Published in final edited form as:

Pharmacol Res. 2011 August ; 64(2): 136–145. doi:10.1016/j.phrs.2011.03.009.

Tea and Cardiovascular Disease

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Abstract

There is increasing evidence for a protective effect of tea consumption against cardiovascular disease. This review summarizes the available epidemiological data providing evidence for and against such an effect. We also review observational and intervention studies that investigated an effect of tea and tea extracts on cardiovascular risk factors, including blood pressure, serum lipids, diabetes mellitus, and obesity. Finally, we review potential mechanisms of benefit, including anti-inflammatory, anti-oxidant, and anti-proliferative effects, as well as favorable effects on endothelial function. Overall, the observational data suggest a benefit, but results are mixed and likely confounded by lifestyle and background dietary factors. The weight of evidence indicates favorable effects on risk factors and a number of plausible mechanisms have been elucidated in experimental and translational human studies. Despite the growing body evidence, it remains uncertain whether tea consumption should be recommended to the general population or to patients as a strategy to reduce cardiovascular risk.

Keywords

Tea; polyphenols; catechins; flavonoids; cardiovascular disease; endothelium

1. Introduction

Tea leaves are obtained from the *Camellia Sinensis* plant. Based on how the leaves are processed, three main types of tea can be produced: non-fermented green tea, partly-fermented oolong tea and fermented black tea. Records from as far back as the 10th century BC indicate use of tea by man, largely because of its medicinal value. This review will focus on possible beneficial effects against cardiovascular disease

Tea leaves contain a large amount of polyphenols (about 30% of the dry substance), mainly flavonoids. The major class of flavonoids in tea are flavanols, which include catechin, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) [1]. Total polyphenol content is similar in different types of tea, but the individual components vary, based in part on the degree of polyphenol oxidation during the manufacturing process. Catechins constitute about 80–90% and flavanols about 10% of the

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total flavonoids in green tea. On the other hand, theaflavins account for 50–60% and catechins only 20–30% of total flavonoids in black tea [2].

Recently, there has been considerable interest in the possibility that consumption of tea reduces risk for cardiovascular disease. Some observational studies suggest a benefit of tea, while other studies have failed to show such an association. Mechanistic studies have shown that tea and tea polyphenols have favorable effects on systemic risk factors and direct effects on the vasculature and platelets that might account for reduced cardiovascular risk. In the following sections, we will summarize the supportive and non-supportive observational studies that investigated a relationship between tea consumption and cardiovascular risk. We will then consider experimental, mechanistic and translational studies that elucidate potential mechanisms of benefit. Finally, we will attempt to put these data into clinical context given the considerable interest in dietary and lifestyle approaches to reduce cardiovascular disease.

2. Epidemiologic studies with tea and cardiovascular disease events

A large number of cross-sectional and prospective outcome studies investigated the relation between tea consumption and cardiovascular disease. In addition several meta-analyses have been performed that pool these data. Overall, the evidence suggests a benefit, for both green and black tea, but the results may be confounded by lifestyle and other dietary factors.

Nearly all of the published studies examining the relation between green tea consumption and cardiovascular risk suggest a reduction in risk. In an early study from Japan, Sato and colleagues followed a cohort of 5,910 women for four years and found that the incidence of stroke and cerebral hemorrhage was two times higher in those with daily green tea consumption less than five cups when compared to those with more than five cups [3]. More recent studies also showed a beneficial effect of green tea consumption in Japan. Nakachi and colleague studied a cohort of 8,552 participants and observed a 28% reduction in death from cardiovascular disease for men and women consuming over 10 cups a day compared to those consuming less than 3 cups per day [4]. Similarly, the Ohsaki National Health Insurance Cohort Study, which followed 40,530 Japanese adults for 11 years, demonstrated a dose relationship between increasing green tea consumption and reduced total and cardiovascular mortality that was strongest in women with a relative risk of 0.69 (95% CI, 0.53–0.90) for women who consumed more than five cups per day [5]. Stroke mortality was particularly reduced in tea drinkers. A case-control study from China also suggested a favorable effect of green and oolong tea consumption against ischemic stroke [6].

Recently, a very large prospective study involving 76,979 Japanese adults examined the relationship between cardiovascular mortality and consumption of several different types of tea. The investigators reported a strong inverse relationship between cardiovascular mortality and consumption of more than six cups of green tea per day [7]. Interestingly, consumption of more than one cup of oolong tea per day was also associated with reduced risk in Japan [7]. Overall, these studies conducted in Japan and China suggested that consumption of relatively large amounts of green tea (5 to 10 cups per day) is associated with reduced cardiovascular events.

Studies performed in Europe and the U.S. suggested a benefit from consumption of black tea. For example, Sesso and colleagues completed a case-control study and observed that individuals with history of myocardial infarction were less likely to be consuming more than a cup of black tea per day compared to age, sex, and community-matched controls (odds ratio of 0.56) [8]. In the Determinants of Myocardial Infarction Onset Study, individuals consuming more than an average of two cups of black tea per day had lower total and cardiovascular mortality during 3.8-year follow-up compared to individuals consuming less tea [9]. The same study demonstrated lower prevalence of ventricular arrhythmia during

hospitalization for myocardial infarction among tea drinkers, possibly suggesting less severe infarction and providing a potential explanation for the reduction in cardiovascular mortality observed during subsequent follow-up [10].

