A Systematic Review of Relationship between Green Tea Consumption and Improvement of Lipid Profile as Action Plan for Preventing Cardiovascular Disease (CVD) Development

Prima Alifian H, Fahmi Dimas Abdul Azis, Fairuza Syarfina, Safira Adilla, Aprillia Tanto
1,2,3,4,5 Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia
E-mail address: primaalifianhergaputra@gmail.com

ABSTRACT
Tea (Camellia sinensis) is one of the most popular beverages in Asia. Tea divided into three categories based on degree of fermentations, one of them is green tea. Many researchers have reported antioxidant activity of green tea to prevent chronic diseases. Daily consumption of green tea can reduce the development of atherosclerotic complication related to stroke, myocardial infarction, coronary heart disease, and cardiovascular diseases (CVD). There are evidences from clinical studies that prove green tea can play protective role in the development of CVD. Various components of green tea, especially polyphenol, have antioxidant and antidyslipidemic activities. The aim of this study was to review the relationship between green tea consumption and CVD development. Published randomized controlled trial (RCT) and meta-analysis (2007-2017) were identified based on searches of on-line databases (Cochrane Library, PubMed, Science Direct). The search terms used included green tea and cardiovascular. From electronic searches database we found 3,642 articles, 6 research articles met inclusion criteria, have been conducted and summarized. There were significant reduction of total cholesterol (TC) (p<.05) found in 3 articles, low-density lipoprotein cholesterol (LDL) found in 4 articles, triglyceride (TG) found in 3 articles, and significant increment of high-density lipoprotein (HDL) found in 2 articles. The articles also showed reduction of CVD risk including blood glucose concentration, blood pressure, inflammatory biomarker and anthropometrical measurements. Green tea consumption might be associated inversely with the development of CVD. The consumption of green tea extract indicates improvement of lipid profile and reduction of CVD risk. The utilization of dietary supplement, such as green tea and its polyphenol component, have promising potential to prevent the development of CVD complications.

Keywords: Green Tea, Cardiovascular Disease, Dietary, Prevention

I. INTRODUCTION

Tea (Camellia sinensis L.; family Theaceae), is the most popular beverage and being widely cultivated in Asia especially in Southeast Asia[24]. Tea is divided into 3 major types based on the processing methods which involved the fermentation process. Green tea is a type of tea that is not fermented and didn’t go through the oxidation process. Fermentation process on the tea leaves may reduce the concentration of tea catechin. Green tea catechin content among other types of tea. Those catechin are epicatechin (EC), epigallocatechin (EGC) and epigallocatechin-3-0-gallate (EGCG) which is the largest component of green tea catechins[4]. Consumption of green tea or its extract may provide protection against chronic diseases, including cardiovascular disease (CVD)[7,25]. Tea catechin exert variety mechanism of actions that responsible for the health benefits of green tea such as antioxidant, anti-inflammatory, anti-hypertensive, anti-diabetic, anti-mutagenic, anti-bacterial and anti-viral effect[25]. The cardioprotective effect of green tea and EGCG were shown in in vivo studies to reduce the development of
atherosclerosis and progression of evolving atherosclerotic lesion in hypercholesterolemic. Daily intake of green tea decreases the incidence of coronary heart disease, stroke, and myocardial infarction. Green tea has been shown to suppress the oxidation of low-density lipoprotein (LDL). It is well recognized that LDL is an important risk factor for the development of CVD. Supplemented green tea catechins in diet or drinking water was shown to reduce ApoB, improve the ratio of ApoA-1/ApoB that associated with higher risk of CVD, up-regulate LDL receptor binding activity and increase the level HDL of HDL-cholesterol in vivo\cite{25,21}.

II. METHOD

We conducted electronic searches in the following databases: Cochrane Library, PubMed and Science Direct. Published randomized control trial (RCT) and meta-analysis of RCT (2007-2017), the search terms used included green tea and cardiovascular. Titles, abstracts, and methods were screened for relevance. The relevant articles were selected for further consideration (Fig. 1).

