Cardiovascular Effects of Green Tea Catechins: Progress and Promise

Mohammed A. Islam*

LECOM School of Pharmacy, Bradenton, Florida 34211, USA

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Abstract: Recently, there is a growing interest in the cardiovascular beneficial effects of green tea. Epidemiological and clinical studies have suggested that consumption of green tea is inversely associated with the risk of developing cardiovascular diseases. Catechins, the major flavonoid constituents of green tea, exert cardioprotective effects through diverse mechanisms that include reversal of endothelial dysfunctions, decreasing inflammatory biomarkers, and providing antioxidant, antiplatelet and antiproliferative effects. Moreover, dietary consumption of green tea catechins has beneficial effects on blood pressure and lipid parameters. This review will focus on discussing the latest research on the cardioprotective effects of green tea catechins and their underlying molecular mechanisms. Several recent patents pertinent to green tea and cardiovascular health will also be discussed. It is noteworthy that clinical studies involving green tea are fraught with multiple complexity and confounding factors. Therefore, a rigorous assessment of the effects of green tea catechins in well-controlled human trials will be required for better understanding of the effects of green tea in cardiovascular health.

Keywords: Antioxidant, anti-inflammatory, atherosclerosis, EGCG, endothelial dysfunction, green tea catechins, HDL cholesterol, LDL cholesterol.

INTRODUCTION

Green tea has been considered as a healthy beverage for centuries in East Asian countries [1]. The consumption of green tea has increased in western countries as a refreshing beverage or as dietary supplements containing dried leaves or extract because of its various alleged health benefits [2, 3]. Consequently, there is an increasing research interest in the effects of green tea in human health [4].

Green tea, similar to black and oolong tea, is produced from the leaves of *Camellia Sinensis*. However, a different processing technique is used that involves quick steaming of the freshly harvested green tea leaves, so that the oxidative enzymes are inactivated and the flavonoid contents are retained during the subsequent rolling and drying processes. The chemical composition of green tea varies due to differences in origin, variety, growing conditions, and production processes [5-7]. The polyphenol contents constitute up to 30% of the dry weight which include flavonoids, flavanols, flavandiols, and phenolic acids [8, 9]. More than 70% of flavonoids in green tea are catechins. (-)-Epigallocatechin-3-gallate (EGCG) is the most active compound biologically and constitutes 65% of the total catechins found in green tea. Other green tea catechins include (+)-catechin, (+)-gallocatechin, and (-)-epicatechin [10, 11]. Besides polyphenols, green tea contains caffeine, theophylline, carbohydrates, lipids, proteins, amino acids, sterols, minerals and trace elements, vitamins (B, C, E), pigments, and some volatile aldehydes and ketones, etc [9]. The over-the-counter green tea supplements are available as concentrated extracts of green tea containing 200-400 mg of EGCG per dose along with caffeine and other polyphenols.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in industrialized countries. 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 [12]. In USA, CVD accounts for 1 of every 3 deaths and more than one-fourth of the U.S. populations live with CVD [13]. Clinical manifestations and pathophysiology of CVD are complex and multifactorial (Fig. (**1**)). In most instances, CVD is attributed to atherosclerosis, a vascular chronic inflammatory condition.

The endothelium is the intrinsic regulator of vascular tone, local inflammation, and angiogenesis via the secretion of various vasoactive substances [14]. Endothelial dysfunction is considered as an early marker of atherosclerosis. The severity of atherosclerosis predicts cardiovascular events such as myocardial infarction, heart failure, cardiac arrhythmias, peripheral arterial disease, and stroke [15]. The *in vivo* endothelial function is assessed by exploiting several technical approaches such as measurement of flow-mediated vasodilation (FMD), arterial compliance, coronary artery diameter, and coronary blood flow. Moreover, altered plasma levels of cytokines, intracellular cell adhesion molecules (ICAM) [16-18], soluble vascular cell adhesion molecules (VCAM-1), plasma nitric oxide (NO) metabolites [19], and C-reactive protein (CRP) [20], commonly serve as circulating predictors of endothelial dysfunction. Additionally, altered levels of endothelin-1 (ET-1) and Von Willebrand factor (vWF) also serve as predictors of endothelial dysfunction

*Address correspondence to this author at the LECOM Bradenton School of Pharmacy, 5000 Lakewood Ranch Blvd., Bradenton, FL 34211, USA; Tel: (941) 782-5694; Fax: (941) 782-5724; E-mail: mislam@lecom.edu

