Tea and Cardiovascular Diseases

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SONG ET AL.: ***Tea and Cardiovascular Diseases.*** *Tea, produced from the tea plant Camellia sinensis, has been consumed as a popular beverage world wide for thousands of years. Catechins are the major constituents in tea that contribute to its biological effects. The anti-thrombogenic, anti-inflammatory anti-hypertensive, and protective effects of tea on endothelium have been widely investigated for decades. Although studies have produced inconsistent results of the protective effect of tea on the cardiovascular system, a relationship between tea consumption and inhibition of cardiovascular diseases has been found in both animal and human studies. The mechanisms of action of tea have also been elucidated in cellular and molecular levels. In this paper, the nutraceutical and medical effects of tea on the prevention and treatment of cardiovascular diseases were reviewed. (J HK Coll Cardiol 2006;14:57-64)*

Cardiovascular disease, catechins, medical effects, tea

摘要

茶葉爲山茶屬的植物，它作爲全球一種受歡迎的飲品已有數千年。兒茶酚是茶葉中的主要成分有著許多生物學效用。在過去的幾十年間茶葉的抗血拴形成、抗炎、抗高血壓和其他對內皮細胞的保護作用被廣泛地研究。雖然茶葉對心血管系統保護作用的研究有著不一致的結果，但是茶葉的消耗與抑制心血管疾病發生這二者間的關係已經在動物和人體研究中證實。茶葉的作用機制在細胞學水準和分子水準得以了闡述。本文復習了茶葉在預防和治療心血管疾病中的營養和醫學作用。

Introduction

Tea, made from the leaves of the plant *Camellia sinensis*, is a popular beverage worldwide. Depending on the degree of oxidation, tea leaves can be categorized into green, oolong, and black tea. Beneficial effects of tea have been shown when used either as a nutritional supplement or as a therapeutic agent. Cardiovascular diseases have become the major cause of mortality and morbidity in the world, and novel agents for the prevention of these disorders are urgently needed. Among life style and dietary changes, tea drinking may exert a beneficial effect on the cardiovascular system. The medical benefits of tea extracts have been studied in a large number of scientific and clinical studies. This article reviewed the major findings of the effect of tea drinking in cardiovascular diseases.

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Constituents and Bioactive Compounds

Fresh tea leaves contain on average (relative to dry substance mass) of 36% polyphenolic compounds, 25% carbohydrates, 15% proteins, 6.5% lignin, 5% ash, 4% amino acids, 2% lipids, 1.5% organic acids, 0.5% chlorophyll as well as carotenoids and less than 0.1% volatile substances.[1,2]

Tea polyphenols include catechins, quercetin, myricetin and kaempferol. The major antioxidant catechins present in green tea are (–)-epigallocatechin-3-gallate (EGCG), 3 (–)-epigallocatechin (EGC),

(–)-epicatechin-3-gallate (ECG) and (–)-epicatechin (EC); with EGCG being the most abundant catechin. In addition, tea contains phenolic acids, mainly caffeic, quinic, and gallic acids. Theanine and glutamic acid can also be found in tea.[3-5] Figure 1 shows the chemical structures of major green and black tea polyphones.

