effects on lipid profile and with reductions of atherosclerotic lesions in various animal models of hyperlipidemia [21, 29, 72]. Although the underlying

mechanisms for the lipid-lowering effect of tea are not fully elucidated, there is some evidence that tea catechins – in particular their gallate esters – reduce cholesterol absorption from the intestine by lowering the solubility of cholesterol in mixed micelles [73]. In a cholesterol-fed hamster model, Vinson *et al.* [33] found that black and green tea consumption significantly reduced cholesterol plasma levels by 20 and 28%, respectively. HDL-cholesterol was significantly increased (black tea 35%, green tea 88%), and triglycerides were decreased (20, 48%) by both teas. Similarly, a diet supplemented with 1% black tea polyphenols decreased lipid levels in the plasma of rats fed a lard/cholesterol diet [74].

Despite these favorable results from animal experiments, results of human studies regarding the effects of tea on plasma lipids are not uniform. In one study, green or black tea consumption of 0.9 L/day did not significantly change plasma lipids after 4 wk, as compared to water control in healthy volunteers [43]. In another study, black tea (six mugs/day) induced no changes in lipids or blood pressure in men and women [75], and a cross-sectional study in Japan found no beneficial effects of green tea on serum lipid levels [76]. On the other hand, Kono *et al.* [77] reported a nonsignificant inverse relationship between green tea and total cholesterol, and a Norwegian study described a negative correlation between black tea consumption and cholesterol levels in 9856 men and 10 233 women without history of cardiovascular diseases or diabetes [11].

A recent study evaluated in a randomized triple cross-over design the effects of tea catechins on postprandial lipid responses in humans. Nine male subjects with mild or borderline hypertriacylglycerolaemia consumed 10 (control), 224 (moderate dose), and 674 mg (high dose) of the assigned tea catechins three times, along with a standardized light meal (bread and 20 g butter). Moderate and high doses of tea catechins reduced incremental area under the plasma triacylglycerol curves by 15 and 29%, respectively [78]. Another study investigated in a double-blind, randomized, placebo-controlled trial the effects of theaflavin-enriched green tea extract on lipids and lipoproteins of subjects with mild to moderate hypercholesterolemia. After 12 wk, total cholesterol (–11%) and LDL-cholesterol (–16%) were significantly decreased in the tea extract group compared to control, suggesting that tea might be an effective supplement to a low saturated-fat diet for reduction of LDL-cholesterol in hypercholesterolemic adults [79].

In conclusion, lipid-lowering effects of tea in humans are, for the most part, moderate. The discrepancies between experimental data and clinical studies may again be explained by the fact that most animal studies were performed with doses of tea or tea components higher than used in human studies. Further randomized controlled studies are necessary to confirm putative beneficial lipid-lowering effects of green and black tea beverages.

4 Hypertension/hypertrophy

4.1 Hypertension

Hypertension is one of the major cardiovascular risk factors associated with CAD, stroke, and congestive heart failure. Hypertension accounts for 20–50% of all causes of cardiovascular death. A link between tea consumption and hypertension has been investigated in a number of epidemiological studies with, however, conflicting results.

Short-term consumption of tea has rather negligible effects on blood pressure. Ingestion of five or more cups of green or black tea *per* day failed to influence blood pressure in Australian and British studies [75, 80]. Green tea consumption was not correlated with blood pressure in a study of 3336 middle-aged men in Japan [81].

Studies investigating long-term effects postulate antihypertensive properties of tea beverages [11, 82]. Black tea consumption was related to lower systolic blood pressure in a Norwegian population [11]. Likewise, Yang *et al.* [82] reported that habitual moderate green or oolong tea consumption for at least 1 year significantly reduces the risk of developing hypertension in a Chinese population. The risk of developing hypertension decreased by 46% with the intake of 120–599 mL/day and was further reduced by 65% with ingestion of at least 600 mL/day. Interestingly, nonhabitual tea drinkers in this study were at higher risk for hypertension than habitual consumers. In an animal model of stroke-prone spontaneously hypertensive rats, consumption of green and black polyphenols for 3 wk equally attenuated the increase in blood pressure observed in the water control group [83].