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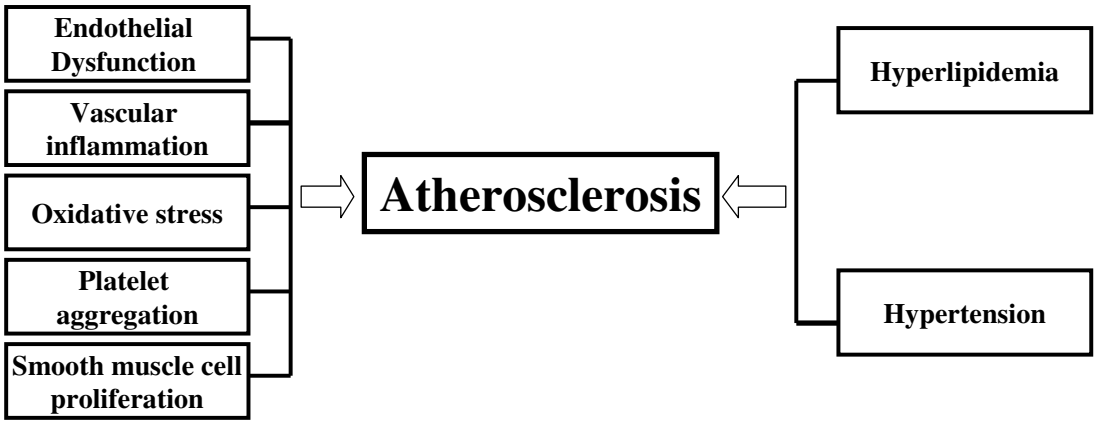

Fig. (1). Pathophysiology and risk factors associated with atherosclerosis

[21, 22]. The pro-inflammatory cytokines, induction of oxidative enzymes, and uncoupling of mitochondrial electron transport are involved in the generation of reactive oxygen species (ROS) which, in turn, contributes to endothelial dysfunction [23, 24] leading to atherosclerosis and myocardial infarction.

The cardiovascular effects of green tea consumption have been extensively studied in human as well as in animal models [25, 26]. There are accumulating evidences from epidemiological and human interventional studies that consumption of green tea is associated with decreased CVD risks [27-30]. The cardiovascular as well as other potential health benefits of green tea consumption have been previously reviewed [1, 31]. Moreover, several recent reviews have focused on the discussion of the underlying mechanisms of cardioprotective effects of green tea catechins [25, 26, 32, 33]. In humans, most of the studies involved the use of green tea beverages or tea extracts. Therefore, it is uncertain whether the cardiovascular benefits are conferred by flavonoids or by other constituents of green tea such as caffeine or theophylline. In addition, variations in green tea sources, manufacturing process, and flavonoid types and contents may further act as confounding factors in the assessment of cardioprotective effects of green tea catechins. Thus, it is important to explore the cardiovascular effects of pure isolated green tea catechins. However, the studies involving isolated pure green tea flavonoids in humans are limited. The present review summarizes current developments on the cardiovascular effects of green tea catechins with special emphasis on recent studies exploring the underlying molecular mechanisms. In addition, studies involving bioavailability are also discussed.

CARDIOVASCULAR DISEASES AND GREEN TEA

Human Studies

Accumulating evidence from population-based studies have suggested an inverse association between consumption of green tea and the risks of CVD [34-38]. Table **1** shows a summary of human interventional studies of green tea and tea catechins in endothelial dysfunction, vascular reactivity and atherosclerosis. Several studies in Japanese population reported significant reduction in mortality from all causes and CVD in individuals who consumed five or more cups of green tea compared with those who consumed less than one cup daily or none [36, 39, 40]. Green tea was found to be beneficial in patients with angiographically proven coronary artery disease (CAD) [41]. In a recent study in Chinese population, Wang *et al*. [42] showed that green tea consumption was associated with decreased prevalence of coronary artery disease that was defined as having at least one significant coronary artery stenosis. Intriguingly, this reduced risk of CAD was observed in male, but not in female patients. A number of human interventional studies examined the effects of green tea flavonoids on endothelium-dependent vascular reactivity and biomarkers for CVD [43-46]. Altered FMD of the brachial artery is an independent predictor of cardiovascular risk. The effect of green tea on brachial artery reactivity was studied in 14 healthy individuals (age 30+/-3 years) with no cardiovascular risk factors except from smoking (50%). Intake of 6 g of green tea significantly increased FMD (by 3.69%, peak at 30 min), but it did not have any effect on high-sensitivity CRP, IL-6, IL-1β, total plasma antioxidative capacity, or total plasma oxidative status suggesting an acute beneficial effect on endothelial function [46]. In another study, consumption of green tea extract for 5 weeks caused enhanced FMD in healthy women (n=14) compared with placebo [47]. Similarly, green tea consumption significantly improved vascular reactivity, increased circulating endothelial progenitor cells, and reduced oxidative stress biomarker, 8-isoprostaglandin $-F_{2\alpha}$ in chronic smokers. In male smokers, consumption of green tea (8 gm/day) for 2 weeks significantly improved FMD [48]. In contrast to the above studies, a recent study showed that daily consumption of high doses of green tea extract did not significantly alter endothelial-dependent and -independent vascular reactivity [44].

A number of studies assessed the effects of acute and chronic exposures of green tea catechins on endothelial function in human. Loke *et al.* have recently shown that acute per oral treatment with pure dietary flavonoid, (-)-epicatechin (200 mg) improves endothelial function in healthy volunteers by augmenting NO status and reducing ET-1 plasma concentrations [49]. Acute and chronic treatment with high dose (580 mg) green tea catechins significantly increased the forearm blood flow (FBF) response in male smokers.