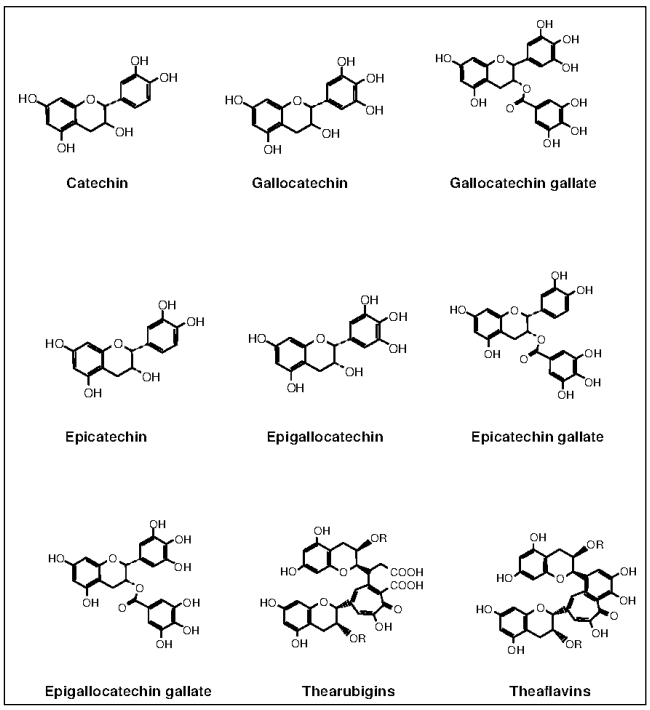

Figure 1. *Chemical structures of major green and black tea polyphones. The phenolic groups provide antioxidant potential. R = galloyl group.*[3]

Tea and Cardiovascular Diseases

Atherosclerotic Coronary Heart Disease

Anti-oxidant Effect

Free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) play an important role in aging, reperfusion injury and pathogenesis of cardiovascular diseases. Endothelium-derived nitric oxide has vasodilatation, anti-inflammatory, anti-thrombotic, and growth suppressing properties but over production of nitric oxide (NO) resulted in the formation of peroxynitrite and other RNS through interaction with oxygen free radicals. These oxidizing species damage the endothelial lining and contribute to atherosclerosis. The atherogenic effect of ROS and RNS can be alleviated by strong antioxidants such as tea flavonoids that include catechins, flavonols, theaflvins and thearubigins. The mechanisms of protection may involve scavenging of free radicals, metal chelation, inhibition of redox-sensitive transcription factors, nuclear factor-κB (NF-κB) and activator protein-1, suppression of "pro-oxidant" enzymes and induction of phase II enzymes. Tea polyphenols can decrease non heme-iron absorption due to their ability to chelate cations, thus reduce the formation of free radicals. Theaflavins, which are more abundantly found in black tea, are dimers of catechins. Since the anti-oxidative property of catechins depends on the presence of hydroxyl residues, so theaflavin gallates are stronger antioxidants than free theaflavins.[6] Table 1 illustrates some of the cellular and molecular targets of tea flavonoinds in cardiovascular diseases.

Effect on Endothelial Dysfunction [7-9]

The endothelium is the largest organ system in the body. "Endothelial function" refers to a multitude of physiological functions of the vascular endothelium that are achieved via secretion of diverse bioactive substances. This renders the endothelium an active participant in the healthy homeostasis of the vascular wall, which includes normal vasomotion, inhibition of platelet aggregation and thrombus generation, and maintenance of relative impermeability. Cardiovascular risk factors activate a number of pro-oxidative genes in the vascular wall resulting in generation of ROS that ultimately promote endothelial release of transcriptional and growth factors, pro-inflammatory cytokines, chemo-attractant substances, and adhesion molecules. This complex cascade of events underlies the transition from normal endothelial function to endothelial dysfunction, which is the main functional abnormality in atherosclerotic coronary heart disease and other cardiovascular diseases. Green tea catechins have been shown to reverse endothelial dysfunction, via inhibition of pro-oxidative genes expression, and radical and oxidant scavenging.[7,10] Both Cheng et al and Kim et al showed that green tea catechins inhibit neointimal hyperplasia and suppress proliferation of vascular

Table 1. Cellular and molecular targets of tea flavonoinds against cardiovascular diseases [26]

Cellular targets	Molecular targets	Flavonoids effects
Oxidative stress	ROS+RNS Oxidized LDL	Antioxidant effect
Vascular tone	eNOS→NO	Stimulatory effect
Aggregation/thrombosis	Factor Adhesion molecules t-PA & urokinase	Anti-thrombogenic effect
Inflammation	NF-κB↔iNOS/COX-2	Anti-inflammatory
Apoptosis	Cytochrome c Caspase 3 Bax, Bid, Bak Bcl-2, Bcl-xl, A1	Inhibitory effect Inhibitory effect Inhibitory effect Stimulatory effect

