Overview

Roles for Epigallocatechin Gallate in Cardiovascular Disease and Obesity: An Introduction

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After water, tea from *Camellia sinensis* is the most consumed beverage worldwide. Tea is rich in catechin flavonoids that possess an array of bioactivity including antioxidant, anti-inflammatory, apoptotic, and probiotic mechanisms of action that may contribute to some of the putative health benefits associated with tea intake. A substantial body of evidence indicates that tea and its principal catechin, epigallocatechin gallate (EGCG) may contribute to a reduction in the risk of cardiovascular disease. Recent studies suggest EGCG may also have a positive impact on glucose tolerance and thermogenesis with implications for an effect on the pathogenesis of type 2 diabetes mellitus and obesity, respectively. This introduction to a symposium on EGCG's role in cardiovascular disease and obesity presented at the 2006 annual meeting of the American College of Nutrition provides a background on tea and tea flavonoids and their possible relationship to health promotion and disease prevention.

INTRODUCTION

Observational studies reveal an inverse association between the consumption of flavonoid-rich foods and beverages and a lower risk of heart disease [1], stroke [2], cancer [3], and other chronic conditions [4]. Tea is a flavonoid-rich beverage and contributes substantially to the intake of dietary catechins. Numerous studies suggest the intake of tea and tea flavonoids lower the risk of cardiovascular disease and cancer [5] and investigations are now expanding to examine its impact on gastrointestinal [6], neurological [7,8], and other functions. While flavonoids are commonly defined as dietary antioxidants and catechins can quench reactive oxygen and nitrogen species [9], their bioactivity may result as well from other mechanisms of action [10], e.g., inhibition of inflammation [11], regulation of nitric oxide [12], stimulation of specific signal transduction pathways, and modulation of other cellular processes such as apoptosis [13].

After water, tea is the most consumed beverage worldwide, although consumption patterns in the amount and type of tea vary markedly between countries. Popkin et al. [14] recently proposed dietary guidelines for the consumption of beverages with those absent calories, specifically water and unsweetened tea and coffee, as the preferable way to meet requirements for hydration. However, consideration for potential health benefits beyond water intake may also be given to the nutrient content of these beverages, especially their constituent phytochemicals.

All non-herbal teas, including green, oolong, black, and white teas, are derived from the leaves of the tropical evergreen *Camellia sinensis.* After harvesting, the leaves of the bush are steamed and dried to produce green tea leaves. If left to ferment (via the action of polyphenol oxidase and peroxidase), the leaves are used for black tea, while the leaves used for oolong tea are only partially fermented. White tea is made from unopened buds that are fired or steamed before drying, and, like green tea leaves, are not subjected to fermentation. The fermentation process forms catechin oligmers and high molecular weight complexes of catechins with proteins, caffeine or other leaf ingredients. Post-harvest fermentation alters the relative catechin content of the leaves. In green tea leaves, the major flavonoids present are the monomer catechins, epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate

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(ECG), and epicatechin (EC) (Fig. 1). In black tea, the polymerized catechins, theaflavin (TF) and thearubigen, predominate (Table 1). Tea also contains some flavonols, particularly quercetin and kaempferol.

Depending on brew time and temperature, a single cup of green tea may contain 100–200 mg EGCG. To control the dose of EGCG administered in experimental studies, green tea solids (GTS) or capsules of green tea extract standardized to EGCG content are often employed. However, Seeram et al. [16] have reported considerable variability in the EGCG content of commercially available dietary supplements, ranging from 12–143% of the tablet or capsule weight. While standardizing tea preparations to EGCG or using highly purified EGCG for research presents an important strategy for the conduct of precise studies as well as the ability to replicate experiments, it is worth noting this approach limits the potential contributions and possible synergy with other bioactive tea ingredients, including caffeine and other flavonoids.

The regulation and control of the *de novo* synthesis of tea flavonoids in *C. sinensis* has not been fully elucidated. The key enzymes in the biosynthesis of tea flavonoids appear to be 5-dehydroshikimate reductase, phenylalanine ammonia lyase, and those associated with the shikimate/arogenate pathway [17]. While commercial formulations extracted from green tea leaves containing ≥90% EGCG have been prepared for use in dietary supplements, methods have recently been developed for the stereoselective synthesis of EGCG and structurally related catechins [18].

Catechin Bioavailability and Pharmacokinetics

Human studies of the bioavailability of green tea catechins reveal these compounds to be poorly absorbed, with <0.1% of ingested catechins appearing in blood. Most ingested EGCG is rapidly cleared from blood with an elimination half-life of ≈3 h and preferentially excreted via bile to the colon. Lee et al. [19] found the mean peak plasma concentration (C_{max}) of EGCG to be 0.17 μM after consuming a single dose of 20 mg/kg GTS dissolved in 200 mL water, the equivalent of 2 c tea; EGC and EC were found in higher concentrations in plasma. EGC and EC were also present in high concentrations in urine, while EGCG and ECG were present in only trace amounts.