A. Search Term and Selection Criteria

The search term used include: “green tea” and “cardiovascular”. These were combined using the Boolean logic AND. Studies were eligible for inclusion: (1) RCTs and meta-analysis of RCTs studies that test the effectiveness of orally administered green tea, extract, or isolated polyphenol of green tea against placebo, (2) subject that involved in this study is healthy subject or those who have high risk CVD factors including overweight, obese, dyslipidemia, diabetes mellitus and hypertension, (3) reported lipid profile (TC, TG, LDL, HDL) and/ or SBP, DBP, pulse pressure, glucose metabolism indices or inflammatory biomarkers, including C-reactive protein (CRP) and Tumor Necrosis Factor-α (TNF-α), and anthropometrical measurements including BMI, WC, and HC.

B. Data Extraction

Five reviewers (P.A.H., F.D.A.Z., F. S., S.A., and A.H.T) independently extract data using data extraction template. The template included the following: authors; subject; dose; duration; results; study design.

C. Outcome

The primary outcomes included in this systematic review on the effect of green tea consumption on preventing CVD were responses of several biomarkers associated with CVD risk factors, including lipid profile (TC, TG, LDL, HDL) and/ or SBP, DBP, pulse pressure response, glucose metabolism indices, such as fasting glucose, fasting insulin levels, and inflammatory biomarkers, including C-reactive protein (CRP) and Tumor Necrosis Factor-α (TNF-α), and anthropometrical measurements including BMI, WC, and HC.

D. Data Analysis

Six studies were assessed based on inclusion criteria. These studies were analyzed for their design, interventions, sample size, and the age and gender of the participants, and outcome. P<.05 and P<.001 was defined as being statistically significant in this study.

III. RESULTS

After literature search through 3 search engines, a total of 3642 were identified. Then 3625 articles were excluded by title screening. Abstracts of the remaining 17 articles were reviewed and 11 articles were retrieved in full text, where did not match inclusion criteria study design such as smokers, cardiovascular incident, lipid lowering agent patient, and relevant results were not reported. These articles were excluded after discussion between five independent investigators (Fig. 1).

As demonstrated in table 1, the studies included here were published between the years 2008 and 2015, with the numbers of subjects ranging from 46 to 111. Among of them, one study was conducted in Japan, two in
Poland, one in USA and two in Taiwan. In terms of study population, eligible subjects consisted of men and women, except for two studies that recruited only women[3,11]. The subject of the studies that included to the review were three studies recruited obese subjects[2,11,20], one trial recruited overweight subjects[3], one trial recruited healthy subjects[18] and one trial recruited older subjects[17]. Six studies instructed the subject to maintain their physical activity and previous diet including polyphenol, catechin, or caffeine.

**Electronic Searches**

- Cochrane Library: n=19
- PubMed: n=184
- Science Direct: n=3,439

**Records screened**

- n=3,642

**Records excluded**

- n=3,625

**Full-text article exclude**

- Smokers: n=2
- CVD incidence: n=4
- Lipid lowering agent: n=1
- No lipid profile result: n=4
- No control group: n=1
- Total: n=11

*One article may contain >1 exclusion criteria

**Article fitting the inclusion criteria**

- n=6

**Figure 1.** Schematic representation of the flow of information during the different phases of the systematic review

All studies that included in this systematic review showed statistically significant (p<.05) results in association between green tea intake and reducing total cholesterol and LDL cholesterol[2,3,11,17,18,20], five studies showing reduction of triglycerides [2,3,11,17,20] and five studies showing protective role of green tea as HDL cholesterol enhancement[2,3,11,17,20]. The metabolic syndrome markers reported in the 6 studies included systolic blood pressure[2,3,11,18,20], diastolic blood pressure[2,3,11,18,20], BMI[2,3,11,18,20], WC[2,3,11,17,20], HC[3,11,17], and CRP[2]. SBP, DBP, HC, and CRP showed no significant difference between baseline characteristic and placebo control groups in all studies. Two studies examined the effect of 379 mg/day GTE supplementation on anthropometric outcome including BMI and waist circumference. A study conducted by Bogdanski et al (2012), reported that there were no significant in BMI and waist circumference after intervention within group and between group (p>.05). However, metabolic markers, CRP (p<.001), showed improvement within and between groups therefore reduce CVD and other metabolic syndrome risk[2]. In the other hand, Suliburska et al (2012) found the significant reduction on BMI (p=.03) and waist circumference (p=.04) on GTE group compared to placebo group.