A large cohort of 37,514 participants in Netherlands was prospectively followed for 13 years with end points of cardiovascular disease morbidity and mortality [11]. In that study, consumption of tea (mainly black tea) 3 to 6 cups daily was associated with a reduced risk of cardiovascular disease mortality. There was no association, however, between tea consumption and all cause mortality. In that study, tea drinking was found to also be associated with a higher educational level, higher physical activity, healthier diet, and lower prevalence of smoking, hypercholesterolemia and diabetes. Although the investigators adjusted for these factors, residual confounding by health behavior could have affected the results. A study from a Norwegian cohort (Oppland County) of 9,856 men and 10,233 women showed a strong trend for a benefit of tea [12]. In that study, there were significant correlations between tea consumption and blood pressure and cholesterol levels, which were lower among individuals consuming one or more cups of tea per day.

Several epidemiological studies failed to show an association between tea consumption and cardiovascular disease. For example, in the Scottish Heart Health Study involving 10,359 men and women there was no association between tea consumption and prevalent coronary heart disease [13]. In a cohort of 1,900 Welsh men, the group with the highest consumption of tea (more than eight cups per day) actually had higher ischemic heart disease mortality compared to the group consuming less than two cups per day [14]. The authors pointed out that tea is often consumed with milk in the United Kingdom and speculated that milk might have affected absorption or increased fat intake and influenced a benefit of tea.

Other factors might explain the lack of benefit in these studies. For example, it has been noted that tea consumption is more common among individuals of low socioeconomic status in the U.K., and the association between lower social status and higher cardiovascular disease risk might obscure a beneficial effect of tea [15]. Another consideration is the baseline flavonoid intake. If the entire U.K. population has a relatively high level of tea intake, then even individuals in the lower range of consumption could be receiving the maximal benefits of tea. Conversely, a study in cohort with relatively low overall tea intake might fail to show a benefit even in the subgroup of individuals in the highest quartile or quintile of tea intake. In this regard, the relationship between tea consumption and cardiovascular events was only a non-significant trend ($P=0.07$) in the Women's Health Study, where only a small proportion of the women in the U.S. consumed more than four cups of tea per day [16]. Sesso and colleagues also observed no significant association between tea consumption and cardiovascular disease in a cohort of 17,228 college alumni (College Alumni Health Study) where the median intake of tea was relatively low (1 cup per day) [17]. This cohort also was relatively healthy and had higher socioeconomic status than some of the other studies, which also may have made it difficult to show a benefit of tea consumption. Such factors might also account for the lack of benefit of tea consumption in a cohort of 34,789 male health professionals [18].

Overall, the bulk of evidence does suggest that higher consumption of both green and black tea is associated with reduction of cardiovascular risk, despite the negative results of some studies. A number of meta-analyses have been performed to more formally address this question. For example, Peters and colleagues examined the relation of tea consumption to stroke, myocardial infarction, and all coronary heart disease in an analysis of 10 cohort studies and seven case-control studies [19]. The incidence of myocardial infarction was estimated to be 11% lower for an increase in tea consumption of 3 cups per day (1 cup= 237 ml). Those investigators, however, acknowledged that their results need to be interpreted

with caution because there was evidence of bias toward preferential publication of smaller positive studies [19]. Also, there was heterogeneity that could be explained by the geographic region where the studies were conducted. The same group pooled data from nine studies involving 194,965 individuals and concluded that consumption of three or more cups of green or black tea per day was associated reduced incidence of ischemic stroke [20].

In regard to the specific components of tea that are responsible for benefit, several epidemiological studies and meta-analyses have examined consumption of flavonoid-containing foods more generally. In addition to tea, such foods include grapes and red wine, chocolate, apples, onions, and other fruits and vegetables. In the Zutphen Elderly Study, which examined a cohort of 805 Dutch men with five-year follow-up, dietary flavonoids were inversely associated with coronary heart disease mortality with relative risk of 0.42 for individuals in the highest versus lowest tertile of flavonoid intake [21]. A similar relationship was observed after 10-year follow-up that remained highly significant after adjustment for cardiovascular risk factors [22]. Flavonoid intake also was inversely related to stroke in the same cohort [23]. In the Seven Countries Study with 25 years of follow-up, there was an inverse correlation between flavonoid intake and incidence of coronary heart disease [24]. In a Finnish cohort of 25,372 male smokers, flavonol and flavone intake was inversely associated with myocardial infarction and there also was a trend for reduced coronary heart disease death [25].

In contrast, there was no significant correlation between flavonoid intake and cardiovascular disease events in a cohort of U.S. women participating in the Women's Health Study [16], but as previously noted, overall flavonoid intake in this cohort was relatively low. Overall, available evidence, including several meta-analyses suggests a benefit of flavonoid consumption against cardiovascular disease [26,27]

3. Tea and risk factors for cardiovascular disease

Given the apparent association between tea consumption and cardiovascular disease events, it is worthwhile to consider the potential mechanisms of benefit. One important potential mechanism is direct effect of tea on cardiovascular disease risk factors. A large number of epidemiological and intervention studies have examined this issue. Despite this large body of work, it remains unclear whether tea consumption has favorable effects on blood pressure, serum lipids, diabetes mellitus, or obesity in human subjects. If present, the beneficial effects of tea on risk factors are likely to be modest.