Table 1. Human studies: endothelial dysfunction, vascular reactivity and atherosclerosis.

Study	Isoflavone Treatment	Outcomes	References
Placebo-controlled, parallel; Healthy men (n=31)	Green tea extract (714 mg green tea polyphenols)/day x 3 weeks	No changes in cardiovascular biomarkers	[44]
Healthy women (n=14)	Taken catechol or placebo for 5 weeks (catechol capsules contained caffeine 150 mg, 375 mg of catechins that included 270 mg EGCG)/day	No changes in total cholesterol, HDL or LDL ↓FMD ↓Oxidized LDL ↓Triglycerides	[47]
Randomized, placebo-controlled, cross-over trial; Healthy men (n=12)	(-)-epicatechin 200 mg, (acute oral administration) Control group-water	↑NO status (plasma S-nitrsothiols) ↓ Plasma endothelin-1 level	[49]
Male healthy smokers (n=30) divided in three groups	Green tea beverage: Control group: 0 mg, middle dose group: 80 mg and high dose group: 580 mg of tea catechins x 2 weeks	↑ FBF, ↑ NO ↓Asymmetrical dimethylarginine, malondialdehyde, CRP, MCP-1, and soluble CD40 ligand	[50]
Healthy male non-smokers (n=22)	7 cups of water/day x 2weeks, then 7 cups of green tea/day x2 weeks	↓LDL oxidation in vivo No effects on platelet aggregation, platelet thromboxane production, or plasma MMPs concentration	[57]
Healthy females (n=5)	Green tea 1.5 g/3 times/day x 2 weeks, then wash out x 1 week, then water only x 2 weeks, green tea x 2 weeks	↓Susceptibility of plasma LDL to oxidation, ↓LDL	[58]
Randomized, double-blind, placebo-controlled; Obese women (n=78 with placebo 37)	Green tea extract (400 mg) 3 times/day x 12 weeks	↓ Triglycerides ↓ Lipid peroxidation ↓LDL ↑HDL ↑Adiponectin	[60]
Double-blind, parallel multicenter trial; Japanese men and women (n=240; treatment 123 and control 117)	Green tea (583 mg catechins) and control (96 mg catechins)/day x 12 weeks	↓Systolic BP ↓LDL ↓Body fat	[61]
Randomized, double-blind, placebo-controlled; Healthy postmenopausal women (n=103)	EGCG (400-800 mg) in capsules/day x 2 months	LDL ↓ Beneficial effects on glucose-related markers	[62]
Healthy men and women (n=40, catechin group 29, control 11)	Polyphenon 70 capsules containing 500 mg catechins once a day x 4weeks	No influence on plasma LDL ↓Circulating Ox-LDL	[63]
Healthy volunteers on controlled diet	Treatment group: 2 cups containing 250 mg total catechins with controlled diet x 6 weeks Control group: only controlled diet	↓Induced DNA oxidative damage in lymphocytes ↓Plasma peroxide levels ↓LDL ↑Plasma antioxidant activity	[64]
Randomized, controlled, prospective; Adults with obesity and metabolic syndrome (n=35)	Green tea beverages (4 cups/day) or extract (2 capsules/day) x 8 weeks	↓ Lipid peroxidation ↓LDL	[65]
Randomized, double-blind, cross-over setting; Healthy endurance-trained men (n=10)	Green tea extract (containing 160 mg total catechins where 70 mg was EGCG/day) x 3 weeks	No effects on lipid parameters, inflammation processes, and oxidative stress.	[66]

(Table 1) Contd….

Study	Isoflavone Treatment	Outcomes	References
Randomized, double-blind, placebo-controlled; Mild to moderately hypercholesterolemic subjects (n=102, men 67 and women 35)	Theaflavins (77.5 mg) or Theaflavins/Catechins (75 and 150 mg, respectively) plus 195 mg other polyphenols in capsules/day	No effects on LDL, triglycerides	[67]
Randomized, controlled; Overweight or obese males (n=46, placebo n=42)	EGCG capsules 400 mg, twice daily x 8 weeks	↓Diastolic blood pressure No effect on insulin sensitivity	[72]
Randomized, controlled, cross-over trial; Males (40-69 yrs)	Decaffeinated green tea extract (400 mg total catechins)/capsules/twice daily x 6 weeks	No effects on BP or biomarkers of metabolic function	[73]

Moreover, chronic consumption of high-dose catechins caused a significant increase in plasma NO associated with decreased levels in malondialdehyde, 4-hydroxynonenal, CRP, monocyte chemotactic protein-1 (MCP-1), and soluble CD40 ligand, and dimethylarginine [50]. In patients with coronary artery disease, daily consumption of green tea or tea flavonoids improved endothelial function [51-53].

