RHYTHMOS

January 2015 • Volume 10 • No 1 (37)

ISSN: 1792-7919 **e-ISSN: 1792-7927**

URL: www.rhythmos.gr / http://rhythmos.info.tm / http://www.evangelismos.dom.gr

ΡΥΘΜΟΣ

EDITORIAL

Moderate Intake of Flavonoid-Rich Tea, Green or Black, Confers Cardiovascular Protection

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A variety of dietary supplements have been proposed for the management of hypertension and other cardiovascular diseases, but the evidence for their efficacy is meagre.[1] However, over the last few years, there is growing interest in the potential benefit of tea in cardiovascular protection.[2-4] Tea is the extract of *Camellia sinensis*, and one of the most widely enjoyed drinks.[2,3] The leaves of the plant are rich in flavonoids, containing several phytochemicals including phenols and catechins, to which potent antioxidant, free radical scavenging, appetite-modifying and hypolipidemic effects have been ascribed.[2-7] Long-term consumption of beverages containing catechins inhibits the formation of oxidized lipids and decreases body fat.[5-9] Over 70% of flavonoids in green tea are catechins. Epigallocatechin-3-gallate (EGCG) is the cardinal (65%) catechin in green tea. In-vitro studies have shown that the epigallocatechins in green tea have angiotensin converting enzyme inhibitor properties,[10] and vasodilatory actions. [11] Molecular and animal studies have demonstrated that green tea catechins enhance processes, thought to stimulate bile acid production, decrease cholesterol concentration in the hepatocytes, inhibit intestinal absorption of lipids and upregulate low-density lipoprotein (LDL) receptors in the liver, mechanisms all leading to favorable blood lipid profile. [2-4,12,13]

Black tea also contains small amounts of catechins. However, due to the fermentation process of black tea, its primary antioxidant polyphenols are theaflavins and thearubigins, equally effective antioxidants to catechins. [14]

Tea is the most widely consumed beverage by people across the globe, next to water. Tea is manufactured in three basic forms, green, black and oolong tea.[6] All forms of tea come from the leaves of the plant *Camellia sinensis*, however the processing that the leaves undergo to make the final tea is different. The leaves for black tea are fully oxidized, while those for green teas are lightly steamed before being dried, so that the oxidative enzymes are inactivated and the flavonoid contents are retained. Oolong tea is a partially oxidized product. Black tea represents approximately 72% of the total consumed tea in the world, whereas green tea accounts for 20-25% and oolong tea for <2%. Green tea is rich in the flavanol group of polyphenols, known as catechins, which may constitute up

to 30% of the dry leaf weight (Table 1). Other components include other polyphenols, caffeine (~3%), along with very small amounts of the other common methylxanthines, theobromine and theophylline. Thearubigins constitute the largest mass of the extractable matter in black tea. Oolong tea is intermediate in composition between green and black teas. Black teas mostly come from plantations in Africa, India, Sri Lanka and Indonesia, while green teas come from the Far East (China and Japan). As indicated above, black and green teas both contain similar amount of flavonoids, however they differ in their chemical structure. Green teas contain more of the simple flavonoids called catechins, while the oxidisation that the leaves undergo to make black tea converts these simple flavonoids to the more complex varieties called theaflavins and thearubigins. Although the oxidisation process modifies the type of flavonoids present, the total level and their overall antioxidant activity, is similar in both teas. [14]

Table 1. Components of Tea

	Black Tea	**Green Tea**
Catechins	3-10%	30-42%
Flavonols	6-8%	5-10%
Theaflavins	3-6%	
Thearubigins	12-18%	
Methylxanthines	8-11%	7-9%
Carbohydrates	15%	10-15%

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world.[15] According to World Health Organization report, CVDs were accounted for 29% of all global deaths in 2004 and about 23.6 million people will die from CVDs by 2030. [2] In the USA, CVD accounted for 32% of all deaths in 2010 and more than one third of the U.S. population live with ≥1 types of CVD. [15] By 2030, 44% of the US population is projected to have some form of CVD. In most instances, CVD is attributed to atherosclerosis, a vascular chronic athero-thrombo-inflammatory condition. [16]