**IV. DISCUSSIONS**

Green tea consumption has been proven to reduce the risk of CVD in both people with the risk factors for CVD or healthy subjects. The substance that responsible for the efficacy produced by green tea is the catechins compound, mainly EGCG[5]. Experimental and translational clinical studies have provided further insight into the mechanisms of benefit for green tea against CVD. Those mechanisms are such as anti-oxidant effects, anti-inflammatory effects, and improvement of endothelial functions[5].

**A. Anti-oxidant Effect**

All catechin compounds in tea have various biological activities with various mechanisms related to their chemical structure. EGCG has an antioxidant activity that scavenging free radicals in the body[8]. Free radicals formed from oxidant compounds in the body when the body experiencing oxidative stress or inflammation. In addition, free radicals also could be formed when the body's immune system responds to pathogenic bacteria. Free radicals can damage cells, DNA, fat, and protein. Research that conducted by Guo et al (1999) and Sutherland (2006) reported that EGCG can scavenge superoxide compounds and hydroxyl radicals comprising 1,1-diphenyl-3-Picrilhidrazil, ROS (Reactive Oxygen Species), radical peroxyl, nitrite oxide (NO), radical Free carbon-center, oxygen singlet and free radical lipids, and peroxynitrite with the nitration barrier of tyrosine.
Mechanism of action of EGCG as free radical scavenger is due to the one electron reduction potential. Antioxidant activity as hydrogen or electron donor is determined by this reduction potential of free radicals. Hou et al (2005) reported that EGCG was auto-oxidized under cell culture conditions. The reaction probably catalyzed by metal ions such as Cu$^{2+}$ in the culture medium, produces superoxide radicals and EGCG radicals (EGCG). The superoxide radical can further react with another EGCG molecule to produce H$_2$O$_2$ and EGCG. Two EGCG molecules may collide to form a dimer. It is more likely, however, for the EGCG to attack the hydroxyl group of another EGCG molecule, which is more abundant, to form a dimer radical (dimer). The dimer radical can react with molecular oxygen to form the EGCG dimer and regenerate the superoxide radical. An alternative mechanism is that the EGCG is oxidized by molecular oxygen to form O$_2$ and EGCG quinone, and the quinone will react with another molecule of EGCG to form the dimer. In either case, the reaction is propagated by the reaction of superoxide with EGCG, generating EGCG dimers and H$_2$O$_2$. Dimers can be further transformed to other compound, presumably polymer, in a similar manner of oxidation. The addition of Super Oxidized Dismutase (SOD) facilitates the conversion of O$_2$ to H$_2$O$_2$ and inhibits the propagation of the chain reactions. Therefore, the auto-oxidation of EGCG is inhibited. More researches is needed to substantiate these mechanisms[10].