Dyslipidemias resulting from elevated levels of LDL-cholesterol, phospholipids, triglycerides, and low plasma HDL-cholesterol levels act as a predisposing factor for the development of atherosclerotic plaques [54]. In a cross-sectional study among 1371 Japanese men, Imai *et al*. [55] found that increased green tea consumption was associated with decreased plasma levels of LDL, total cholesterol, and triglycerides, but increased levels of HDL. After meta-analysis of 14 eligible randomized controlled trials with a population of 1136, Zheng *et al*. [56] concluded that consumption of green tea catechins is associated with significant reduction in total and LDL cholesterol levels, but not in HDL cholesterol. Green tea-mediated decreased plasma levels of total cholesterol and LDL cholesterol were consistently reported in a number of studies, however, the findings on the effects on triglycerides and HDL-cholesterol were mixed and inconsistent [57-65]. Moreover, several recent randomized, placebo-controlled trials involving healthy or moderately hypercholesterolemic subjects reported no effects of green tea catechins on lipid parameters [47, 66, 67].

Hypertension is the most common form of CVD and is one of the major risk factors for cardiovascular-related mortality. Green tea consumption has been believed to exert antihypertensive effects. Epidemiological evidence regarding the beneficial effects of green tea on blood pressure is inconsistent [68, 69]. In Chinese population, habitual consumption of 120 mL /day or more of green tea was reported to reduce the risk of developing hypertension [70]. Similarly, in another study in older women, Hodgson *et al.* reported that long-term consumption of green tea may lower the risk of hypertension [71]. In a double-blind, parallel multicenter trial in Japan, green tea catechins have shown to decrease systolic blood pressure [61]. Similarly, reduction in diastolic blood pressure was observed in obese males who took EGCG (800 mg/day in divided doses for 8 weeks) [72]. However, oral administration similar doses of decaffeinated EGCG for 6 weeks failed to alter blood pressure [73].

Animal Studies

A number of animal models have been exploited to explore the cardiovascular effects of green tea catechins and their underlying molecular mechanisms. As summarized in Table **2**, green tea catechins have been reported to impart cardioprotective effects through improvement of vascular reactivity, reduction of inflammation, potent antioxidant activity, and prevention of platelet aggregation and vascular smooth muscle cell (VSMC) proliferation. Moreover, green tea catechins were found to reduce the risk of cardiovascular diseases through improved cholesterol metabolism and antihypertensive effects. Interaction of green tea catechins with a number of molecular targets and cell signaling pathways underlie their cardiovascular beneficial effects.

EFFECTS OF GREEN TEA ON VASCULAR HOMEOSTASIS

There have been extensive *in vitro* as well as *in vivo* animal studies to test the effects of green tea flavonoids in vascular homeostasis. Acute treatment of isolated rat thoracic aortas with green tea catechins resulted dose-dependent vasodilation against phenylephrine-induced contractions [74-76]. Similarly, in rat mesenteric veins, EGCG (1–100 μM) demonstrated a dose-dependent vasodilation which was blocked by l-NAME (a NO synthase agonist) or the phosphatidylinositol-3-kinase (PI3K) inhibitor [74].

The effects of green tea catechins against vascular dysfunction were evaluated in different animal models of chronic cardiovascular and metabolic disorders. In spontaneously hypertensive rats, daily supplementation of 200 mg EGCG/kg for 3 weeks significantly improved vascular tone of mesenteric vascular beds and reduced systolic blood pressure [74]. Ihm *et al.* [77] found that daily treatment with 30 mg/kg catechin for 12 weeks significantly reduced blood pressure, fasting sugar, and improved endothelium-dependent aortic relaxation in an *ex vivo* setting in prediabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Thus, green tea flavonoids may confer beneficial effects against endothelial dysfunction and hyperglycemia. Consistently, in Goto-Kakizaki (GK) rats with type 2 diabetes, the green tea catechins improved blood pressure and blood glucose levels [78]. Of interest, in a rat model of angiotensin-II-

Table 2. Mechanisms by which green tea catechins confer cardioprotection.

Reversal of Endothelial Dysfunction: • ↑NO • ↑eNOS activity • ↑cGMP • ↑PI3K/Akt • ↓ET-1 expression
Reduction of Vascular inflammation: • ↓VCAM-1 • ↓Cytokines • ↓ Chemokines • ↓ Adhesion molecules • ↓MCP-1 mRNA and protein expression • ↓Leucocyte infiltration • ↓p38 MAPK and NF-kappa B activation
Antioxidant effects: • ↑Antioxidant enzymes (superoxide dismutase, catalase, and glutathion peroxidase) • ↓Pro-oxidant enzymes • Scavenging free readicals • Chelating redox ions • ↓OxLDL • ↓LOX-1 mediated signaling
Antiplatelet and antithrombotic activity: • ↓Intracellular Ca2+ mobilization • ↓Inositol 1,4,5-triphosphate formation • ↓Binding of fibrinogen-GPIIb/IIIa • ↓Phospholipase $C\gamma_2$phosphorylation • ↓Protein tyrosine phosphorylation • ↓Arachidonis acid liberation • ↑Cellular prostaglandin D_2 levels
Inhibition of cardiomyocyte apoptosis during oxidative myocardial injury: • ↓Expression of telomere repeat-binding factor 2 (TRF-2) proteins • ↑p53 and p21 protein levels
Inhibition of VSMC Proliferation: • Arrest VSMCs in G_i phase by inactivating pAkt • ↓Expression of VEGF by blocking PDGF and ERK1/2 signaling • ↓Matrix protein degradation • ↓Cell migration through ↓expression of MMP-2 and MMP-9