3.1 Hypertension

Epidemiological and intervention studies provide evidence that consumption of tea and other polyphenol-containing foods lower blood pressure. In a large epidemiological study involving over 20,000 Norwegian participants, systolic blood pressure was 2.1 and 3.5 mmHg lower in men and women, respectively, who consumed five or more cups of tea per day [12]. In a study of 218 elderly women, tea consumption and urine 4-O-methylgallic acid (a measure of polyphenol consumption) correlated inversely with systolic and diastolic blood pressure, with a 2.2 mmHg lower systolic blood pressure for each cup of tea consumed [28]. While these absolute changes in blood pressure may seem small, changes of this magnitude on a population basis would result in the prevention of many cardiovascular events and strokes [29]. Yang and colleagues examined incident hypertension in a cohort of 1,507 men and women in Taiwan and observed a reduction in the risk of developing new hypertension in individuals consuming more than 120 ml of green or oolong tea per day after adjusting for other risk factors, lifestyle, sodium intake, and coffee consumption [30]. On the other hand several very large studies have shown no relation between tea consumption and blood pressure [31–33].

Intervention studies provide additional information about the effects of tea consumption on blood pressure. This question is complicated because, in addition to flavonoids, tea contains caffeine, which causes a short-term increase in blood pressure. Hodgson observed an increase in blood pressure 30 min after ingestion of green or black tea in normotensive men that was no longer evident at 60 minutes after [34]. Interestingly, this increase in blood pressure was actually greater than the effect of an equivalent dose of caffeine alone suggesting that tea or tea polyphenols might cause acute increases blood pressure. Consumption of either form of tea for seven days had no effect on 24-hour ambulatory blood pressure in the same population [34]. The same group of investigators observed that the acute hypertensive effect of tea consumption was blunted when tea was consumed with food [35].

Nagao and colleagues completed a study of green tea extract (583 mg of catechin) in Japanese men and women with abdominal obesity [36]. In the subgroup of participants with baseline systolic blood pressure of 130 mmHg or higher, tea extract significantly reduced blood pressure compared to placebo [36]. Brown and colleagues examined the effects of EGCG on blood pressure and other metabolic risk factors in overweight or obese men and observed a 2.7 mmHg reduction in diastolic blood pressure [37]. More recently, Nantz and colleagues completed a double-blind trial in 111 healthy volunteers comparing the effects of a standardized capsule containing 200 mg of decaffeinated catechin green tea extract to placebo [38]. They observed a 5 mmHg decrease in systolic blood pressure that was significantly different from the effect of placebo.

The apparently favorable effects of tea and tea components on blood pressure in intervention studies contrast with the results of a large number of other clinical studies examining the effects of tea on a variety of physiological endpoints. Taubert and colleagues recently completed a meta-analysis pooling five parallel group and cross-over studies that reported on the effects of tea on blood pressure in a total of 343 participants with a median duration of four weeks [39]. The meta-analysis revealed no significant effect of tea consumption on blood pressure. Interestingly, they did observe a favorable effect of chocolate consumption on blood pressure using the same approach.

Overall, the available studies do not provide a definitive answer to the question of whether tea consumption lowers blood pressure. Many of the studies examined normotensive populations and populations already well controlled on anti-hypertensive therapy, where it is difficult to demonstrate a blood pressure lowering effect with any intervention. Furthermore, few of the studies used 24-ambulatory blood pressure monitoring or treated subjects for an extended period of time. Any benefit of tea flavonoids must overcome the short-term blood pressure raising effects of caffeine. Thus, despite the large number of prior epidemiological and interventional studies, further definitive studies are needed to determine the acute and chronic effects of tea consumption on blood pressure in patients with hypertension and whether blood pressure effects could explain the observed associations between tea consumption and reduced cardiovascular risk.

3.2 Dyslipidemia

Improvement in serum lipid profile is another possible mechanism that would account for a beneficial effect of tea on cardiovascular disease, and several observational studies suggest that tea might have such an effect. Kono and colleagues reported that total serum cholesterol was 8 mg/dl lower in 1,306 Japanese men consuming nine or more cups of green tea per day [40]. Stensvold reported a comparable reduction in total cholesterol in Norwegian men and women consuming more than five cups of black tea per day [12]. On the other hand, several observational studies have shown no relationship between green or black tea consumption and total or LDL cholesterol levels [41,42].

The question of a lipid-lowering effect of tea has also been examined in randomized intervention studies that allow for control of potential confounding variables. Davies and colleagues completed a placebo controlled, double blind crossover study of five cups of black tea and placebo beverage in 15 mildly hypercholesterolemic adults and observed a reductions of 6.5% and 11.1% in total and LDL cholesterol, respectively [43]. In a much larger (n=240) and well-designed randomized crossover study, Maron and colleagues observed comparable reductions in LDL cholesterol with consumption of flavin-enriched green tea for 12 weeks [44]. Several other intervention studies have shown cholesterol lowering effects of green and black tea as well as tea extracts [38,45–48]. Other studies have failed to show such an effect [37,49–51]. Interestingly, there is evidence that tea consumption may have a favorable effect on post-prandial lipids, which are particularly atherogenic [45] and a favorable effect on HDL cholesterol in patients with diabetes mellitus [52].

Overall, the published studies examined many different patient populations with varying degree of baseline dyslipidemia and background therapy. The available studies also examined many different preparations and extracts of tea. This heterogeneity in study design likely explains the divergent results. In an extensive meta-analysis involving 133 interventions studies examining the effects of various flavonoid-containing foods, Hooper and colleagues concluded that green tea consumption has significant albeit modest LDL lowering effect [53].