ROS: reactive oxygen species, RNS: reactive nitrogen species, LDL: low-density lipoprotein, eNOS: endothelial nitric oxide synthase, NO: nitric oxide, t-PA: tissue plasminogen activator, NF-κB: nuclear factor-κB, iNOS: inducible nitric oxide synthase, COX-2: cycloooxygenase-2, Bax, Bid, Bak: a family of proapoptotic multidomain proteins, Bcl-2, Bcl-xl, A1: a family of antiapoptotic multidomain proteins

smooth muscle cells in a rat carotid artery balloon injury model leading to reduce atherosclerotic lesions.[11,12]

Effect on Altered Lipids

Altered lipoprotein (a) and low-density lipoprotein (LDL) particle size are found in atherosclerotic coronary heart disease and oxidized LDL plays a central role in early events leading to atherosclerosis. Homology between lipoprotein (a) and plasminogen raises the possibility that lipoprotein (a) may inhibit endogenous fibrinolysis through competition with plasminogen. They were found to be co-localized within atherosclerotic lesions, and to induce chemo-tactic activity at the vascular endothelium. Lipoprotein (a) also appears to act on tissue factor and plasminogen expression. Green tea consumption has been shown to be associated with decreased serum concentrations of total cholesterol and LDL.[13] In a model of hyperlipidemic rats fed with high-sucrose diet, triglyceride level was normalized by the consumption of green and black teas on day 18 and by oolong tea extract on day 25. Total cholesterol level was normalized by green tea on day 18 and by oolong tea and black tea on day 25.[14] Other investigators have observed that consumption of 5 cups of black tea per day for 5 weeks resulted in the improvement of flow-mediated dilation leading to normalizing the endothelial function.[15]

Anti-thrombogenic Effect

Altered thrombosis is another hallmark of cardiovascular diseases. Studies on tissue plasminogen activator, fibrinogen, and homocysteine, all of which contribute to altered thrombosis, predict cardiovascular events.[16] Platelet aggregations play a critical role in the pathogenesis of acute coronary syndromes, including myocardial infarction and other cardiovascular diseases.[9] There is extensive evidence that antiplatelet therapy reduces cardiovascular disease risk.[17] A potent inhibitor of thromboxane formation is found in green tea leaves. Animal studies of the effects of tea on platelet aggregation suggested that tea may have benefits. However, studies of short term and long term tea consumption on ex vivo platelet aggregation demonstrated no effect of tea consumption on platelet function.[9,18] It is obvious that additional studies are required to clarify the effects of tea on platelet function.

Anti-inflammatory Effect

Currently there is much interest in the importance

of systemic inflammation as a pathogenic mechanism of cardiovascular risk.[19] Formation of atherosclerotic lesions resulted from chronic inflammation. The fatty streak, which signifies the beginning of atherogenesis, is characterized by the presence of inflammatory cells, such as macrophages and T-lymphocytes. They aggravate inflammatory responses throughout the development of atherosclerotic plaque. Cytokines including interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and interferon γ (IFN-γ), are released by a variety of cells in response to inflammatory stimuli. During inflammation, cell adhesion molecule expression is enhanced on endothelial cells as well as on leukocytes and platelets. Green tea has an inhibitory effect on TNF-α gene expression mediated through inhibition of NF-κB. EGCG also inhibits transcription factor-mediated gene activation via NF-κB and AP-1. Thus tea may exert a preventive effect on chronic inflammatory diseases.[20,21]