Since tea also contains caffeine, which is associated to a certain extent with an increase in arterial pressure, caffeine may antagonize blood pressure effects of polyphenols contained in tea beverages. Hodgson *et al.* [80] have shown that tea (four standard cups containing 180 mg caffeine) transiently increased blood pressure more than caffeine alone (180 mg) in people who fasted and avoided caffeine for >12 h. Interestingly, this acute pressure effect was abolished when tea was consumed after a meal. The authors concluded that the capacity of food to modulate effects of tea on blood pressure, observed in the fasting state, may help to explain the partially discrepant study results [46, 84].

Several underlying mechanisms for the reduction in blood pressure have been discussed. The vasodilator and antioxi-

dant effects of polyphenols described above appear to be important. In particular, sustained improvement in endothelial function may contribute to lower blood pressure [85, 86].

4.2 Hypertrophy

Hypertrophy develops as a consequence of cardiac overload induced by chronic hypertension. It is characterized by an increase in heart weight compared to body weight and ultimately leads to heart failure.

In a rat model of chronic renal failure leading to hypertrophy, supplementation of green tea extracts to the animals for 4 wk attenuated the increase in heart weight and left ventricular hypertrophy [87]. The increase in blood pressure observed in the control animals was attenuated in the green tea group. In isolated cardiac myocytes from the same animals, the increase in the production of reactive oxygen species (ROS) and in the growth of the cells without cell division (hypertrophic state) was inhibited by the addition of green tea extract.

The hypertrophy of VSMC is a critical event in the development of vascular disorders. In a recent study it was shown that angiotensin II-stimulated hypertrophy of VSMCs was blocked by EGCG [88]. As underlying mechanism, the authors propose the inhibition of the angiotensin II-stimulated c-Jun kinase (JNK) pathway. Interestingly, another catechin, EGC, was without effect.

As evidenced by the limited number of studies available so far, green tea and green tea catechins might prevent the development of hypertrophy by interfering with signaling pathways which lead to a hypertrophic cell state.

5 Ischemia/reperfusion

Myocardial ischemia/reperfusion (I/R) injury following an acute coronary occlusion event leads to cell apoptosis and myocardial damage. In an animal model, male Wistar rats were subjected to myocardial ischemia (30 min) and reperfusion (2 h). During the time of reperfusion, one group was treated with EGCG (10 mg/kg/h) intravenously. Myocardial damage was significantly reduced in the EGCG group, in comparison to control animals. The reduction in myocardial damage was associated with decreased plasma levels of IL-6 and creatine phosphokinase. Activation of NF-κB and AP-1, two transcription factors involved in inflammatory responses, was blunted by EGCG treatment [89].

Since apoptotic cell death is a hallmark of ischemia/reperfusion injury in the heart, the influence of tea constituents on protection against apoptosis in cardiac myocytes was investigated. EGCG protected cardiac myocytes against I/R-induced apoptotic cell death *via* reduced STAT-1 phosphorylation, a transcription factor involved in promotion of apoptosis [90]. In the same study, rat hearts were subjected *ex vivo* in a Langendorff apparatus to ischemia and reperfusion for 30 min and 2 h, respectively. Preischemic infusion of isolated rat hearts with EGCG (100 μM) significantly reduced the extent of infarct size and attenuated the magnitude of myocyte apoptosis. More importantly, oral administration of green tea extract to animals once a day for 7 days led to ameliorated cardiac function during the postischemic phase, after experimental I/R injury in isolated hearts from those animals, compared to the control group receiving water only. These results were accompanied by limited extent of infarct size and decreased myocyte apoptosis [90].

These data indicate that green tea and tea constituents are able to reduce myocardial damage after ischemia/reperfusion injury and protect cardiac myocytes from I/R-induced apoptosis. However, more data are needed to substantiate and verify these findings.