1.3.3 Diabetes and obesity—Type 2 diabetes mellitus is a major cardiovascular disease risk factor and is increasing in prevalence, in large part due to the ongoing obesity epidemic [54]. Insulin resistance is the primary pathophysiological mechanism in type 2 diabetes mellitus, and there is experimental evidence that polyphenols found in tea can improve insulin sensitivity. Observational and intervention studies suggest that this mechanism may be operative in humans. In a study of 17,413 Japanese adults, Iso and colleagues reported that the incidence of new diabetes was inversely associated with consumption of more than six cups of green tea per day, while there was no association with black or oolong tea [55]. Interestingly, there also was an inverse association between diabetes mellitus and coffee consumption in that study. Greenberg and colleagues observed that consumption of two cups of “regular tea” (presumably black tea) per day was associated with a reduction in the incidence of diabetes during an 8.4 year follow-up period in participants of the National Health and Nutrition Examination Survey (NHANES) who were age 60 or younger [56]. On further subgroup analysis, this relationship applied to the individuals who had lost weight during the follow-up period. The Whitehall II study also showed decreased incidence of diabetes mellitus in 5,823 participants followed for 11.7 years that was not significant after adjustment for concomitant risk factors [57]. Finally, in the Women’s Health Study, Song and colleagues observed a borderline significant relationship between tea consumption (≥ 4 cups day) and the incidence of new diabetes mellitus over an 8 year follow-up period with a relative risk of 0.72 (95% CI 0.52 – 1.01) [58].

In contrast, several very large studies showed no relationship. For example, in reports from the Nurses Health Study and Health Professionals’ Follow-up Study, there was no significant relation between tea consumption, although interestingly there was a relationship with coffee consumption [59,60]. There also was no relation between tea consumption and diabetes in a large cohort of 46,906 African American Women [61]. Despite these negative studies, Huxley and colleagues completed a meta-analysis examining the effects of caffeinated beverages on incident diabetes combining data from 18 studies with information from nearly half a million individuals [62]. In regard to tea, they found that overall the relative risk of new diabetes was significantly reduced (RR 0.84, 95% CI 0.73 – 0.94).

As for the other risk factors discussed above, clinical intervention studies examining the effects of tea and tea polyphenols on endpoints related to diabetes provide additional insight into the question of whether tea might affect diabetes mellitus. Hosoda and colleagues observed that consumption of oolong tea (1,500 ml/day) for 30 days in a placebo controlled crossover study lowered fasting glucose in 20 patients with type 2 diabetes mellitus on hypoglycemic drugs [63]. Consumption of one gram of black tea by healthy volunteers lowered the blood glucose and blood insulin responses to an oral glucose load (glucose tolerance test) suggesting an improvement in insulin sensitivity [64].

In contrast, Fukino and colleagues completed a placebo controlled study examining the effects of green tea (administered as a extract powder containing 544 mg polyphenols mixed with hot water) in a group of 66 patients with diabetes mellitus or borderline diabetes [65]. Compared to the effects of placebo, there were no effects of green tea on measures of glycemic status, including blood glucose, insulin, hemoglobin A1C, or the homeostasis model assessment of insulin resistance (HOMA-IR). Interpretation of this study is complicated by a relatively similar intake of polyphenols in the active (747 mg/d) and placebo (469 mg/d) groups and the observation that these glycemic variables improved in both the active and placebo groups. It is possible that an effect of green tea would have been detected if polyphenol intake had been limited in the placebo group, as is often done in studies of this type. Ryu and colleagues also observed no effect of green tea consumption compared to water in a crossover for four weeks in 55 patients with type 2 diabetes mellitus.

Interestingly, there have been studies showing an effect of tea consumption on body weight. For example, Chantre and colleagues administered green tea extract to moderately obese subjects for 3 months observed a 4.6% decrease in body weight and 4.5% decrease in waist circumference by 4.48% [66]. In a study of 38 healthy Japanese men with normal body mass index randomized to consume green tea or a low catechin control, Nagao and colleagues reported that green tea consumption produced a 2.4 kg decrease in body weight and favorable effects on waist circumference, body fat mass, skin-fold thickness, and total subcutaneous fat areas (tested by computed tomography) [67]. The same group subsequently completed a larger randomized, placebo-controlled study in 240 Japanese men and women and observed a 1.7 kg decrease in body weight and significant changes in body fat and fat distribution with consumption of green tea extract [36]. Recently, Basu and colleagues showed a decrease in body weight following eight weeks of green tea or green tea extract compared to placebo in a group of 35 obese individuals with the metabolic syndrome [49]. The mechanisms accounting for weight loss with tea or tea components remain unclear. It has been suggested that they may increase sympathetic nervous system activity and stimulate thermogenesis, which would increase calorie consumption [68].

As for other risk factors, the available studies provide inconsistent findings. Some studies showed weight loss and reduction of diabetes, while others did not. Differences in study population and tea preparation likely explain these inconsistencies. Overall, the available evidence, including a large meta-analysis, suggests that tea consumption reduces the incidence of new diabetes mellitus. There is a modest level of evidence supporting a favorable effect of tea components on insulin sensitivity. Finally, tea consumption appears to induce a modest amount of weight loss. These conclusions must be tempered by the possibility of publication bias and the relatively small size of most of the published intervention studies.