induced hypertrophy, treatment with green tea extract prevented hypertension and target organ damage [79, 80]. A mixture of dietary supplements containing green tea catechins among other constituents strongly reduced the development of atherosclerotic lesion in female ApoE*3Leiden transgenic mice [81]. Similar effects were observed in atherosclerosis susceptible C57BL/6J, apolipoprotein E-deficient mice [82]. In Apolipoprotein E-null mice, administration of EGCG (10 mg/kg, i.p., 42 days) significantly reduced carotid artery injury-induced atherosclerotic plaque formation; however, EGCG failed to reduce the established atherosclerotic plaque [83]. Similarly, in LDL receptor knockout mice, green tea catechins when given with high cholesterol diet prevented the development of atherosclerosis and target organ damage when compared with control group.

ENDOTHELIAL FUNCTION AND NO METABOLISM

The endothelium maintains the vascular homeostasis through a balanced regulation of vasodilation and vasoconstriction [84]. NO, synthesized from arginine by endothelial nitric oxide synthase (eNOS), acts as a vasodilator as well as prevents leukocytes adhesion, platelet aggregation, and release of pro-inflammatory cytokines [85]. In an impaired endothelium, induction of pro-inflammatory endothelial phenotype and reduced generation of NO promote progression of atherosclerosis and future cardiac events [84, 86, 87]. There is convincing evidence from animal studies that green tea catechins exert beneficial effects against endothelial dysfunction by increasing NO production. Recent studies provided evidence that EGCG resulted in endothelium- and NO-dependent vasodilation in rat aortic rings [88, 89]. Benito *et al.* further showed that the endothelium-dependent vasodilation involved increased eNOS activity, NO production, and cyclic guanosine-3′,5′-monophosphate (cGMP) production [90]. Consistently, green tea catechins concentration-dependently increased NO production in human umbilical cord endothelial cells (HUVEC) [91] and bovine aortic endothelial cells [88]. In consistent with *in vitro* animal studies, studies in cultured endothelial cells have also documented that the EGCG-induced increased NO production involves increased activity of eNOS, phosphatidylinositol-3-hydroxy kinase, and Akt signaling pathways [74, 92].

NO and ET-1 interplay as natural counterparts in maintaining the vascular tone. Recent data suggest that an imbalance between these two mediators contributes to endothelial dysfunction leading to the progression of cardiovascular diseases [93]. ET-1 is a potent vasoconstrictor produced by vascular endothelial cells [94]. Several lines of evidence from human and animal studies suggest that elevated levels of ET-1 is implicated in endothelial dysfunction leading to abnormal control of vascular tone and blood pressure [95-98]. Recently, Reiter *et al.* [99] have shown that in human aortic endothelial cells EGCG decreased ET-1 expression in endothelial cells via Akt- and AMPK-stimulated FOXO1 regulation of the ET-1 promoter.

ANTI-INFLAMMATORY EFFECTS

The vascular inflammation is now increasingly considered as a key process in the pathogenesis of atherosclerosis which is initiated with the adhesion of monocytes to the vascular endothelial cells and their subsequent transmigration into sites of inflammation [100]. This atherosclerotic process is dependent on the expression of MCP-1 and interleukin-8 (IL-8) along with several adhesion molecules such as ICAM-1, and VCAM-1, and endothelial leukocyte adhesion mole-

cule-1 (E-selectin) [101, 102]]. Besides these, NO, cytokines, prostacyclin, and cellular processes such as cell growth and differentiation are involved in vascular inflammatory processes. Ramesh *et al.* [103] recently showed that daily administration of EGCG (100 mg/kg, i.p.) significantly decreased the expression of CRP, with concomitant decrease in hematological parameters of inflammation in atherosclerotic rats. Similarly, *in vitro* experiments in VSMCs showed that EGCG concentration-dependently inhibited ET-1-stimulated expression of CRP both in protein and mRNA levels [104].

