Review Article

Tea flavonoids and cardiovascular disease

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Drinking tea could have a significant impact on public health. Health benefits are believed to be largely due to the presence of high levels of flavonoids. Tea is a rich source of flavonoids, and often the major dietary source. Tea intake and intake of flavonoids found in tea have been associated with reduced risk of cardiovascular disease in cross-sectional and prospective population studies. In addition, flavonoids have consistently been shown to inhibit the development of atherosclerosis in animal models. A variety of possible pathways and mechanisms have been investigated. The focus of this review is on the potential of tea and tea flavonoids to improve endothelial function, and reduce blood pressure, oxidative damage, blood cholesterol concentrations, inflammation and risk of thrombosis. There is now consistent data to suggest that tea and tea flavonoids can improve endothelial function. This may be at least partly responsible for any benefits on risk of cardiovascular disease. Additional studies are needed to investigate whether regular consumption of tea can reduce blood pressure, inflammation and the risk of thrombosis. The evidence for benefit on oxidative damage and cholesterol reduction remains weak.

Key Words: tea, flavonoids, polyphenols, cardiovascular disease, atherosclerosis, endothelial function, blood pressure, oxidative stress, cholesterol, inflammation, platelet function

INTRODUCTION

The term 'tea' refers to the plant *Camellia sinensis*, its leaves, and infusions derived from them. Tea has been consumed as a beverage for well over 2000 years, and it is now commonly consumed in most regions of the world. The worldwide consumption of tea is second only to water, and thus any health effects could have a significant impact on public health. Although tea has historically been thought to promote good health, research into the possible health benefits of tea is only recent. This review briefly discusses data from population studies, animal models of atherosclerosis and randomized controlled trials to have investigated effects on cardiovascular disease-related endpoints.

TEA FLAVONOIDS

Health benefits of tea are believed to be largely due to the presence of high levels of polyphenols, primarily flavonoids. Tea can be classified as green and black. Black teas are produced by promoting the enzymatic oxidation of tea flavonoids. Enzymes involved in polyphenol oxidation are inactivated to produce green tea. Both green and black teas are rich in flavonoids (Table 1). One cup of tea (2 g of tea leaves infused in hot water for 1 to 3 min) will provide 150 to 200 mg of flavonoids. As little as 2 to 3 cups/d of tea will supply the major contribution to total flavonoid intake in most individuals.

TEA, FLAVONOIDS AND CARDIOVASCULAR DISEASE RISK: RESULTS OF POPULATION STUDIES

The relationship between black tea consumption and cardiovascular disease has been explored a number of population studies. Peters et al[1] performed a meta-analysis of tea consumption in relation to myocardial infarction. The analysis included 10 cohort and seven case-control studies. The incidence rate of myocardial infarction was estimated to decrease by 11% with an increase in tea consumption of 3 cups per day.[1] Epidemiological studies have also explored the relationships between dietary flavonoids and cardiovascular disease. The intake of flavonoids has been related to lower risk of heart disease, stroke and total mortality. A meta-analysis of seven prospective studies of flavonoids in relation to coronary heart disease found that the highest tertile of flavonoid intake was associated with a 20% reduction in the risk of fatal coronary heart disease in comparison with the lowest tertile of flavonoid intake.[2]

ATHEROSCLEROSIS IN ANIMAL MODELS

The apo E deficient mouse and hamsters have been used as animal models to investigate the effects of flavonoid-rich foods or extracts on the development of atherosclerosis. In the apo E deficient mouse inhibition of atherosclerotic lesion development has been demonstrated with tea and tea-derived flavonoids, red wine-derived flavonoids, isolated quercetin or catechin, and a pure phenolic acid

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Table 1. Flavonoid composition of tea: percent by dry weight

Component	Green tea	Black tea
Total flavonoids	15-25	15-25
Total catechins	12-18	2-3
(-) Epicatechin	1-3	<1
(-) Epicatechin gallate	3-6	<1
(-) Epigallocatechin	3-6	<1
(-) Epigallocatechin gallate	9-13	1-2
Flavonols	2-3	1-2
Theaflavins	<1	4
Other polyphenols	2-4	7-15

derivative from honey. Similar inhibition has been found with red grape extracts in the cholesterol-fed hamster.[3]

ENDOTHELIAL FUNCTION

The development of endothelial dysfunction may contribute to the pathogenesis of cardiovascular disease. One of the most important molecules released by the endothelium is nitric oxide (NO). This molecule is an important regulator of arterial wall tone. Endothelial dysfunction is characterized by the loss of normal endothelium-dependent and NO-mediated vasodilation in the artery.