4. Mechanistic studies with tea and cardiovascular diseases

Experimental and translational clinical studies have provided further insight into the mechanisms of benefit for tea against cardiovascular disease and Table 1 contains a partial

list of such mechanisms. These include antioxidant effects, anti-inflammatory effects, and improvement of endothelial function. This section will review these possible mechanisms.

4.1. Antioxidant effects of tea and tea components

According to the oxidative hypothesis of atherosclerosis, LDL oxidation is a key step in the atherogenic process [69]. Based on this hypothesis, considerable effort was made to determine whether antioxidant compounds that inhibit LDL oxidation might prevent cardiovascular disease in humans [70]. A large number of studies, including large clinical trials were conducted, and overall there remains little evidence that antioxidant supplements, including vitamins E and C and beta carotene, reduce cardiovascular disease. While it is clear that atherosclerosis is associated with increased oxidative stress, it is now understood that reactive oxygen species play important signaling roles in the vasculature and that simply scavenging reactive oxygen species or inhibiting LDL oxidation is not an effective strategy to inhibit atherosclerosis [71]. In this context, it is known that tea polyphenols have antioxidant effects *in vitro* [72–75] and many studies sought evidence for antioxidant effects of tea in humans.

In regard to *in vitro* effects, tea and tea extracts have been shown to scavenge superoxide and other reactive oxygen species [76]. Tea and tea components have also been shown to inhibit lipid peroxidation [75,77–80]. Furthermore, exposure of isolated endothelial cells to tea limits their ability to oxidize LDL [81]. Tea flavonoids can chelate redox active metal ions, which limits production of reactive oxygen species via the Fenton reaction [82]. There is animal evidence for antioxidant effects of tea following oral administration [83–85]. Consistent with the more recent human data, green and black tea inhibited LDL oxidation following oral administration to hypercholesterolemic rabbits, but the effect did not relate to changes in extent of atherosclerosis [84].

As mentioned, studies show that tea influences plasma antioxidant status in humans. For example, several studies have shown that tea consumption increases the ability of plasma to scavenge reactive oxygen species [46,86,87]. Studies have also shown that LDL isolated from plasma is less susceptible to oxidation following tea consumption [88], while other studies have failed to show such an effect [51,75,87,89,90]. In regard to preventing oxidation of lipids, proteins, or DNA *in vivo*, the evidence for beneficial effects of tea are less clear. Hakim and colleagues reported that green tea, but not black tea, by cigarette smokers decreased urinary levels of 8-hydroxy-deoxyguanosine, a marker of DNA oxidation [91]. Klaunig and colleagues reported a similar finding [92]. Erba and colleagues reported a reduction of DNA oxidative damage in lymphocytes isolated from healthy volunteers [46]. Other studies failed to show evidence that consumption of tea inhibits markers of lipid or DNA oxidation in human subjects [90,93,94].

As was observed in intervention studies examining the effects of tea consumption on risk factors, the data are mixed regarding antioxidant effects of tea consumption. Some of the discrepant results may reflect differences in tea preparations and the studied populations. Overall, there are reasonably convincing studies to indicate that consumption of tea or tea components can influence antioxidant capacity plasma. However, the bulk of the evidence does not support an *in vivo* antioxidant effect following consumption of relevant amounts of tea.

4.2 Anti-inflammatory effects

Inflammation is now known to be an integral part of atherosclerosis and is involved from the earliest stages of atherogenesis to later stages of plaque vulnerability and rupture, which causes clinical events such as myocardial infarction and stroke [95]. There is strong

evidence in experimental models and in animals that suggest anti-inflammatory effects of tea and tea components. *In vitro* studies have shown favorable effects on inflammatory cells. For example, EGCG inhibits migration of neutrophils through an endothelial cell monolayer [96], decreases the activity of neutrophil elastase [97], and reduces ROS production and chemokine-induced chemotaxis of neutrophils [98,99]. EGCG also inhibits adhesion and migration of CD8+ T cells [100]. EGCG and other catechins have been shown to inhibit cytokine-induced adhesion molecule expression and monocyte adhesion in cultured endothelial cells [101]. EGCG blocked lipopolysaccharide-induced tumor necrosis factor alpha (TNF-alpha) production and lethality in mice [102] and had reduced inflammatory activation in the lung in a mouse model of pulmonary fibrosis [103].

In humans, epidemiological and intervention studies have examined anti-inflammatory effects of tea consumption. Serum levels of C-reactive protein and other markers of inflammation relate strongly to cardiovascular risk, and several epidemiological studies examined the effects of tea consumption on such markers. For example, tea consumption was inversely related to C-reactive protein levels in a cohort of 1031 health men [104]. Other studies failed to show such a relationship [58,105,106]. More generally, flavonoid consumption and fruit and vegetable consumption are associated with lower levels of C-reactive protein [107,108], making it harder to confirm a specific relationship with tea consumption.

In regard to intervention studies, Neyestani and colleagues reported a decrease in C-reactive protein following consumption of black tea extract for four weeks in 46 patients with type 2 diabetes mellitus [109]. Steptoe and colleagues also reported a decrease in C-reactive protein and pro-inflammatory monocyte-platelet aggregates following four weeks of black tea consumption in healthy men [110]. Green tea consumption reduced C-reactive protein levels in male smokers [111]. Other well-done studies, however, showed no such effects in patients with risk factors or coronary artery disease [65,90,112,113].