Hypertension

Recent studies demonstrated that the involvement of ROS in not only atherosclerotic coronary heart disease, but also hypertension.[23] Several mechanisms of anti-hypertensive effect of tea have been showed in publishes including inhibition of angiotensin-converting enzymes (ACE) activity, anti-oxidant and scavenging of metal chelation et al.[23,25] Tea polyphenols decrease blood pressure, which may help to prevent the development of left ventricular hypertrophy and reduce the incidence of stroke in hypertensive subjects.[22] An imbalance in vascular function in which contraction predominates over relaxation is thought to be a major pathophysiological feature of hypertension. Several studies showed green tea extract decreased blood pressure in animal models due to the antioxidant or NO free radical scavenging effect of tea flavonoids.[23,24] ACE inhibition is an important therapeutic approach in the treatment of high blood pressure. Actis-Goretta et al has demonstrated that flavanols could inhibit ACE activity which may explain their antihypertensive effects.[25] Although animal and population studies have shown a good blood pressure-lowering effect of tea, short-term intervention trials, mainly in normotensive individuals, were ineffective. Nevertheless, Negishi et al have further demonstrated that both black and green tea polyphenols attenuated blood pressure increase in spontaneously hypertensive rats.[23] Since the amount of polyphenols that they used in their study are equivalent to those found in one liter of tea solution, therefore, regular consumption of black and green tea may also provide some protection against hypertension in humans.

Epidemiologic Studies on Tea

A number of epidemiologic studies on tea have showed the inverse effect of tea to the risk factors of cardiovascular disease.[27-35] In Netherland, Geleijnse et al followed up 7983 men and women aged over 55 years old for 5.6 year, found out the inverse association of tea and flavonoid intakes with incident myocardial infarction (MI).[27] In Saudi, Hakim et al concluded that tea consumption had a protective effect against coronary heart disease (CHD).[28] In Japan, comparison of green tea intake in patients with or without angiographic coronary artery disease showed a significant inverse association with MI and CHD in tea taker group.[29,30] A meta-study include 10 cohort studies and 7 case-control studies carried out in Europe, UK and USA showed the preventable effect of tea on cardiovascular diseases.[31] In another meta-study, 2087 fatal CHD events involved, showed reduced mortality of CHD by tea in taking.[32] Tea consumption decreased the risk of developing hypertension to 1507 patients newly diagnosed hypertension in China.[33] But in France, tea flavonoids decreased SBP in women but no relation to SBP in men.[34] Table 2 showed the recent studies of tea on human.

Animal Studies on Tea

Cellular and molecular targets of tea components against cardiovascular diseases have been investigated in animal studies (Table 1). Mechanisms of effects of tea have been explained in several studies.[11,25,46,48-58] Catechins inhibit intimal hyperplasia through the up regulation of tissue inhibitors of metalloproteinases-2 (TIMP-2) expression to modulate matrix metalloproteinase (MMP) activity.[11] Catechins attenuated inflammatory factors were changed with altered Th1/Th2 cytokine

Table 2. Studies of effects of tea on human

Reference	Treatment	Results
15	5 cups of black tea/d for 4 weeks	Endothelium-dependent dilatation of the brachial artery: 2.3%, P=0.008; Endothelium-independent dilatation of the brachial artery: 4.2%, P=0.03
24	5 cups of tea/d for 4 weeks	Degree of increase in 4OMGA excretion inversely associated with the change in FMD responses
36	400 ml green tea Hot water	Green tea had NS effect on SBP and DBP, heart rate, fasting plasma lipid, or glucose concentration; green tea consumption significantly increased FBF during reactive hyperaemia
37	600 mg green tea polyphenol/d(11)	β-carotene was higher in the tea group; lag time of LDA was significantly prolonged by 13.7 in the tea group
38	1.5 mmol ECG, EGC or EGCG	Catechin levels in plasma: (t1/2elim) significantly different: EGC: 1.7h,ECG:6.9h,EGCG:3.9h
39	Tea alone; Water alone Meal with water; Meal with tea	Endothelium-dependent dilatation: significantly increased by meal with tea; not significantly increased by tea alone; SBP: significantly increased by tea alone
40	Black tea with milk	Higher tea intake and higher 4OMGA excretion associated with significantly lower SBP and DBP
41	2 g tea solids in 300 ml water	Tea induces a significant rise in plasma antioxidant activity in vivo; addition of milk to tea does not abolish this increase
42	Acute 450 ml of black tea(2h); Chronic 900 ml of black tea/d(4w)	Endothelial function at baseline correlated with dietary flavonoid intake and with baseline plasma EC concentration
43	0.7 mmol quercetin-3-rutinoside	Quercetin-3-rutinoside did not significantly affecthomocysteine concentrations
44	690 mg catechins/d,12w 22 mg catechins/d(control),12w	Significant time-by-group interaction for VE and MDA-LDL concentration
45	Intake black tea, green tea, green tea polyphenol isolate	Tea drinking had no effect on the levels of the inflammation, haemostasis and endothelialcardiovascular risk factors measured