The cardiovascular effects of green tea consumption have been extensively studied in human as well as in animal models.[2] There is accumulating evidence from epidemiological and human interventional studies that consumption of green tea is associated with decreased CVD risks. [17-22]

To date, many of the catechins' effects have been demonstrated, although the exact underlying mechanisms have not been fully elucidated. The most important biological actions are their antioxidant and free radical scavenging properties.[23] In addition to their direct antioxidant effect, they can also indirectly increase endogenous antioxidants to mitigate oxidative damage. Catechins can also protect cells from lipid peroxidation and DNA deamination induced by oxidative stress. Epigallocatechin gallate (EGCG) has been shown to modulate apoptotic pathways to protect against oxidative stress. Catechins can also modulate apoptosis by altering antiapoptotic and proapoptotic gene expression. However, a divergent effect of catechins on apoptotic pathways may exist, as in low concentrations catechins may demonstrate antiapoptotic effects, while high doses may promote apoptosis. Similarly, in addition to the evidence of catechin-conferred cytoprotection via antioxidant and antiapoptotic actions, other observations suggest that catechins may also be prooxidant, mostly at high concentrations. However, the prooxidant effects of high-dose catechins may induce an up-regulation of endogenous antioxidants, which may enhance cytoprotection. Additionally, catechins appear to have anti-inflammatory effects,[18] partly due to their scavenging of nitric oxide (NO) and reduction of NO synthase (NOS) activity, and/or the inhibition of inducible NOS (iNOS).

The antilipidemic properties of catechins have been well-documented and can lead to CVD prevention. They have been shown to inhibit the oxidative modification of LDL. [13] Furthermore, catechins can inhibit LDL-induced human vascular smooth muscle proliferation, which is associated with atherogenesis. [2,24,25]

In vitro and *in vivo* studies have suggested potential antiplatelet and antithrombotic effects of tea catechins.[2] Exposure of human platelet concentrates to EGCG has been shown to maintain platelet aggregability and preserve platelets by inhibiting platelet activation and apoptosis. There is accumulating evidence that tea catechin supplementation may improve platelet aggregation and thrombosis through diverse mechanisms.

Finally, catechins have proven efficacy as prophylactic and neuroprotective agents against neurodegenerative/ neuroinflammatory diseases such as Parkinson's disease, Alzheimer's disease and multiple sclerosis, primarily due to their antioxidant and anti-inflammatory properties.[23] Catechins are also potent agents in preventing the neuronal damage that occurs after a stroke. [23]

Many cell culture and animal studies have shown that catechins are potent natural inhibitors of several tyrosine kinase receptors (RTKs). [24] Enhanced RTK activity has been associated with the development of proliferative diseases such as atherosclerosis and cancer. Hence, catechins, which inhibit the growth factor-RTK-mediated signal transduction pathways and exert an antiproliferative / antiapoptotic effect, can have a role in the prevention and management of such diseases.

Case-control, epidemiological, and small randomized controlled studies and several meta-analyses and reviews

have suggested that tea intake has a cardioprotective effect, with beneficial effect on blood pressure, insulin resistance, inflammation and oxidative stress, and on lipid profile in patients with cardiovascular disease.[13,19-22,25-27]

In a Polish double-blind, placebo-controlled trial, 56 obese, hypertensive patients were randomized to receive a daily supplement of 1 capsule that contained either 379 mg of green tea extract or a matching placebo, for 3 months.[18] According with these results, daily supplementation with 379 mg of green tea extract favorably influenced blood pressure, insulin resistance, inflammation and oxidative stress, and lipid profile in this small cohort of patients with obesity-related hypertension. [18]

According to a Japanese study, men who drank ≥4 cups of green tea per day exhibited an inverse association with coronary atherosclerosis.[19] The favorable effect of catechins on vascular diseases has been ascribed, in part, to the catechins' antioxidant properties that prevent low-density lipoprotein (LDL) oxidation. [20]

A meta-analysis of 20 randomized controlled trials comprising 1536 subjects revealed a significant, albeit small, reduction in systolic blood pressure conferred by green tea (mean difference-MD: -1.94 mmHg; p = 0.0002).[21] Similar results were also observed for total cholesterol (MD: -0.13 mmol/l; p < 0.0001) and LDL cholesterol (MD: -0.19 mmol/l; p = 0.0004). The authors concluded that green tea intake results in significant reductions in systolic blood pressure, total cholesterol, and LDL cholesterol.