As has been observed for other tea intervention studies, the discrepant results are likely attributable to differences in tea preparations and patient characteristics. No formal meta-analysis has examined the effects of tea consumption on C-reactive protein or other markers of inflammation. However, the bulk of the evidence does not suggest a strong anti-inflammatory effect of tea consumption, despite promising experimental studies.

4.3. Endothelial function

The endothelium is a major regulator of vascular homeostasis and controls arterial tone, thrombosis, the composition of the arterial wall, and local inflammation by production of a variety of factors, including nitric oxide [114]. Abnormalities of endothelial function relate to cardiovascular risk factors, predict cardiovascular events, and respond to risk reduction therapies, including drugs, lifestyle changes, and dietary interventions. Recently, there have been several studies showing beneficial effects of tea on endothelial function, particularly endothelium-dependent vasodilation.

In a placebo-controlled crossover study, Duffy and colleagues showed that consumption of black tea (900 ml per day for four weeks) improved endothelium-dependent flow-mediated dilation of the brachial artery in patients with coronary artery disease [115]. Hodgson and colleagues showed a similar benefit of black tea consumption in patients with mildly elevated cholesterol levels [116]. Green tea has also been reported to improve brachial artery flow-mediated dilation [117,118] and circulating endothelial progenitor cells, which contribute to maintenance of vascular health [118]. One study suggested that green and black tea have equivalent effects on flow-mediated dilation in post-menopausal women [119]. Favorable effects on endothelial function have been reported with tea components,

including EGCG [120]. In addition to improving FMD, green tea improves endothelium-dependent dilation of forearm microvessels in response to acetylcholine infusion in cigarette smokers and this improvement was associated with an increase in plasma nitric oxide [111]. On the other hand, tea consumption had no effect on carotid-femoral pulse wave velocity, a measure of arterial stiffness that depends in part on endothelial function [121].

Experimental studies have shed light on the mechanisms accounting for improved nitric oxide bioavailability following tea consumption. Initially investigators hypothesized that tea flavonoids might scavenge reactive oxygen species and prevent “inactivation” of nitric oxide, but as discussed above, there is little evidence that the plasma concentrations of tea flavonoids achieved following tea consumption are high enough to act via this mechanism. More recent studies indicate that tea extracts and individual tea polyphenols, including EGCG stimulate phosphorylation of endothelial nitric oxide synthase (eNOS) at serine 1177, a response that increases production of nitric oxide. The response occurs via activation of the phosphatidylinositol 3-kinase (PI3 kinase)/Akt signaling pathway [122–124]. Subsequent studies suggest that this process also involves activation of p38 MAP kinase and transactivation of estrogen receptor alpha [125].

A number of other mechanisms contribute to the observed increase in eNOS activity following exposure of endothelial cells to tea components. For example, green tea polyphenols down regulate expression of caveolin-1 (Cav-1), a negative regulator of eNOS activity and this effect also involves activation of p38 MAP kinase [126]. Other polyphenol mixtures have been shown to activate AMP-kinase, a key regulator of cellular energy status, which also leads to activation of PI3K/Akt and eNOS phosphorylation [127].

Overall, there is a large body of working showing that tea consumption improves endothelium-dependent vasodilation in healthy human subjects and in patients with risk factors and established atherosclerosis. The effects are particularly strong following acute consumption of tea and occur despite acute effects of caffeinated tea to increase blood pressure. Many studies also show sustained improvements in endothelial function with longer-term tea consumption, while purified EGCG has an acute, but no chronic effect [120]. Experimental studies provide strong evidence that tea acts via specific signaling pathways in endothelial cells that are relevant to the pathogenesis of atherosclerosis. Given the strong links between endothelial dysfunction and the pathogenesis of atherosclerosis, a favorable effect of tea on the endothelium is a plausible mechanism that might account for reduced cardiovascular risk among individuals with higher tea consumption.

4.4. Anti-platelet effects

It is well established that clinical coronary syndromes such as unstable angina and acute myocardial infarction involve platelet aggregation and that anti-platelet agents such as aspirin and clopidogrel reduce cardiovascular risk [95]. A number of experimental studies suggest that tea has anti-platelet effects that might reduce cardiovascular risk. For example, Kang and colleagues reported that administration of EGCG or green tea extract to mice prolongs bleeding time, and prevents collagen-induced pulmonary thrombosis and death [128]. They also observed that EGCG inhibits agonist-induced aggregation of human platelets *in vitro*. The effects may be attributed to alterations in intracellular calcium signaling [129] and prostaglandin metabolism [130]. Theaflavins in black tea and green tea catechins have been shown to be potent inhibitors of platelet activating factor biosynthesis and platelet aggregation in a rabbit model [131]. It is important to note that the concentrations of EGCG and other tea components used in some of these *in vitro* studies (50 to 100 μ M), greatly exceed the concentrations measurable in plasma following consumption of tea or EGCG supplement in humans [90,120].

In regard to human studies, Hodgson and colleagues observed that tea consumption by healthy volunteers reduced plasma levels of P-selectin, a marker of *in vivo* platelet aggregation, but *ex vivo* platelet aggregation was unaffected in that study [132]. Green tea consumption also lowered P-selectin levels in male smokers [112]. Steptoe and colleagues observed that black tea consumption for four weeks reduced platelet-leukocyte aggregates, an important measure of platelet activation that is relevant to coronary plaque rupture [110]. Duffy and colleagues also observed no effect of tea consumption on *ex vivo* platelet aggregation following consumption of black tea in patients with coronary artery disease [133], although that study may be limited by the background aspirin treatment in all of the study subjects.

