Commentary

Tea flavonoids and cardiovascular health

R.A. RIEMERSMA, C.A. RICE-EVANS¹, R.M. TURRELL², M.N. CLIFFORD³ and M.E.J. LEAN⁴

From the Cardiovascular Research Unit, University of Edinburgh, ¹Wolfson Centre for Age-Related Diseases, King’s College London, ²Department of Pharmacy and Pharmacology, University of Bath, ³Food Safety Research Group, University of Surrey, and ⁴Department of Human Nutrition, University of Glasgow, UK

Summary

Tea is rich in antioxidant polyphenols (catechins, flavonols, theaflavins and thearubigins). Epidemiological evidence relating regular consumption of tea or related polyphenols to CHD is equivocal. Catechins are absorbed from tea, but low plasma concentrations are attained. The bioavailability of theaflavins and thearubigins is unknown. Tea does not reduce blood pressure or plasma lipids in well-controlled human trials. Tea polyphenols inhibit LDL lipid peroxidation in vitro, but the effect ex vivo is small. The plasma antioxidant potential increases after drinking green but not black tea. Tea consumption tended to reduce the development of aortic atherosclerosis in rabbits. Tea polyphenols exert marked effects on cells, and inhibit neutrophil migration and inflammatory responses, sometimes at low concentrations. These diverging results suggest potential beneficial effects, but emphasize the need for good human trials of tea using early markers of CHD before firm conclusions can be drawn.

Introduction

Consumption of fruit and vegetables is associated with lower coronary heart disease (CHD) mortality rates.¹ The reason for this association is not clear. Fruit and vegetables are rich in fibre, potassium, antioxidant vitamins and polyphenolic substances and may displace other nutrients, such as saturated fatty acids, that could lead to CHD. These diets tend to be low in saturated fatty acids and rich in mono- and/or polyunsaturated fatty acids, which may also be protective.

Early epidemiological observations did not relate tea drinking to reduced CHD mortality. However the risk of myocardial infarction was reduced by 40% in one study but not in two others (Figure 1).²⁻⁴ It is difficult to explain discrepancies between general surveys, due to lack of detail about exposure to tea, e.g. quantity, strength and variety.

Tea is an unusual ‘food’. It is not classified as ‘fruit and vegetable’ and contains few conventional nutrients, but a high amount of flavonoids (e.g. flavonols including catechins, flavonols, theaflavin, thearubigin).⁵ Recently, several large-scale epidemiological studies have re-examined the relation between consumption of tea and CHD by including estimates of flavonol consumption.⁶⁻¹⁰ Some, but not all, support the view that tea or flavonoids reduce the risk of CHD (Figure 1). The design of these prospective studies was highly variable in other respects, particularly in the average tea consumption. In the Finnish study examining the
relation between flavonoid intake and CHD, tea consumption was so low that it was not recorded.\textsuperscript{6} Less than 10\% of the US population drank tea as their preferred beverage.\textsuperscript{7,10} On the other hand very few Welsh or Dutch men did not drink tea at all, and tea was the most important source of dietary flavonoids.\textsuperscript{5,9}

Dietary and lifestyle factors are usually related. It is possible that those who do or do not drink tea, or who consume large amounts of flavonoids regularly, differ in some other way that affects CHD risk, such as cigarette smoking. In the UK, tea consumption and CHD are both high in manual workers, perhaps due to the strong association between socio-economic factors and CHD.\textsuperscript{4,9} The association between increased CHD mortality and tea remained after adjusting for socio-economic factors.\textsuperscript{9} Residual confounding is a possibility,
because tea consumption in the US study is associated both with factors that increase (age, hypertension) and decrease (non-smoking, dietary fibre) the risk of CHD. These opposing influences might tend to cancel each other. It is difficult to ensure full adjustment.

In this article we examine critically the various aspects of food-derived polyphenols originating from tea which might be related to cardiovascular protective properties in (cell) systems in vitro, in animal models and in humans.

**Tea flavonoids**

Flavonoids are widespread in plants and in food of plant origin. Most flavonoids occur naturally with a sugar molecule attached, although the catechins of tea do not share this feature. Flavonoids are classified into six categories according to the oxidation level of the central heterocyclic ring (Figure 2). Analysis of the diet is simplified by converting the glycosides to 25–30 aglycones, but only a few are relevant to tea. A typical cup of tea (200 ml) contains 24–40 mg catechins, 8–15 mg flavonols plus flavones, ~85 mg thearubigins and 7–15 mg theaflavins, which together amount to 166–193 mg per cup (D.A. Balentine, personal communication). The yellow, brown and red pigments (theaflavins, thearubigins) are ‘derived polyphenols’ generated during processing of tea. These heterogeneous, large polymers are difficult to analyse. Dietary intake of phenols and polyphenols ranges from 100 to 2000 mg per capita per day. Black tea is therefore one important source of dietary phenols.