FMD: flow-mediated dilatation, 4OMGA: 4-O-methylgallic acid, FBF: forearm blood flow, SBP: systolic blood pressure, DBP: diastolic blood pressure, MDA: malondialdehyde, NS: not significant, LDL: low density lipoprotein, EGCG: (–)-epigallocatechin-3-gallate, EGC: 3 (–)-epigallocatechin, ECG: (–)-epicatechin-3-gallate, EC: (+/-)-epicatechin

balance and suppressed NF-κB activation and cell proliferation.[54] Flavanols could inhibit ACE activity on the membranes of rat kidney.[25] Green tea extract has inhibitory effect on aortic collagen and intestinal absorption of cholesterol.[50, 51] Table 3 showed the studies of effects of tea on animals.

Conclusion

In summary, a number of scientific studies have provided evidences on the therapeutic effects of tea. In this review, the cardiovascular effects of the tea were examined based on research studies reported since 2000.

Table 3. Studies of effects of tea on animal

Reference	Animals	Results
11	Rat carotid arterial injury	Catechins inhibit intimal hyperplasia in a rat balloon-injury model through the upregulation of TIMP-2 expression to modulate MMP activity
14	Sprague-Dawley rats	Green tea exerted greater antihyperlipidemic effect than oolong tea
23	SHRSP	Both black and green tea polyphenols attenuate blood pressure
25	Rat kidney membranes	Flavanols could inhibit ACE activity
46	E-null mice	EGCG reduced cuff-induced evolving atherosclerotic plaque size; EGCG had no effect on established lesions in the aortic sinuses or the rest of the aorta
47	Mice	Chronic ingestion of tea extract prevents the development of atherosclerosis without changing the plasma lipid level
48	Rats	Green tea flavonoids suppress the LDL oxidation
49	Rats	LDL level decreased, HDL cholesterol levels increased, leading to dose-dependent improvement of the atherogenic index
50	Rats	The fluorescence in the aortic collagen was remarkably inhibited and the skin collagen was not significantly inhibited by the green tea extract
51	Rats	Green tea has a profound inhibitory effect on the intestinal absorption of cholesterol
52	Human LDL	TF present in black tea possess the same antioxidant potency as catechins present in green tea
53	PC12 cells	Increased DNA breakdown and activation of apoptotic markers, caspase 3 and PARP increased
54	Murine cardiac allografs	Catechins attenuated inflammatory factors were changed with altered Th1/Th2 cytokine balance and suppressed NF-κB activation and cell proliferation.
55	Vascular smooth muscle cells	GTE prevent MMP-2 expression and its activation by a direct inhibition of MT1-MMP
56	Cultures of cardiac myocytes / isolated rat heart	Consumption of green tea is able to mediate cardioprotection and enhance cardiac function during I/R injury
57	Rats heart tissue	Oxidative damage was significantly reduced by catechin supplementation
58	Murine cardiac allografs	Tea catechin administration did not statistically prolong allograft survival

SHRSP: stroke-prone spontaneously hypertension rats, PARP: poly-(ADP-ribose) polymerase, MT1: membrane type1, GTE: green tea extract, MMP: matrix metalloproteinase, TIMP: tissue inhibitors of metalloproteinases, TF: theaflavin, ACE: angiotensin converting enzyme, DNA: deoxyribonucleic acid, LDL: low density lipoprotein, HLD: high density liporotein, I/R: ischemia/reperfusion

Tea catechins possess various biological activities that have been reported to benefit the cardiovascular system, i.e., anti-oxidative, anti-endothelial dysfunction, anti-thrombogenic, anti-inflammatory and anti-hypertensive effects. It is clear that more research should be done, particularly in clinical settings, to substantiate the beneficial effects of tea in cardiovascular disorders.

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