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Recommended Citation
Liyan Song, Bernard MY Cheung, Marcel WL Koo, Chu-Pak Lau, Tea and Cardiovascular Diseases Journal of the Hong Kong College of Cardiology 2022;14(2) https://doi.org/10.55503/2790-6744.1101

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Tea and Cardiovascular Diseases

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From Departments of ¹Medicine and ²Pharmacology, The University of Hong Kong, Hong Kong SAR

SONG ET AL.: Tea and Cardiovascular Diseases. Tea, produced from the tea plant Camellia sinensis, has been consumed as a popular beverage worldwide 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

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 lifestyle 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.

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.¹²

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

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Received November 1, 2006; accepted November 11, 2006
(-)-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. Theanine and glutamic acid can also be found in tea. Figure 1 shows the chemical structures of major green and black tea polyphenols.

**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, theaflavins 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. Table 1 illustrates some of the cellular and molecular targets of tea flavonoids in cardiovascular diseases.

**Effect on Endothelial Dysfunction**

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. Both Cheng et al and Kim et al showed that green tea catechins inhibit neointimal hyperplasia and suppress proliferation of vascular smooth muscle cells.
Table 1. Cellular and molecular targets of tea flavonoids against cardiovascular diseases

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


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 chemotactic 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. 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. 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.

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. Platelet aggregations play a critical role in the pathogenesis of acute coronary syndromes, including myocardial infarction and other cardiovascular diseases. There is extensive evidence that antiplatelet therapy reduces cardiovascular disease risk. 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. 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

smooth muscle cells in a rat carotid artery balloon injury model leading to reduce atherosclerotic lesions.
of systemic inflammation as a pathogenic mechanism of cardiovascular risk.\textsuperscript{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-\(\alpha\) (TNF-\(\alpha\)) and interferon \(\gamma\) (IFN-\(\gamma\)), 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-\(\alpha\) gene expression mediated through inhibition of NF-\(\kappa\)B. EGCG also inhibits transcription factor-mediated gene activation via NF-\(\kappa\)B and AP-1. Thus tea may exert a preventive effect on chronic inflammatory diseases.\textsuperscript{20,21}

**Hypertension**

Recent studies demonstrated that the involvement of ROS in not only atherosclerotic coronary heart disease, but also hypertension.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{27} In Saudi, Hakim et al concluded that tea consumption had a protective effect against coronary heart disease (CHD).\textsuperscript{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.\textsuperscript{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.\textsuperscript{31} In another meta-study, 2087 fatal CHD events involved, showed reduced mortality of CHD by tea in taking.\textsuperscript{32} Tea consumption decreased the risk of developing hypertension to 1507 patients newly diagnosed hypertension in China.\textsuperscript{33} But in France, tea flavonoids decreased SBP in women but no relation to SBP in men.\textsuperscript{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.\textsuperscript{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.\textsuperscript{11} Catechins attenuated inflammatory factors were changed with altered Th1/Th2 cytokine
### Table 2. Studies of effects of tea on human

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

**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:** (−)-epigallocatechin, **ECG:** (−)-epicatechin-3-gallate, **EC:** (+/−)-epicatechin

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**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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animals</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Rat carotid arterial injury</td>
<td>Catechins inhibit intimal hyperplasia in a rat balloon-injury model through the upregulation of TIMP-2 expression to modulate MMP activity</td>
</tr>
<tr>
<td>14</td>
<td>Sprague-Dawley rats</td>
<td>Green tea exerted greater antihyperlipidemic effect than oolong tea</td>
</tr>
<tr>
<td>23</td>
<td>SHRSP</td>
<td>Both black and green tea polyphenols attenuate blood pressure</td>
</tr>
<tr>
<td>25</td>
<td>Rat kidney membranes</td>
<td>Flavanols could inhibit ACE activity</td>
</tr>
<tr>
<td>46</td>
<td>E-null mice</td>
<td>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</td>
</tr>
<tr>
<td>47</td>
<td>Mice</td>
<td>Chronic ingestion of tea extract prevents the development of atherosclerosis without changing the plasma lipid level</td>
</tr>
<tr>
<td>48</td>
<td>Rats</td>
<td>Green tea flavonoids suppress the LDL oxidation</td>
</tr>
<tr>
<td>49</td>
<td>Rats</td>
<td>LDL level decreased, HDL cholesterol levels increased, leading to dose-dependent improvement of the atherogenic index</td>
</tr>
<tr>
<td>50</td>
<td>Rats</td>
<td>The fluorescence in the aortic collagen was remarkably inhibited and the skin collagen was not significantly inhibited by the green tea extract</td>
</tr>
<tr>
<td>51</td>
<td>Rats</td>
<td>Green tea has a profound inhibitory effect on the intestinal absorption of cholesterol</td>
</tr>
<tr>
<td>52</td>
<td>Human LDL</td>
<td>TF present in black tea possess the same antioxidant potency as catechins present in green tea</td>
</tr>
<tr>
<td>53</td>
<td>PC12 cells</td>
<td>Increased DNA breakdown and activation of apoptotic markers, caspase 3 and PARP increased</td>
</tr>
<tr>
<td>54</td>
<td>Murine cardiac allografts</td>
<td>Catechins attenuated inflammatory factors were changed with altered Th1/Th2 cytokine balance and suppressed NF-κB activation and cell proliferation</td>
</tr>
<tr>
<td>55</td>
<td>Vascular smooth muscle cells</td>
<td>GTE prevent MMP-2 expression and its activation by a direct inhibition of MT1-MMP</td>
</tr>
<tr>
<td>56</td>
<td>Cultures of cardiac myocytes / isolated rat heart</td>
<td>Consumption of green tea is able to mediate cardioprotection and enhance cardiac function during I/R injury</td>
</tr>
<tr>
<td>57</td>
<td>Rats heart tissue</td>
<td>Oxidative damage was significantly reduced by catechin supplementation</td>
</tr>
<tr>
<td>58</td>
<td>Murine cardiac allografts</td>
<td>Tea catechin administration did not statistically prolong allograft survival</td>
</tr>
</tbody>
</table>

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.

References