6 Obesity

Obesity is an important risk factor and a predictive value for the onset and progression of cardiovascular disorders. The incidence of obesity has dramatically increased worldwide in recent years and has become a major health problem in industrialized countries. Green tea is proposed to have favorable effects on body mass and to exert a beneficial impact in the prevention of obesity. A great number of recently published data support this assumption. Healthy human volunteers in a Japanese study consumed a tea extract rich in catechins for 12 wk and had a significant lower body weight, body mass index (BMI), waist circumference, body fat mass, and subcutaneous fat area than the control group [91]. In another study, 22 patients with CAD, who consumed one liter of oolong tea daily for one month had higher plasma levels of adiponectin, as well as a trend toward larger plasma LDL particles [92]. The effects of green tea and tea catechins on obesity have been extensively investigated in rodent models. Administration of green tea to rats for 3 wk reduced adipose tissue weight, and plasma levels of cholesterols and free fatty acids, without changes in body weight. Underlying mechanisms involved reduced glucose uptake in adipose tissue and the modulation of adipogenesis-related transcription factors [93]. Long-term feeding of tea catechins to high-fat diet-induced obese rats suppressed body fat accumulation [94]. Intake of green tea powder, as well as caffeine and theanine, reduced body weight in mice fed with these diets for 16 wk, when compared to controls [95]. Supplementation of green tea cate-

chins for 11 months together with a high-fat diet resulted in significant reduction of the high-fat diet-induced body weight gain and liver fat accumulation in those mice [96]. To determine the effects of dietary supplementation of pure EGCG on the development of diet-induced obesity, rats were given EGCG together with a high-fat diet for 5 months. EGCG supplementation prevented diet-induced increases in body weight and in plasma levels of glucose, triglycerides, and leptin [97]. The same authors studied the effects of EGCG supplementation on the regression of diet-induced obesity in Sprague–Dawley rats. The rats were made obese with a high-fat diet for 5 months and thereafter received EGCG for 4 wk. Supplementation with EGCG reversed the established obesity in these rats [97]. Similar results were obtained in an analog study in mice. Dietary EGCG led to an attenuation of body fat accumulation during a high-fat diet for 4 wk [98].

The above data provide compelling evidence for a beneficial effect of tea and tea catechins on obesity, especially in animal models. These experimental data call for studies to provide further data in humans.

7 Discussion

Cardiovascular diseases are the leading cause of death in industrialized countries. Since there is accumulating evidence that a healthy diet is associated with a reduction in cardiovascular morbidity and mortality, primary and secondary prevention strategies focus increasingly on dietary approaches. In this context, beneficial health effects of tea beverages represent important public health issues, especially in light of the fact that worldwide consumption of tea is second only to water. Polyphenols, mainly flavonoids in green and black tea, are considered to contribute to the protective cardiovascular effects of tea consumption. Although a growing number of epidemiological and experimental studies suggest favorable effects of tea polyphenols on cardiovascular diseases – particularly with regard to atherosclerosis and CAD – other investigations do not support the conclusion of cardioprotective effects of tea components. The underlying reasons for these inconsistencies are incompletely understood. However, heterogeneities in study design, populations, tea manufacturing and production processes, polyphenol content and metabolism, as well as accompanying lifestyle patterns may be relevant.

Evaluation in epidemiological studies of the health benefits of tea consumption requires consideration of potential confounding factors and modifications by lifestyle and other dietary factors. Higher tea consumption may represent a surrogate for a better lifestyle and a healthier diet. Trends toward inverse association of tea consumption with smoking, BMI, and dietary risk factors have to be evaluated [6, 11, 13, 99]. Accordingly, additional confounding factors and lack of controls for lifestyle elements may explain why some studies reported protective effects of tea beverages related to cardiovascular diseases while others did not.

An important factor with regard to study interpretation is the complexity of determination of tea exposure. In addition, measures of intake, absorption, and metabolism of tea beverages are poorly defined. Studies from East Asia (Japan and China) have generally investigated green tea. Many other studies simply refer to "tea". Since tea comprises a heterogeneous group of beverages (such as black, oolong, and green tea), and several forms of ice teas as well as fruit or herbal teas, conflicting study results may be attributed to the use of divergent tea forms. Moreover, even within the same kind of tea, further differences exist in the composition and concentrations of constituents, depending on the geographical origin and the manufacturing process. It is important to consider that fluctuations in flavonoid content among different teas may be due to blends of different teas, and are dependent on type, area of production and cost. The flavonoid content of the tea leaves is very sensitive to environmental conditions such as amount of light energy and pollutants [1]. Whereas most studies assess the frequency of tea consumption, techniques of the consumers to prepare tea beverages, which may influence polyphenol content and availability, are not available in the majority of cases.