Henning et al. [20] found that when similar quantities of tea flavonoids were administered in the form of brewed tea or as GTS, the solids were more effective in elevating serum flavonoid concentrations. Plasma concentration of EGCG from brewed green tea (231.6 mg) was 0.07% of intake, whereas the absorption of EGCG from GTS (193.3 mg) was significantly greater at 0.14%. However, in urine the excretion of both preparations was the same at 0.06% of intake. When the same doses of EGCG, EGC, ECG or EC were administered either as brewed green tea or GTS, the GTS significantly increased C_{max}, area under the plasma concentration time curve (AUC), and the time to achieve C_{max} (t_{max}) by >1 h for all catechins tested. Interestingly, Lee et al. [19] reported considerable inter-individual variability in pharmacokinetic parameters with the administration of EGCG as GTS with caffeine (20 mg/kg), but not with decaffeinated green tea solids (20 mg/kg) or pure EGCG (2 mg/kg).

There appears to be no significant differences between the pharmacokinetics of defined decaffeinated green tea extracts and purified ECGC when administered in a single dose containing 200–800 mg [21, 22]. Peak plasma levels of EGCG (0.4–0.8 μM) were observed after the administration of these formulations at single EGCG doses equivalent to 8–16 c green tea [22]. Chow et al. [23] also reported that after 4 wk of daily administration, the AUC of free EGCG increased significantly from 95.6 to 145.6 min μg/mL with a single daily dose of 800 mg EGCG and from 46.5 to 158.4 min μg/mL with the same dose of the extract. However, no significant AUC changes were observed with 400 mg/d of the extract administered twice daily. Possible mechanisms for the observed increase with the single high daily dose are unknown, but the inhibition of non-enzymatic degradation, the metabolism of intestinal flora, methylation and/or intestinal efflux of EGCG may have been contributing factors.

Tea catechins are largely methylated or metabolized to glucuronide and sulfate conjugates, with valerolactone ring-fission

Table 1. Principal catechins in tea infusions*

Compound	Green tea	Black tea	Oolong tea
EGCG	105	14.6	66.2
EGC	26.8	6.77	21.8
ECG	25.2	12.5	14.7
EC	20.0	15.2	8.3
TF	-	4.4	-

* Infusions were prepared by brewing 2.2 g tea leaves with 250 mL boiling H_2O for 5 min (adapted from [15]).

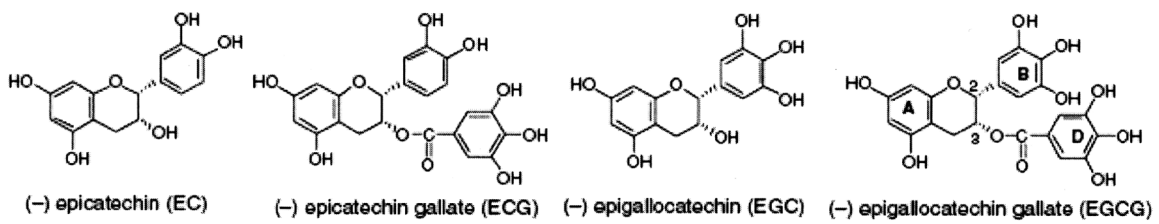

Fig. 1. Structures of the principal catechins present in tea.

metabolites detected as well, in plasma and urine. It remains to be determined whether polymorphisms of catechol-*O*-methyl transferase or other enzymes involved in the biotransformation of catechins influence its metabolite profile. Importantly, tea extracts and GTS preparations appear safe and well tolerated by healthy subjects though some mild, adverse gastrointestinal symptoms have been reported following high dose, chronic intakes. However, much more research is required to better understand factors affecting the bioavailability and metabolism of tea polyphenols both to better inform the design of human studies and to investigate their mechanisms of action.

Recent Research Directions on Tea and EGCG

The growing interest in the role of EGCG in health promotion and disease prevention is reflected by an exponential growth of research publications in this field. Using EGCG as a search term in Medline reveals 990 articles published during the last 5 y. While the principal focus of this work continues to emphasize cancer and heart health, new studies are examining the potential for effects of EGCG on outcomes such as Alzheimer's and Parkinson's disease [24], bone health [25], endurance capacity [26], and rheumatoid arthritis [27]. Recent research on the role of tea polyphenols in heart health have indicated beneficial effects on hypercholesterolemia [28,29], platelet activation [30], endothelial progenitor cells [31], and psychophysiological stress responsivity [32]. During this period 68 studies have measured vascular reactivity as an important outcome measure of the bioactivity of tea on cardiovascular function and risk of coronary artery disease. Further, this recent literature also reveals 35 studies investigating the effect of tea on glucose tolerance and other biomarkers of the risk for type 2 diabetes mellitus as well as 25 reports regarding the impact of tea and EGCG intake on measures of obesity, weight loss, energy expenditure or thermogenesis. The articles in this supplement of the *Journal of the American College of Nutrition* reflect the proceedings of a symposium on EGCG's role in cardiovascular disease and obesity held at the annual meeting of the American College of Nutrition in 2006 and sponsored by DSM Nutritional Products.

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