Another recent meta-analysis of 13 randomized controlled trials evaluating the effects of green tea on blood pressure in 1,367 subjects suggested that green tea consumption significantly decreased systolic (by -1.98 mmHg; P <0.001), and diastolic blood pressure (by -1.92 mmHg; P = 0.002), compared with the control group. [22] Subgroup analyses suggested that the positive effect of green tea polyphenols on blood pressure was only showed in studies using a low-dose green tea polyphenol, and with long-term tea intake, and in those studies which excluded the confounding effects of caffeine. The authors concluded that low-dose long-term green tea consumption had a favorable effect on blood pressure.

A recent meta-analysis of 11 studies examined the effect of black tea (4-5 cups/day) on blood pressure in 378 patients. [26] The pooled mean effect of regular tea ingestion was -1.8 mmHg (P = 0.0013) for systolic and -1.3 mmHg (P<0.0001) for diastolic blood pressure. In covariate analyses, studies using tea extract powders found larger reductions in systolic blood pressure than studies using leaf tea. Baseline systolic and diastolic blood pressure had a significant impact on the effect of tea ingestion on blood pressure, with a ~1 mmHg larger reduction for every 10 mmHg higher baseline blood pressures. The authors concluded that regular consumption of black tea can reduce blood pressure.

In a review of 11 randomized controlled trials with a total of 821 individuals, 7 trials examining intake of green tea and 4 trials examining intake of black tea, the results suggested that tea has favourable effects on CVD risk factors.[3] Black tea was found to produce significant reductions in LDL cholesterol (mean difference – MD, 0.43 mmol/L) and blood pressure (systolic blood pressure –SBP: MD -1.85 mmHg; diastolic blood pressure - DBP: MD -1.27 mmHg) over 6 months. Green tea was also found to produce significant reductions in total cholesterol (MD -0.62 mmol/L), LDL cholesterol (MD -0.64 mmol/L) and blood pressure (SBP: MD -3.18 mmHg; DBP: MD -3.42). When both tea types were analyzed together, they showed favourable effects on LDL cholesterol (MD - 0.48 mmol/L) and blood pressure (SBP: MD -2.25 mmHg; DBP: MD -2.81 mmHg).

In another recent meta-analysis of 21 randomized controlled trials examining the effects of tea intake on blood pressure in 1323 subjects, the mean systolic and diastolic blood pressures were -1.8 mmHg and -1.4 mmHg lower, respectively, in individuals drinking tea compared with the controls.[27] Subgroup analyses showed that the blood pressure-lowering effect was apparent in the subjects who consumed tea over a median of 12 weeks and for both green and black types of tea. The authors concluded that long-term (≥12 weeks) ingestion of a tea (green and black tea) resulted in a significant reduction in systolic and diastolic blood pressure.

A final word of caution relates to usage of green tea extract capsules containing very high doses of polyphenols and EGCG (up to 750 mg of polyphenols per tablet) and involves liver toxicity.[21, 28] Recommended daily allowance should be limited to 10 mg of extract per kg of body weight with maximum dose of 750 mg/day. It is difficult to exceed the recommended daily allowance by drinking green tea. A cup of green tea contains on average only 80 mg of EGCG. In countries, like China, Japan, India, where people regularly drink 9 - 10 glasses of green tea a day, no cases of toxicity have been reported. Toxicity involves only green tea extract capsules, and in most cases, liver function returns to normal upon discontinuation of high dosage of EGCG. According to randomized controlled studies, adverse events may occur where the daily intake of EGCG exceeded 200 mg. Animal and in vitro studies have shown that there could be an increased risk of adverse events when concentrated green tea is consumed on an empty stomach.[21] On the other hand, in vivo studies have shown that green tea consumption may be hepatoprotective, and pharmacokinetic studies in humans

have demonstrated that green tea consumption is quite safe. [21]

Although promising human and animal data have been accumulated indicating a cardioprotective effect of tea flavonoids, either green tea catechins or black tea thearubigins and theaflavins, further rigorous and well-designed randomized controlled human interventional trials are needed to confirm and provide better understanding of the potential beneficial effects of tea on cardiovascular disease.

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