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The role of tea in cardiovascular disease

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ABSTRACT

Tea is an infusion of the leaves of the *Camellia sinensis* plant, which is not to be confused with so-called 'herbal' teas. Some biologically active chemicals in tea include flavonoids, caffeine and fluoride. For as long as people have been drinking tea, there have been health benefits associated with it. However, it has only been within the past 20 to 30 years that scientific studies have been conducted to investigate the validity of these claims. Many animal studies, and recently an increasing number of human studies, including epidemiological studies and clinical trials, have examined the relationship between tea drinking and health. Overall, observational studies in humans suggest that daily consumption of at least 3 cups of tea may be associated with a risk reduction of mortality (44%) after myocardial infarction compared with non-tea drinkers. The possibility that tea consumption reduces the risk of cardiovascular events remains open to the need for further clinical trials to clarify the effects of tea polyphenols in humans in order to recommend their use against cardiovascular diseases.

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INTRODUCTION

The Indonesian National Health Survey 2001 showed that the main cause of death among the Indonesian population was cardiovascular disease (diseases of the heart and great vessels), amounting to 26.3% of all deaths. When compared with the mortality rates due to cardiovascular disease in 1975, 1986 and 1995 of 5.9%, 9.1%, and 19%, respectively, these values indicate an increasing trend in the mortality rate of cardiovascular disease.[1] Epidemiological observations and clinical trials have established an association between regular tea consumption and health, particularly prevention of cardiovascular disease and stroke.[2,3]

Dietary factors may both reduce and contribute to risk of cardiovascular disease (CVD) in a number of ways. Antioxidants, such as vitamin C, vitamin E and a range of other plant compounds, such as the flavonoids, are considered beneficial.[4] It is widely known that the incidence of coronary events (death definitely or probably due to coronary heart disease or non-fatal myocardial infarction) is

substantially lower in the Japanese than in Western populations, although this is still open to question.[5] In Japan, as well as in other Asian countries, tea consumption is very high, and green tea, in particular, is favored by the Japanese.

Chemical composition of tea

Tea is an infusion of the leaves of the tea plant *(Camellia sinensis L.)* and its consumption worldwide is second only to that of water. The tea plant is found in 30 countries, but it originally came from China, where it was cultivated about 4000 years ago. However, recent archeological evidence has revealed that the plant was already utilized about 500,000 years ago.[6] Although the belief in the beneficial qualities of tea had been closely associated with this beverage since its discovery, scientific studies on tea and the substances contained therein were initiated only around 30 years ago.

There are three kinds of tea, namely green tea, black tea and oolong tea, which differ in the processing methods used in the curing of the tea leaves. Green tea is prepared from unfermented tea leaves and has been demonstrated to have the highest catechin content. Black tea undergoes a fermentation process, such that most of its catechins are converted into theaflavins and thearubigins. On the other hand, oolong tea is processed by partial fermentation. Black tea is mainly consumed in Europe, North America and North Africa (except Marocco), whereas green tea is consumed in Asia and oolong tea is renowned in China and Taiwan. Most of the tea produced is black tea, amounting to 76-78%, which is consumed throughout the world. Production of green tea is around 20-22% of the global tea production, whereas oolong tea production is only 2%.[7]

Tea contains a number of polyphenols, particularly flavonoids. The classification of polyphenols and the origins of the chemical substances contained in the tea plant are listed in Table 1.[8] Flavonoids are phenol derivatives that are found in a variety of plants and exhibit an enormous diversity, as more than 40,000 kinds have been recognized.[9] The principal flavonoids present in green tea are the catechins, such as epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG). The catechins of black tea undergo polymerization (fermentation/enzymatic oxidation) to form mainly theaflavins and thearubigins. The amount of catechin found in tea depends on the curing process, geographic location and cultivation methods.[8]

Epidemiological studies

Mukamal KJ, et al. carried out a cohort study on patients with acute myocardial infarction, who were asked about their tea drinking habits in the last year before the occurrence of the attack, and subsequently observed for two to four years. Those patients who consumed less than 14 cups per week (moderate tea drinkers) had a hazard ratio of 0.69 (95% CI 0.53 to 0.89), whereas those consuming 14 or more cups per week (heavy tea drinkers), had a hazard ratio of 0.61; 95% CI 0.42 to 0.86). Both groups had a mortality lower risk when compared with persons who did not drink tea.[2]

Sesso and colleagues used a case-control design to examine the relation between tea and coffee consumption and mycocardial infarction.[9] They examined tea and coffee intake by questionnaire in 340 subjects and 340 matched controls from the Boston Health Study and observed a 44% reduction in cardiovascular risk in individuals drinking more than one cup of tea per day. No significant relationship was found between coffee consumption and cardiovascular disease.