Inducible nitric oxide synthase (iNOS) contributes to the pathophysiology of atherosclerosis through the generation of NO [105]. Recently, Ahn *et al.* [106] reported increased expression of iNOS in HUVEC. Moreover, in HUVEC, EGCG and ECG dose-dependently inhibited cytokine-induced VCAM-1 expression and monocyte adhesion [107]. In LDL receptor knock-out mice, catechin administration significantly suppressed VCAM-1 expression in atherosclerotic lesions [108]. Green tea catechins have been found to reduce the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules that are regulated by the nuclear transcription factor NF-kappa B [109, 110]. Moreover, Hong *et al.* reported that tea catechins inhibited phorbol 12-myristate 13-acetate-induced MCP-1 mRNA and protein expression in human endothelial cells and thereby reduced leucocyte infiltration and their subsequent transmigration through cultured human endothelial monolayers by suppressing p38 MAPK and NF-kappa B activation [111]. In consistent with the above studies, EGCG reduced TNF-α -induced MCP-1 production in bovine coronary artery endothelial cells by inhibiting Akt phosphorylation as well as TNF activation of TNFR1 [112]. EGCG suppresses pro-inflammatory actions of TNF-α through over expression of heme oxygenase-1 in vascular endothelial cells via p38 MAPK and Nrf-2 signaling pathways [113].

ANTIOXIDANT EFFECTS

There is a growing number of evidence that green tea catechins exert antioxidant activity through a number of mechanisms that include induction of antioxidant enzymes, inhibition of pro-oxidant enzymes, scavenging free radicals, chelating redox ions, and inhibiting transcription factors for redox reaction [114]. In animal models, green tea catechins have been reported to upregulate antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase [115, 116]. In apolipoprotein E null mice, a mouse model of human atherosclerosis, EGCG increases the antioxidant capacity in systemic circulation as well as in local vascular tissues [83]. Catechins and their metabolites, (−)-epicatechin-5-O-β-glucuronide and (+)-catechin-5-O-β-glucuronide, serve as electron donors and highly efficient scavengers of free radicals such as nitric oxide (NO), peroxynitrite, superoxide anions, and singlet oxygen [114, 117].

The cellular proliferative and apoptotic processes involve catalytic generation of superoxide free radicals through endothelial NADPH oxidase, a multisubunit enzymatic complex comprising of two membranes bound subunits, gp91 and $p22^{phox}$. The assembly of the active NADPH complex is regulated by two cytoplasmic subunits ($p47^{phox}$ and $p67^{phox}$) and a G-protein, Rac-1 [118]. In vascular endothelial cells, activation of Rac-1 and $p47^{phox}$ is involved in the generation of superoxide that stimulates inflammatory gene expression through redox-sensitive signaling mechanisms [119]. Green tea catechins have been reported to inhibit NADPH oxidase activity leading to the reduced production of ROS [120]. In a recent study in the prediabetic OLETF rat model, daily catechin treatment (30 mg/kg for 12 weeks) reduced the expression of p22phox and p47phox NADPH oxidase subunits as well as ROS formation in aortic endothelial cells [77].

Oxidative modification of LDL (ox-LDL) plays an important role in the development of atherosclerosis. High level of ox-LDL triggers inflammatory reactions, decreases activities of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, and causes lipid peroxidation leading to endothelial dysfunction and formation of atherosclerotic plaques [121]. Earlier studies reported that catechins can inhibit the oxidation of LDL both *in vitro* and in animal studies [58, 122-125]. In vascular endothelial cells, activation of LOX-1, a lectin-like receptor for oxLDL, has been suggested to increase intracellular ROS, including H_2O_2 and singlet oxygen [126]. Recently, Ou *et al.* have shown that EGCG exerted significant cytoprotective effects in cultured human umbilical vein endothelial cells through inhibition of the oxLDL-induced LOX-1 mediated signaling pathway [127].

During cardiac dysfunction involving oxidative myocardial injury, telomere signalling plays a role in regulating cardiomyocyte apoptosis through decreased expression of telomere repeat-binding factor 2 (TRF-2) proteins and upregulation of p53 and p21 protein levels. *In vitro* experiments in H9c2 cells have demonstrated that EGCG suppresses H_2O_2-induced cardiomyocyte apoptosis and telomere attrition [128].

ANTI-PROLIFERATIVE EFFECTS

During atherosclerosis, the intimal and medial thickening contributes to vascular VSMC proliferation and migration. In animal models, EGCG has been shown to suppress of VSMC proliferation induced by high glucose [129], angiotensin-II [130], and platelet derived growth factor (PDGF) [131, 132]. EGCG treatment has been shown to arrest VSMCs in G_1 phase of the cell cycle by inactivation of pAkt, leading to subsequent apoptosis [131]. Similarly, catechins have been found to inhibit angiotensin-II-induced VSMC proliferation in rat aorta through inhibition of mitogen-activated PK signaling [130]. Animal studies and cell culture experiments revealed that the anti-proliferative effects of green tea catechins were mediated through the inhibition of a number of signaling pathways including mitogen-activated PK, downstream PI3K/Akt PKC, and ERK1/2 signaling [131, 132]. In human VSMCs, EGCG has been reported to dose-dependently decrease the expression of vascular endothelial growth factor (VEGF) expression via blocking PDGF and ERK1/2 signaling [133]. A further study showed that EGCG inhibited cell proliferation by blocking the interaction of PDGF with its receptor [134].