Endothelial function may be assessed in a number of ways. Isolated vessels from animals can be used to assess the effects of potentially vasoactive substances *in vitro*. The results of several *in vitro* studies indicate that tea and tea flavonoids cause vasorelaxation of rat aortic rings which is NO and endothelium-dependent.[4] In humans, one of the main methods has been to use ultrasonography to measure flow-mediated dilatation of conduit vessels, such as the brachial artery. This is a non-invasive technique that measures NO-dependent vasodilation of the artery in response to shear stress induced by increased blood flow. At least eight controlled trials have now investigated the effects of tea or pure flavonoids present in tea on endothelial function using this procedure. Most of these studies have shown a significant improvement in flow-mediated dilatation.[4] Green and black teas appear to have similar effects. Similar improvements have been demonstrated using flavonoids derived from chocolate, but the results of studies using red wine derived flavonoids are less consistent.[3]

BLOOD PRESSURE

The results of animal models to investigate the effects of tea and flavonoids derived from tea on blood pressure are inconsistent. Results of population studies suggest that long-term regular ingestion of tea may lower BP.[4] However, because tea intake is generally associated with a range of lifestyle factors which are related to cardiovascular disease risk, controlled trials are needed to address the question.

Acutely, tea can increase blood pressure. Both flavonoids and caffeine, present in tea at about 3% of dry weight, cause a transient increase in blood pressure in subjects who avoided caffeine for 12 hours or more.[5] The relevance of these acute effects to any longer term effects of regular consumption is uncertain. In five controlled trials, the short-term regular ingestion of tea for up to 8 weeks has not been found to alter blood pressure in largely normotensive individuals.[3,4] A recent meta-analysis of these trials showed no overall effect on systolic or diastolic blood pressure, whereas analysis of a similar number of trials using flavonoid-rich dark chocolate did show significant blood pressure lowering.[6] It is possible that longer-term effects on vasodilator function may be required to alter vascular tone and blood pressure. There have been no controlled trials investigating the longer-term effects of regular ingestion of tea. Therefore, although there is some support for the idea that tea and tea flavonoids can attenuate the development of hypertension and reduce blood pressure, further trials are needed.

OXIDATIVE DAMAGE

The antioxidant flavonoids found in tea are suggested to be responsible for reduced cardiovascular disease risk. More than 50 studies now convincingly show that flavonoids possess potent antioxidant activity *in vitro*. However, despite the many animal and human studies in this area, there remains limited evidence that flavonoids can actually inhibit oxidative damage *in vivo*.[7,8] Good support for a lack of systemic antioxidant activity of flavonoids *in vivo* comes from studies showing that inhibition of atherosclerosis in animal models is not associated with markers of change in oxidative damage.[9] Thus, it is possible that antioxidant activity is not an important mechanism for benefits of tea flavonoids on endothelial function, atherosclerosis and cardiovascular disease risk.

CHOLESTEROL

Results of *in vitro* studies, studies in animal models and population studies suggest that flavonoids could reduce blood cholesterol concentrations. However, many human intervention studies have found little or no change in blood lipid and lipoproteins with increased flavonoid intake from black tea. It is less clear whether flavonoid intake from other sources might improve blood lipid and lipoproteins.[3,8] For black tea, there have been at least seven randomised controlled trials, with all but one showing no significant effect. Thus, if there is an effect of black tea on circulating cholesterol concentrations, it is small. Fewer randomised controlled trials have used green tea, where results are mixed.

INFLAMMATION

Inflammation is thought to play a significant role in the initiation and progression of vascular disease. Inflammatory processes in the vascular wall may be mediated by a range of factors, such as cytokines, eicosanoids and NO, which in turn modulate cellular signaling, cell growth and differentiation and a variety of other cellular processes. Results of *in vitro* studies suggest that flavonoids present in tea and other foods have effects on inflammatory mediators consistent with anti-inflammatory effects.[10] However, to date there is little support for anti-inflammatory effects in randomized controlled trials. Several studies have shown no effect of regular ingestion of tea for up to 8 weeks on circulating C-reactive protein

concentrations, a non specific marker of inflammation.[11] Effects of tea on other inflammatory markers remain less clear.

PLATELET FUNCTION AND THROMBOSIS

Excessive platelet activation results in an increased susceptibility to aggregation and clotting. This can be an important cause of thrombosis leading to myocardial infarction and stroke. I*n vitro* studies have shown that isolated flavonoids at high physiological concentrations can reduce platelet aggregation and markers of platelet activation.[12] A number of intervention studies in humans have investigated the effects of flavonoid-rich foods and beverages on platelet function.[13] The data for cocoa and red grape supplements generally suggest reduced platelet activation. The data for tea are less consistent. For tea, four of five trials to assess effects of tea on *ex vivo* platelet aggregation found not effect.[14,15] However, two trials have shown that regular ingestion of tea for 4 weeks results in a reduction in circulating p-selectin concentrations,[11,14] which is a marker of platelet activation. It is possible that *ex vivo* platelet aggregation is not a sensitive marker of platelet activation and thrombotic risk. Further trials are needed.

CONCLUSIONS

Available data suggests that tea is likely to provide modest protection against cardiovascular disease. Effects of tea flavonoids on endothelial function may be at least partly responsible for any benefits on risk of cardiovascular disease. Additional studies are needed to further investigate whether regular consumption of tea can reduce blood pressure and reduce inflammation and the risk of thrombosis. Reduced oxidative damage and cholesterol reduction are unlikely to be important mechanisms for cardiovascular protection.

AUTHOR DISCLOSURES

Jonathan M Hodgson, no conflicts of interest.

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