**Figure 2.** Autooxidation EGCG mechanism of action[10]

**Table 1.** Characteristics of enrolled clinical trials and study design

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Dose</th>
<th>Duration</th>
<th>Results</th>
<th>Study Design</th>
</tr>
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<tbody>
<tr>
<td>Bogdanski et al., 2012</td>
<td>Obese adults; n = 56; 20-60 years</td>
<td>379 mg GTE(208 mg of EGCG)/ day</td>
<td>3 month</td>
<td>↓TC, LDL, TG; ↑HDL (significant different between groups)</td>
<td>Randomized double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>Suliburska et al., 2012</td>
<td>Obese adults; n = 46; 30-60 years</td>
<td>379 mg GTE(208 mg of EGCG)/ day</td>
<td>3 month</td>
<td>↓TC, LDL, TG (significant different between groups); ↑HDL (no significant different between groups)</td>
<td>Randomized, double-blind, placebo-controlled</td>
</tr>
<tr>
<td>Miyazaki R. et al., 2013</td>
<td>Older adults; n = 52</td>
<td>630,9 GTC/ day</td>
<td>14 months</td>
<td>↓TC, LDL (significant different within group); ↓TG, ↑HDL (no significant different within group)</td>
<td>A randomized controlled trial using a double-blind, placebo-controlled design</td>
</tr>
<tr>
<td>Nantz, Meri P., 2008</td>
<td>Healthy adults; n = 111; 21-70 years</td>
<td>200 mg GTC/ daily</td>
<td>3 weeks</td>
<td>↓TC, LDL (significant different within group)</td>
<td>A randomized, double-blind, placebo-controlled parallel study.</td>
</tr>
<tr>
<td>Hsu et al., 2008</td>
<td>Obese subjects; n = 100; 16-60 years</td>
<td>400mg GTE/ daily</td>
<td>12 weeks</td>
<td>↓LDL, TG, ↑HDL (significant different between group)</td>
<td>A randomized, double-blind, placebo-controlled clinical trial.</td>
</tr>
<tr>
<td>Chen et al., 2015</td>
<td>Overweight adults; n = 92; 20-60 years</td>
<td>500mg GTE(285.6 mg EGCG)/ daily</td>
<td>12 weeks</td>
<td>↓TC, LDL (significant different between group); ↓TG, ↑HDL (no significant different between group)</td>
<td>A randomized, double-blind, placebo-controlled clinical trial</td>
</tr>
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Abbreviation: HDL=High-density lipoprotein; LDL= Low-density lipoprotein; TC= Total cholesterol; TG= Triglyceride
B. Anti-inflammation Effect

Inflammation is one of the processes that involved in the earliest stage of atherogenesis to later stage of plaque formation and rupture which causes clinical events such as myocardial infarction and stroke[13]. In vitro studies have proven the effects of green tea catechin towards inflammatory cells. Leukocyte has the important role in the inflammation process, it migrates from the intravascular space into the tissues to attack microorganisms and EGCG have found to be a potent inhibitor of leukocyte migration through endothelial cell monolayer[16]. Besides leukocyte neutrophils also play an essential role in host defense and inflammation. EGCG has strong effects in inhibiting the neutrophil elastase. Both oral EGCG and GTE block neutrophil-mediated angiogenesis in vivo in an inflammatory angiogenesis model[6]. Green tea catechins have been shown in inhibiting the cytokine-induced adhesion molecule expression and monocyte adhesion in cultured endothelial cells[16].

C. Improvement of Endothelial Function

The endothelium is a major regulator of vascular homeostasis and controls arterial tone, thrombosis, the composition of the arterial wall, and local inflammation by production of a variety of factors, including nitric oxide nitric oxide[23]. Recent studies indicate that green tea extracts and individual GTC, including EGCG stimulate phosphorylation of endothelial nitric oxide synthase (eNOS) at serine 1177, a response that increases production of nitric oxide[1,14,15]. In in vitro studies, Caveolin-1 (Cav-1), a negative regulator of eNOS, was down regulated by green tea polyphenols[17]. Experimental studies provide strong evidence that green tea acts via specific signaling pathways in endothelial cells that are relevant to the pathogenesis of atherosclerosis. It shows the strong links between endothelial dysfunction and the pathogenesis of atherosclerosis. Therefore, this mechanism might account for reducing the cardiovascular risk among individuals with higher green tea consumptions[5].

Several limitations of studies such as uncontrolled diet and physical activity, time consumption of green tea, inadequate of sample-size and short-terms study may cause bias of the study and clinical effect association. However, none of the studies were sponsored by pharmaceutical companies and were not indicated any conflict of interest. Further meta-analysis assessing the summary effects of green tea was precluded because of study heterogeneity caused by the dosage and duration of green tea consumption, varied condition outcomes, different P-value that defined as statistically significant outcomes and so on.

V. CONCLUSION

The consumption of green tea extract improved lipid profile such as LDL, TC, TG, and HDL and therefore potentially reduce CVD development.

REFERENCES

[9] Hofbauer, R., Frass, M., Gmeiner, B., Handler, S., Speiser, W. and Kapiotis, S., 1999. The green tea extract epigallocatechin gallate is able to reduce neutrophil transmigration through monolayers of...