VSMCs migrate from the tunica media to the sub-endothelial region during atherogenesis and in response to vascular injury that may occur clinically after organ transplantation, stent implantation, or angioplasty. Matrix metal-

loproteinases (MMPs), particularly, MMP-2 and MMP-9 have been implicated in cell migration and tissue remodeling process due to their ability of degrading extracellular matrix proteins [100, 135]. Catechins, in a dose-dependent manner, have been shown to prevent matrix protein degradation and cell migration by inhibiting expression or activity of MMP-2 [136, 137] and MMP-9 [138]. Gouni-Berthold *et al*. showed that catechins exert their antiproliferative and apoptotic effects through the inhibition of growth factor-RTK-mediated signal transduction pathways. Enhanced RTK activity has been associated with the development of atherosclerosis [139]. Thus, above *in vitro* studies suggest a potential antiatherogenic action of catechins at pharmacological doses. However, the relevance of these *in vitro* findings to clinical situation remains to be further evaluated.

ANTIPLATELET AND ANTITHROMBOTIC ACTIVITY

Platelets play an important role in the development of acute thrombotic events as well as in the pathogenesis of atherosclerosis. Vascular endothelial injury promotes rapid platelet hyper-reactivity and aggregation leading to a formation of thrombi which could trigger acute myocardial infarction [140]. *In vitro* and *in vivo* studies have reported potential antiplatelets and antithrombotic effects of tea catechins [141-144]. Catechins dose-dependently inhibit various stimuli-induced *in vitro* platelet aggregation of humans [145, 146] and animals [143, 144]. Exposure of human platelet concentrates to EGCG (50 and 100 microgram/ml) maintained platelet aggregability and preserved the platelets by inhibiting the activation and apoptosis [145]. There is accumulating evidence that tea catechin supplementation improved platelet aggregation and thrombosis through interacting with a diverse signaling mechanisms [147]. In human platelets, catechins inhibit intracellular calcium mobilization *via* activation of Ca^{2+}-ATPase and inhibition of inositol 1,4,5-triphosphate formation leading to the attenuation of fibrinogen-GPIIb/IIIa binding [142]. Recently, Jin *et al*. [144] have shown that antiplatelet activity of EGCG is attributable to interaction with multiple cellular targets such as inhibitions of phospholipase $C\gamma_2$ phosphorylation, protein tyrosine phosphorylation, arachidonic acid liberation, and elevation of cellular prostaglandin D_2 levels.

Inflammatory conditions are associated with increased release of platelet activators such as arachidonic acid, prostaglandins, endoperoxides, and thromboxane A2 [148]. Sugatani *et al.* [149] have shown that tea catechins reduced PAF- and TPA-induced rabbit platelet aggregation through inhibiting acetyl-CoA:1-alkyl-sn-glycero-3-phosphocholine acetyltransferase enzyme. Several other studies have explored the antiplatelet and antithrombotic effects of tea catechins through their suppressing effects on arachidonic acid release and thromboxane A_2 synthase activity [143, 144].

EFFECTS ON LIPID METABOLISM

Tea catechins have been reported to favorably affect lipid metabolism in a number of animal models. In rats with hypercholesterolemia, EGCG improves hyperlipidemia by reducing LDL-cholesterol, but elevates HDL-cholesterol levels [150-153]. Similarly, improved blood glucose and lipid profiles have been observed in diabetic rats that received EGCG (25 mg/kg/day) for 8 weeks [154]. Studies in animal models explored several possible mechanisms explaining the effects of green tea catechins on lipid metabolism. Green tea catechins modulate cholesterol metabolism mainly by targeting its biosynthesis [155] and intestinal absorption [156-158]. Hydroxy-3-methyl-glutaryl-CoA reductase (HMGR) is the rate-controlling enzyme in the biosynthesis of cholesterol. Cuccioloni *et al.* [159] have shown that EGCG potently inhibits the *in vitro* activity of HMGR by competitive binding to the cofactor site of the enzyme. In addition, catechins may also have direct inhibitory effect on squalene epoxidase, another rate limiting enzyme of cholesterol biosynthesis [160]. Catechins enhance intestinal lipid absorption through direct interference with the emulsification, hydrolysis, micellar solubilization of lipids, formation of insoluble co-precipitates of cholesterol, and interaction with pancreatic phospholipase A_2 [156, 157, 161-163]. Moreover, tea catechins have also been reported to modulate specific transport proteins located on the brush border membranes that play a significant role in lipid uptake by enterocytes [164]. Green tea catechins enhances cholesterol 7 α-hydroxylase mRNA expression and promoter activity in human hepatoma cells which may underlie the hypocholesterolemic effects of catechins [165]. Using DNA microarray analysis and real-time PCR technique, Goto *et al.* [166] recently demonstrated that EGCG treatment improved cholesterol metabolism by up-regulating LDL receptor mRNA expression level and decreasing extracellular apoB levels.