The bioavailability of tea components in humans is relatively low. It is known that flavonoids undergo significant metabolism and conjugation during absorption in the small intestine and the colon. In the small intestine these modifications lead primarily to the formation of glucuronide conjugates and *O*-methylated forms that have altered physiological properties. The microflora of the colon induces further modifications by degrading flavonoids to smaller phenolic acids and valerolactones [100]. All these processes can modify the bioavailability and biological properties of tea polyphenols and may explain discrepancies between *in vitro* data and human studies.

The accompanying diet represents an important aspect, which may partially explain inconsistencies among results from acute studies (*i.e.*, involving hypertension) and from studies of regular tea ingestion. There are several lines of evidence that the effects of tea differ depending on whether tea is consumed with or without food. Some evidence indicates that food alters the absorption and bioavailability of tea constituents and in this way influences measured study parameters [46]. In a recent study in healthy human volunteers, maximum plasma concentrations of EGCG were significantly higher in individuals taking a supplemented catechin mixture in a fasting state, in comparison to individuals having a light breakfast together with catechin administra-

tion [101]. People usually drink tea with and between meals rather than in a fasting state.

Another potential explanation for discrepant study results of the effects of tea in cardiovascular health may be related to the addition of milk to tea. There is some evidence that dietary milk proteins may bind tea polyphenols and inhibit absorption, thereby altering bioavailability and the physiological effects of tea *in vivo* [102]. Other authors, however, found little influence of milk on plasma tea polyphenol concentrations in humans [40, 103]. In the United Kingdom, milk is usually added to tea. Hertog *et al.* [16], who reported that more than 99% of tea drinkers in Britain add milk, hypothesized that this habit might explain why their results did not evidence of beneficial antiatherogenic effects of tea. In accordance, Serafini *et al.* [36] showed that adding milk to black and green tea abolished their *in vivo* plasma antioxidant potential. Other studies could not find an influence of milk on plasma concentrations of tea flavonoids or on plasma antioxidant activity in subjects given tea with or without milk [39, 103, 104]. At present, it is not precisely clarified whether addition of milk to tea beverages substantially modifies the biological activities of tea polyphenols *in vivo*.

A question of much debate is whether green tea has better cardiovascular health benefits than black tea. Green tea contains more catechins than black tea, due to the enzymatic oxidation of catechins during fermentation. There is some evidence, however, that the total quantities of phenolic compounds in green and black tea are not significantly different [105, 106]. As an overall picture, in studies investigating simultaneously the effects of black and green tea, it was found that study design and endpoint determine whether one of the two tea types (black or green) exhibited better compliance. However, green tea seems to have higher antioxidant potential than black tea in many studies. To date, there is no clear evidence that green tea is superior over black tea in overall beneficial cardiovascular effects. Since there are major regional differences in the kind of tea consumed (green tea most likely in East Asia, black tea in Europe, *etc.*), such information may be associated with important public health issues.

8 Summary

In conclusion, numerous epidemiological, clinical, and experimental studies suggest that consumption of tea beverages is associated with beneficial cardiovascular effects – in particular with prevention of atherosclerosis and CAD, hyperlipidemia, and hypertension. Promising findings have also been published with regard to ischemia/reperfusion, hypertrophy, and obesity. The underlying mechanisms involve vasculoprotective, antioxidative, anti-inflammatory, antiproliferative, antithrombogenic, and lipid-lowering effects. However, study results are not evenly consistent. A number of reports failed to demonstrate beneficial cardiovascular effects of green or black tea. To date, no prospective intervention study results are available on the cardiovascular impact of tea or of the intake of tea polyphenols. Consequently – and despite favorable results in some studies – substantiation of the effects of tea in primary or secondary prevention of cardiovascular diseases will require the design of randomized clinical trials with standardized tea preparations or tea extracts, and with simultaneous assessment of plasma levels of tea polyphenols. The application of tea and tea constituents in human studies represents a fast-developing, highly promising tool in the prevention and/or treatment of a variety of cardiovascular disorders, and might in the future result in clinically applicable drugs.

9 References

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