In general, studies that examined *ex vivo* platelet aggregation failed to show beneficial effects, but measures of *in vivo* platelet activation appear to be improved following tea consumption. Experimental studies provide evidence of plausible mechanisms. Thus, the bulk of the available data support the hypothesis that platelet inhibitory effects might explain the observed relations between tea consumption and reduced cardiovascular risk.

4.5. Anti-proliferative effects

Another mechanism that might affect cardiovascular disease is the observed anti-proliferative and anti-migratory effects of tea components on vascular smooth muscle cells. EGCG arrests vascular smooth muscle cell proliferation in the G1 phase of the cell cycle and decreases the proliferative response following arterial injury in apolipoprotein E-null mice, a dyslipidemic model that is prone to develop atherosclerosis [134]. EGCG also inhibits vascular smooth muscle cell activation and proliferation by platelet-derived growth factor [135]. EGCG inhibits vascular smooth muscle cell migration through a reconstituted basement membrane barrier in an *in vitro* model that is relevant to atherogenesis [136]. Although there currently is no human evidence of such an effect, the anti-proliferative properties of EGCG have prompted investigators to consider developing EGCG-eluting polymeric stents for prevent of restenosis following angioplasty, a process that is primarily driven by vascular smooth muscle cell proliferation and migration [137].

5. Clinical Implications

The reviewed epidemiological studies and meta-analyses suggest that tea has protective effects against cardiovascular disease. In regard to the mechanisms that might account for such effects, there is evidence that tea might lower blood pressure and have favorable effects on blood lipids, glucose, and body weight. In addition, experimental studies and human intervention studies suggest that tea may have anti-inflammatory, anti-thrombotic, and anti-proliferative effects, and may improve the function of the vascular endothelium. Although tea polyphenols can scavenge reactive oxygen species and protect LDL against oxidation *in vitro*, human studies argue against an important *in vivo* anti-oxidant effect of tea. While the effects are modest compared to the effects of pharmacological interventions, in the opinion of the authors, the overall evidence suggests that tea consumption reduces cardiovascular risk by plausible mechanisms. The case for tea is strengthened by a similar body of work for protective effects of other polyphenol-containing foods and beverages such as grapes and red wine, cocoa, berries, and other fruits and vegetables [21,53,138–140]. The question is whether these findings translate to specific dietary recommendations for the general population and for patients with cardiovascular disease.

Making specific dietary recommendations about tea consumption as an approach to prevent or treat cardiovascular disease is problematic for several reasons. Importantly, there are no randomized clinical outcome trials with tea. Epidemiological studies of tea are unavoidably confounded by the lifestyles of tea drinkers and non-tea drinkers, background tea intake of

the population, and many other factors. Most of the current management guidelines in the field of cardiovascular disease, particularly recommendations about drug treatment, are based on randomized clinical trials and meta-analyses of clinical trials that can control for such factors. There have been randomized studies of dietary approaches such as the Mediterranean diet to reduce cardiovascular risk, but none with tea. In drug studies, the control group can be randomized to a placebo and have zero intake of the studied factor. Tea, on the other hand, is a ubiquitous part of the diet and it is not possible or ethical to have a control group that consumes no tea over the three to five years needed to accumulate a sufficient number of cardiovascular events.

A number of other difficulties would make it extraordinarily difficult to conduct a randomized clinical trial with tea. It remains unclear what type and dose of tea to recommend or to study. Another barrier is the question of specific populations studied. Pharmaceutical studies focus on patients with cardiovascular disease, but the results are not expected to apply to the general population. Finally, there is the question of cost. Clinical outcome studies are extraordinarily expensive and unlike pharmaceutical studies, there is no sponsor with a profit motive to bear the cost of studying a whole food, such as tea.

Similar issues influence the utility of the available observational studies to guide dietary recommendations. The available epidemiological studies suggest favorable effects of green, oolong, and black tea and benefit from modest to only extremely high amounts of tea consumption. Smaller scale intervention studies looking at risk factors and mechanistic surrogate endpoints also examined a wide variety and types and doses of tea. Variable bioavailability due to differences in food matrix and human gut absorption further clouds the issue. Thus, it remains extremely difficult to formulate dietary recommendations about how much and the type of tea to consume for the general population. Making recommendations for disease population is even more problematic.

Another important clinical implication of the reviewed studies is the potential use of tea extracts or individual tea components, such as EGCG, to promote cardiovascular health or prevent cardiovascular disease. Food, beverage and dietary supplement products designed to promote heart health are now a multi-billion dollar category in the U.S., with comparable markets in Europe, Japan and Australia. In regard to extracts, there is a lack of uniformity to the studied preparations, doses, and endpoints that make it hard to make specific recommendations and as for whole tea, there are no randomized outcome studies. For purified components, such as EGCG, there is a large body of evidence for favorable effects, but studies suggest that the benefits are limited to short-term acute effects reflective of the short plasma half-life of one to two hours [120]. To be beneficial, some type of slow-release preparation would be needed to provide a sustained increase in blood levels. Consideration of such preparations likely crosses the line from dietary supplements to drugs, with the attendant regulatory issues.