Tea polyphenols, catechins and flavonols scavenge reactive oxygen species and chelate transition metal ions in a structure-dependent manner. These flavonoids are antioxidants by virtue of the number and arrangement of their phenolic hydroxyl groups. Flavonoids found in tea scavenge NO and peroxynitrite (produced from superoxide radical and NO). Tyrosine is particularly vulnerable to nitration by peroxynitrite, and increased levels of 3-nitrotyrosine have been reported in atherosclerotic lesions. It is not known whether tea polyphenols prevent the accumulation of nitrotyrosine in atherosclerotic lesions.

![Figure 2](image-url)

**Figure 2.** Tea polyphenols. Tea contains polyphenolic flavonoids. In green tea, catechins (catechin, epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate) represent 80–90% and flavonols (kaempferol, quercetin and myricetin glycosides) <10% of total flavonoids. These polyphenols form complex condensation products (theaflavins, thearubigins) during the production of black tea. The catechin content of black tea is only 20–30%, whilst the theaflavins and thearubigins represent ~10 and 50–60% of total flavonoids. The structure proposed for thearubigins is hypothetical. The reducing properties of tea polyphenols depend on the dihydroxybenzyl ring and their ability to delocalize free electrons. Adjacent keto- and hydroxy-groups are important for ion-chelation.
Bioavailability of flavonoids

Knowledge of the absorption and metabolism of flavonoids is crucial to the understanding of whether these compounds or their metabolites have the potential to exert the biological activity in vivo that the in vitro studies suggest. Almost 50% of orally administered radiolabelled catechin was excreted in the form of urinary metabolites. This indicates that catechins and/or their gut flora metabolites are well-absorbed. Plasma concentrations of catechins peak at 1.5–2.6 h in almost all subjects. The increase in plasma total catechin concentrations is greater after ingestion of a single large dose of green tea than one of black tea solids (equivalent to 3–6 cups), ranging from 0.63 to 1.8 μmol/l and from 0.2 to 0.34 μmol/l, respectively.21–24 Plasma levels returned to baseline at 24 h. Less than 10% of epigallocatechin and epicatechin was excreted 3–6 h after ingestion of 1.2 g tea solids by healthy volunteers. Interestingly, catechin gallates were not detected in their urine.25

Absorbed flavonoids are extensively modified and converted to glucuronides and sulphates predominantly in the liver and some are methylated by catechol-O-methyl transferase.26 There are no published data concerning the absorption of theaflavins and thearubigins. Thearubigin is likely to be extensively metabolized by the colonic microflora, and some of its antioxidant effects in vivo may be related to a range of phenolic acids (e.g. 3,4-dihydroxyphenylacetic acid, etc.). Some of these low-molecular-weight molecules are readily absorbed and may retain the antioxidant properties of their parent compound.27 The absorption, metabolism and excretion of flavonoids from tea has been reviewed in more detail elsewhere.26,28

Effects in vivo

The effects of tea (6 cups/day for 4 weeks) on serum cholesterol and blood pressure have been examined. Neither black nor green tea affected serum cholesterol21,32,36 or blood pressure in controlled trials.36,37 Observational studies had previously suggested that five or more cups tea/day reduced serum cholesterol and blood pressure slightly.38 This may be due to the confounding association between tea consumption and lifestyle factors (e.g. an inverse association with coffee consumption, which may increase serum cholesterol).38,39

One study reported that one cup of green or black tea increased the plasma antioxidant potential (ability to scavenge free radicals) by 40–50%, with addition of milk preventing this rise.40 Other tea studies showed little or no increase in the plasma antioxidant potential after drinking one cup equal to the strength of 4 to 6 cups with or without milk.23,24,25,35,34 Regular tea consumption also does not increase plasma antioxidant potential.30,31 The designs of all these studies were optimized to observe an effect. Often the influence of dietary flavonoids from other sources was reduced, and large amounts of tea (up to 10 cups/day) were drunk for up to 4 weeks. A small transient increase in plasma antioxidant potential was reported for green tea.31,34