Table 1. Classification of polyphenols and origin of chemicals in tea plants[8]

Category	Classes	Major Food Sources
Phenolic acids	Ferulic acid	Dietary fibre – hemicelluloses
	Caffeic acid:	Many fruits and vegetables, coffee
	- Chlorogenis acid	
	Condensed tannins	Mango fruit
	Hydrolyzable tannins:	Blackberries, raspberries, strawberries,
	- Gallotannins:	wine, brandy aged in oak barrels
	- Ellagitannins	
Flavonoids	Flavones	Sweet red pepper, celery
	Flavonols:	Tea, onions, apples, many other fruits
	- Quercetin	and vegetables
	Flavanols:	Tea, especially green tea, chocolate,
	- Catechins :	cocoa
	epicatechin (EC)	
	epicatechin-3-gallate (ECG)	
	epigallocatechin (EGC)	
	epigallocatechin-3-gallate (EGCG)	
	Flavanones :	Oranges, citrus fruits
	- Hesperetin	
	Isoflavones :	Soybeans, soy protein-containing foods
	- Genistein	
	- Daidzein	
	Anthocyanins :	Red fruits: cherries, plums, strawberries,
	- Cyanidin	raspberries, blackberries, grapes, red and black currants
	Proanthocyanidins	Apples, pears, grapes, red wine, tea
Lignans	Enterodiol	Flaxseed, flaxeed oil
Stilbenes	Resveratrol	Red wine

A Dutch study demonstrated that tea drinking may reduce the risk of fatal heart attacks. The sudy was performed on 4,807 men and women aged 55 years and older, who had suffered no heart attacks during the past five years or more. Persons drinking more than 375 mL of tea daily had a lowered risk of myocardial infarction, in comparison with non-tea drinkers.[10] In contrast, a 7.7 year follow-up on participants of the Scottish Heart Study showed no relationship between tea drinking and cardiovascular disease.[11]

Peters et al. have recently pooled data from the USA and Europe into a meta-analysis and reported a protective effect of tea on myocardial infarction (11% per three cups per day).[12] This analysis specifically excluded data from the UK and thus has not clarified the issue. Meta-analysis is a powerful statistical tool, but it cannot account for exclusion of major confounding factors, such as dietary intake of other antioxidants (eg. vitamin C and E), or social factors. Cross-culturally this is a major drawback, since the social patterns of tea consumption and its relationship to CVD in the UK are the opposite of those in other countries. Even controlling for a confounding factor, such as social class,

is often not adequate to remove the whole effect of interest.[13]

Dreger et al. have demonstrated the protective effect of EGCG and theaflavin-3,3'-digallate (TF3) against oxidative stress on rat cardiac muscle, when the substances were administered one hour before induction of oxidative stress by means of hydrogen peroxide. Thus green tea and black tea extracts, containing EGCG and TF3 respectively, may protect the heart muscle against oxidative stress.[14]

Several possible mechanisms could explain an association between tea consumption and survival among patients with acute myocardial infarction. A recent randomized trial found that acute and chronic black tea consumption improved endothelial function in patients with coronary heart disease in an additive fashion.[15] This provides a suggestive mechanism for a beneficial impact of tea intake on survivors of acute myocardial infarction, given the adverse prognosis associated with coronary endothelial dysfunction in patients with coronary heart disease.[16] Flavonoids also inhibit LDL oxidation, perhaps by reducing macrophage superoxide production.[17] Oxidized LDL may promote atheroma formation by increasing macrophage uptake, monocyte recruitment, and direct endothelial cell damage, thus antioxidant use may prevent myocardial infarction, at least in some patients.[2] Platelet aggregation is a precipitating event in cardiovascular disease, and tea contains antioxidant flavonoids that are known to decrease platelet aggregation in vitro. Plasma flavonoids increase with acute and chronic tea consumption, indicating adequate absorption of tea flavonoids. A randomized cross-over design demonstrated that acute and chronic black tea consumption does not affect ex vivo platelet aggregation in patients with coronary artery disease. This finding suggests that an effect of tea flavonoids on platelet aggregation is unlikely to be the explanation for the reduction in risk of cardiovascular events noted in epidemiological studies.[18]

Antioxidant capacity of tea

Experimentally it has been shown that tea flavonoids may increase the number of gap-junctions, stimulate B cell proliferation, and inhibit cytochrome P_{430} enzymes in hepatic cells in vitro.[19] By oxygen radical absorbance capacity (ORAC) assessment it was found that both green and black tea had a higher antioxidant capacity against peroxyl radicals than vegetables such as garlic, kale, spinach and Brussels sprout. Additionally, by determination of ferric reducing antioxidant power (FRAP) it turned out that green tea had a higher antioxidant capacity.[20]

The in-vitro antioxidant capacity of tea depends on the test used and does not reflect factors such as bioavailability and metabolism. Thus, for determining the benefits of tea, an in-vivo antioxidant capacity test would be more appropriate.