In 2006, Ito En, Ltd., a manufacturer of green tea and green tea products filed a petition to the U.S. Food and Drug Administration (FDA) to make a qualified health claim for green tea and green tea extracts based on studies showing favorable effects on cardiovascular disease risk factors [141]. The FDA reviewed observational studies that examined the relationship between green tea and cardiovascular disease endpoints, including many of the studies discussed in this review. They also considered intervention studies that examined the effects of green tea on blood pressure and blood cholesterol as surrogate endpoints for cardiovascular disease. Although they considered many observational studies, they argued that intervention studies provide the most scientifically valid information. For this reason, they particularly focused on four intervention studies that failed to show a benefit of green tea on blood pressure [34] and lipids [51,87,142] and three intervention studies that failed to

show an effect of green tea extract on cholesterol [51,93,143]. On the basis of these studies, they concluded that there was no credible evidence to support a relationship between consumption of green tea and reduced risk of cardiovascular disease. They cited the data for vitamin E and folate as examples of other dietary supplements that showed strong associations in observational studies, but no benefit in randomized trials, further justifying their decision to discount many of the observational studies suggesting favorable effects. While they did not find that green tea was unhealthy, they decided that the available evidence did not support a qualified health claim for a benefit against cardiovascular disease. Table 2 continues a partial list of randomized intervention studies examining effects of tea on risk factors that have been published since the FDA ruling in 2006. Many of these studies show benefit, raising the possibility that the question of a qualified health claim for tea might be reconsidered.

At this time, however, manufacturers cannot make claims about benefits against cardiovascular disease in advertising and labels for green tea or black tea. Advertising claims are different from guidelines and recommendations from non-commercial entities, such as the American Heart Association (AHA). In the most recent dietary guidelines, the Nutrition Committee of the AHA recommended that individuals consume a diet rich in fruits and vegetables to reduce the risk for cardiovascular disease [144]. Such a diet includes green and black tea.

6. Conclusion

In this article, we have reviewed a representative portion of the extensive published literature on tea and its role in cardiovascular disease prevention. Some, but not all observational studies suggest a reduction in cardiovascular disease. There also are mixed data about the effects of tea on risk factors from observational and intervention studies. Mechanistic studies in experimental models and human subjects have identified a number of plausible mechanisms of benefit, including anti-inflammatory and anti-platelet effects as well as favorable effects on the vascular endothelium. No randomized trials have examined the effects of tea on cardiovascular events, and there are many barriers to the conduct of such a trial. Thus, no definite conclusion can be drawn from the current data and no specific dietary recommendations can be made about whether tea promotes or reduces risk for cardiovascular disease. Furthermore, the available literature does not provide a clear answer about the type and/or amount of tea that should be consumed as part of a heart healthy diet.

At the present time, it is clear that tea is a popular, economical and safe drink which is enjoyed daily by millions of people all across the world. Given the high consumption and distribution of tea worldwide and the potential health effects of tea, further study is justified. In the meantime, freshly brewed green or black tea appears to be a reasonable dietary choice to consider as part of lifestyle and dietary approach to prevent heart disease.

Acknowledgments

Dr. Vita previously received research grant support from the North America Tea Trade Health Research Association, Unilever, Inc., Welch's, Inc., USANA Health Sciences, Inc. He has current research grants from DSM Nutritional Products, Ocean Spray, Inc., The Almond Board of California. He has received consultation fee or speaker honoraria from Unilever, USANA, DSM, Ocean Spray, and the Almond Board of California. He also is supported by research grants from the National Institutes of Health (HL083801, HL081587, HL083269, and HL75795 and HL102299).

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Table 1**Potential Mechanisms of Benefit for Tea Against Cardiovascular Disease**

Blood pressure lowering
Improved dyslipidemia
Improved insulin sensitivity
Weight loss
Antioxidant effects – scavenging reactive oxygen species and preventing oxidation of lipids, proteins, and DNA
Anti-inflammatory effects
Improved endothelial function
Platelet inhibition
Inhibition of smooth muscle cell proliferation and migration

Table 2

Intervention studies of tea on blood pressure and lipids since the FDA decision in 2006

First author [reference]	Endpoint	Study design	Result
Nagao [36]	Body fat, LDL, blood pressure	Green tea extract, randomized parallel group, 12 weeks, n=240	Benefit
Bertigaglia de Santana [48]	LDL, HDL, triglycerides	Green tea, randomized parallel group, 90 days, n=25 per group	No benefit
Fujita [47]	LDL, triglycerides, body weight	Black tea, randomized parallel group, 3 months, n=47	Benefit
Brown [37]	Blood pressure, LDL, HDL,	EGCG, randomized parallel group, 8 weeks, n=88	Benefit on blood pressure, no benefit for lipids
Nantz [38]	Blood pressure, LDL	Tea extract, randomized parallel group, 3 weeks, n=111	Benefit on LDL and blood pressure
Basu [49]	Blood pressure, LDL, body weight	Green tea extract, randomized parallel group, 8 weeks, n=35	Benefit on body weight, no benefit on LDL
Trautwein [50]	Serum lipids	Black tea extract, randomized parallel group, 11 weeks, n=102	No benefit
Hooper [53]	LDL	Meta-analysis of 133 green tea intervention studies	Benefit on LDL

LDL= low density lipoprotein cholesterol, HDL= high density lipoprotein cholesterol