CURRENT & FUTURE DEVELOPMENTS

Extensive studies have been performed on the cardioprotective effects of green tea and tea catechins in human as well as *in vitro* and *in vivo* animal models. The health benefits of green tea catechins such as maintenance of endothelial function, vascular homeostasis, and associated reduction of CVD risks are becoming increasingly recognized. There are mounting evidences emerged from epidemiological [28-30, 36], human interventional [46, 47, 50, 59] as well as animal studies [74-78, 80].

Several recent patents have described the promising effects of green tea catechins against cardiovascular diseases. Epicatechins and derivatives and their salts have been found to reduce of infarct size in the heart with total coronary occlusion in animals as well as in humans [167]. Bukowski and Walters patented their intriguing discovery of cardiovascular beneficial effects of tea-derived compositions comprising predetermined amounts of EGCG and L-theaine. They found that encapsulated tea components of defined composition when given orally twice daily for 12 weeks significantly lowered blood pressure, LDL cholesterol, and chronic inflammation as measured by decreased serum amyloid alpha levels [168]. Several other recent patents described the use of green tea extracts or tea catechins as an ingredient of pharmaceutical compositions intended for the treatment of cardiovascular and other ailments [169-171].

There are substantial inconsistencies in the published data emerged from human interventional studies that investigated the effects of green tea or its flavonoids on CVD markers [36, 44]. In a recent randomized controlled trial,

consumption of catechin-enriched GT (100- 400 mg/day) for 9 weeks did not affect serum adiponectin, one key factor in atherosclerosis, and other cardiovascular disease (CVD) risk factors in apparently healthy subjects [172]. As previously discussed, green tea exerted antiatherosclerotic benefits in patients with angiographically proven coronary artery disease [41], however, Hirano *et al.* [173] reported no relationship between green tea consumption and coronary artery disease in 393 patients who underwent coronary angiography. Moreover, in a meta-analysis of 30 randomized control trials, seventeen studies provided evidence of significant beneficial effects of green tea against CVD [36]. It is difficult to explain these discrepancies because most of the published studies related to cardioprotective effects of green tea and tea catechins in humans suffer from limitations of poor study design, short study duration, and small sample size. Moreover, the evaluation of cardioprotective effects of green tea and tea catechins in humans is difficult because of other confounding factors such as different forms of green tea supplements, variable amounts of catechins, their interactions with other potentially active ingredients such as caffeine, and food matrix affecting the bioavailability of green tea catechins. The bioavailability of the dietary nutrient is an important factor in the determination of the beneficial effect. It is possible that the bioavailability of one key catechin can be affected by the interactions with other competitive nutrients in the level of absorption, metabolism, and membrane transportation. After ingestion, green tea catechins are absorbed and metabolized and appear in blood and urine [174, 175]. However, little is known about how catechins absorption is affected by food matrix effect. In a recent study, Auger *et al.* [176] demonstrated that co-ingestion of green tea catechins with bread, cheese, or glucose did not significantly affect the absorption, metabolism, and excretion of tea catechins. However, Chow *et al.* [177] reported that bioavailability and the pharmacokinetic profile of EGCG is enhanced when taken orally in the fasting condition. Enhance the bioavailability of EGCG has been reported when administered as encapsulated nanolipid particles in comparing with free EGCG [178-180]. Improved bioavailability of green tea catechins have been reported from formulations stabilized with addition of natural antioxidants such as vitamin C or vitamin C analogs [181]. Similarly, modification of green tea polyphenol formulations by adding one or more ester-linked fatty acids have also been shown to enhance bioavailability [182].

Animal and cell line studies with isolated green tea flavonoids and catechins have shown promising cardioprotective effects and mechanistic insights on their effects. Green tea catechins exert cardiovascular effects through multiple mechanisms, including, improved vascular homeostasis through NO signaling, anti-inflammatory, antioxidant, antiproliferative, and anti-thrombogenic mechanisms. Moreover, in ischemic myocardium, EGCG has been reported to inhibit apoptotic cell death by inhibiting STAT-1 activity [183]. EGCG has also been found to suppress oxidative stress-induced apoptosis and telomere attrition in cardiac cells [128]. However, extrapolation of the results of animal or cell culture studies to human clinical situations is uncertain mainly because of the concentrations of green tea catechins used in animal or *in vitro* studies (usually 1 μM/L to 100 μM/L) are far higher than the plasma concentrations achievable in human after green tea consumption [184]. It is difficult to achieve therapeutic concentration (~10 μM/L) by ingesting high dose (800 mg capsules of pure EGCG by mouth [185]. Moreover, the results from animal studies should be interpreted with caution due to the inherent biological variations as well as pharmacokinetic and pharmacodynamic differences of the test agents in animals versus humans. Although current evidences of the cardioprotective effects of green tea catechins from human as well as animal studies are promising, further rigorous and well-designed human interventional trials are warranted to provide better understanding of the effects of green tea in cardiovascular health.

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CONFLICT OF INTEREST

There is no conflict of interest.

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