Recently, several clinical trials have shown that drinking tea increases plasma antioxidant levels in adults after 30 to 60 minutes.[21] The statistically significant increase in plasma antioxidant levels ($p<0.001$) was determined by the FRAP assay, after the subjects had consumed 300 mL of tea infusion (prepared from 20 g tea leaves in 500 mL water) or 2 g of green or black tea extract (equivalent to 3 cups).[21,22] On average, plasma antioxidant levels were raised about one to two hours after drinking tea and subsequently decreased rapidly.[7]

Drinking tea or tea extract repeatedly within one to four weeks appeared to decrease biomarkers of oxidative stress. A study on 40 Chinese male cigarette smokers and 27 American males and females in the USA, found that drinking 6 cups of green tea daily for one week reduced the levels of DNA oxidation damage, lipid peroxidation, and free radical

synthesis.[23] Similarly, among ten patients with type 2 diabetes who consumed high doses of flavonoids for two weeks, including 6 cups of black tea, there was a reduction in oxidative stress against lymphocyte DNA.[24] Plasma malondialdehyde level, another indicator of lipid peroxidation, was reduced in 20 healthy women aged 23 to 50 years, who ingested capsules containing linoleic acid and tea extract (equivalent to 10 cups of green tea). However, administration of placebo did not change the concentration of 8-isoprostaglandin $F_{2\alpha}$ and oxidized glutathione in blood.[25] The results of the latter study are somewhat misleading, because some individuals in both the intervention and the control groups had also consumed black tea up to 560 mL per day.

Tea and endothelial cell function

It is now generally accepted that endothelial dysfunction plays a role in the early development of atherosclerosis.[16,26] The endothelium is made up of squamous cells lining the blood vessels, and produces vasoactive factors, such as nitric oxide (NO) and prostacyclins. These substances are active in vasodilation dan platelet inhibition. Impairment of nitric oxide activity of endothelial cells may contribute to the pathogenesis of atherosclerosis and disorders of coronary blood flow, which subsequenly may cause coronary heart disease.[27]

Recent research findings indicate that black tea may reduce the risk of heart disease by contributing to the maintenance of endothelial cell functions. Presumably there are chemical substances in tea that enhance the dilatory capacity of the arteries. A study by Sudjarwo SA on 30 rabbits has proved that catechin administration may decrease plasma malondialdehyde production and enhance acetylcholine-induced endothelium-dependent relaxation of the aorta in rabbits on a cholesterol-rich diet.[28]

In a cross-sectional study by Duffy SJ et al., freshly infused black tea and plain water were randomly assigned to subjects, in whom brachial artery dilation was monitored using Doppler ultrasound. Both short-term (2 hours after drinking 450 mL black tea) and long-term (900 mL black tea daily for 4 weeks) consumption may enhance vasodilation ($p < 0.001$). This phenomenon is associated with increased plasma levels of tea polyphenols. On administration of 200 mg caffeine or nitroglycerin no vasodilatory effect was found.[15]

Nagaya N et al. also reported that administration of 400 mL green tea to cigarette smokers may increase the blood circulation in the arms.[29] It is a well-known fact that free radicals in cigarette smoke may impair endothelial function. Therefore further research is needed to prove that antioxidants in green tea can lower the risk of cardiovascular events. Vasodilation in patients with coronary heart disease is impaired, in comparison with healthy individuals, thus this study proved that tea can enhance endothelial cell function of the blood vessels.

Tea drinking is inversely related to atherosclerosis formation and progressivity. In the Rotterdam study involving 3,454 adults aged 55 years or older, who were followed-up for two to three years, Geleijnse et al. reported on radiological assessment of aortic atherosclerosis by measuring calcification in the abdominal aorta. The results showed that individuals drinking 1-2 cups of tea per day had an odds ratio of 0.54, which was reduced to 0.31 in those drinking 4 cups or more.[10] Sasazuki et al. assessed atherosclerosis by coronary arteriography in 512 Japanese over the age of 30 years, and reported that tea provides protection against atherosclerosis.[30]

Debette S et al. observed 6,597 French men and women aged ≥65 years, and reported that the frequency of plaque formation in the common carotid artery was in 44% women who did not drink tea, 42.5% in those drinking 1–2 cups of tea per day, and 33.7% in those consuming ≥3 cups daily. Thus there was a reduction in the frequency of common carotid artery plaque formation when drinking ≥3 cups of tea daily. (P<0,0001). In this study, tea consumption in men had no effect on common carotid artery plaque formation.[31]

Drinking 5-6 cups of green tea daily or 200-300 mg EGCG, as reported by Wolfram S, may maintain cardiac health and metabolic functioning of the body.[32] These studies indicate that tea antioxidants may help prevent atherosclerosis, particularly coronary heart disease.

CONCLUSIONS

Tea is a excellent source of dietary antioxidant flavonoids, whose actions on endothelial function may help explain the cardioprotective effects of tea drinking that has been observed in several countries. Both green and black tea have strong in-vitro and in-vivo antioxidant capacities. Tea plays a role in lowering the risk of cardiovascular disease and stroke. Tea is a drink of global renown, thus further research should be of appropriate design, by measuring total daily consumption of tea and its polyphenol content, with an emphasis on its role in primary and secondary prevention of cardiovascular disease.

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