LDL oxidation in vitro and ex vivo

There is substantial evidence that ‘oxidized’ LDL is central to early events leading to atherosclerosis. Minimally oxidized LDL induces the expression of monocyte chemoattractant protein 1, monocyte adhesion molecules and metalloproteinase 1, and thereby promotes monocyte infiltration and formation of foam cells in the coronary arterial wall.29 Flavonoids from green and black tea (and red wine), when added directly to isolated LDL, protect against lipid peroxidation induced by free radicals, copper ions and cells.11,22,30,31 Studies with purified tea catechins confirm these observations.22 The resistance of isolated LDL (0.17 mg protein/ml) to oxidation induced by CuSO₄ in vitro was already demonstrable at 50 μg/l in one study.32 A higher concentration is necessary when LDL particles are preincubated with tea flavonoids, re-isolated and then subjected to copper-mediated lipid peroxidation (≥50 mg/l or ~80–160 μmol/l).22,31

In contrast to the protective effects of flavonoids against LDL oxidation in vitro, ingestion of green or black tea fails to inhibit LDL oxidation ex vivo.22,31–33 These results were explained by the fact that the concentrations of the tea catechins had risen insufficiently to delay the onset of lipid peroxidation following the ingestion of tea.31,33 The possibility that these water-soluble compounds (including flavonoid glucuronides) were lost during LDL isolation from plasma was recently explored.34,35 Lipoprotein fatty acid oxidation of dilute, whole serum (presumably reflecting predominantly LDL particles) was therefore used. Four cups of black (but not green) tea increased resistance slightly, and onset of the rapid phase of lipid peroxidation was delayed by 7 ± 4% (p = 0.05).34 These results were not confirmed in another study.35 It is doubtful whether such a marginal effect could influence LDL oxidation in vivo.31 The possibility that tea might affect the development of atherosclerosis by other cellular mechanisms has apparently not been addressed.
Effects in cellular systems

Several, but not all, polyphenols inhibit cell growth and proliferation, particularly of transformed cells, and promote programmed cell death (apoptosis). Tea polyphenols enhance cellular antioxidant enzyme activity or antioxidant defence. However, the relevance of some of these cancer-related studies is not certain, in view of the high polyphenol concentrations used (40–400 μmol/l) (reviewed in reference 41).

Epigallocatechin gallate, at a physiologically relevant concentration (0.6 μmol/l), inhibited neutrophil migration through cultured human endothelial cell monolayers.42

Furthermore, polyphenolic compounds of green tea may prevent endothelial cell-mediated LDL lipid peroxidation and thereby inhibit expression of haem oxygenase gene.43 These observations could be important, since haem oxygenase has been linked with the transformation of monocytes to resident macrophages.44

NFκB plays a central role in the inflammatory response by the expression of TNFα and NO synthase. Epigallocatechin gallate (2.5–10 μmol/l) inhibited lipopolysaccharide and interferon-γ-induced nitrite production by mouse peritoneal macrophages by more than 50%.45 Some of these effects could be relevant to endothelial dysfunction and the development of atherosclerosis, but considerable further work is needed to elucidate the cellular mechanism(s) of any protective cardiovascular effect of tea polyphenols.

Atherosclerosis

Green and black tea flavonoids provided in drinking water (3 g/l for 21 weeks) reduced the tendency of LDL to oxidize ex vivo, but failed to reduce the development of aortic atherosclerotic lesions in cholesterol-fed female rabbits.46 Despite the fact that a large number of animals were examined (20/group), the study lacked statistical power to confirm an apparent 30% reduction in the atherosclerotic lesion after green tea (p = 0.11). The cholesterol-fed atherosclerotic rabbit may not be the best model to study the role of antioxidants in preventing atherosclerosis,46 as the predominant lipoprotein of the rabbit β-VLDL is avidly taken up by macrophages, with no requirement for oxidative modification.47

The effect of tea consumption on the development or regression of atherosclerotic lesions in humans has not been directly examined.

Conclusion

These diverging experimental and epidemiological results emphasize the need for specially designed well-controlled studies of tea or tea flavonoids using early markers of CHD, such as endothelial dysfunction or atherosclerotic progression as an endpoint. Doubts about any protective effect of tea will remain until such trials have been conducted.

Acknowledgements

The authors are members of the Brooke Bond Tea Scientific Advisory Board.

References


