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Green Tea as Inhibitor of the Intestinal Absorption of Lipids: Potential Mechanism for its Lipid-Lowering Effect[1]

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Abstract

Animal and epidemiological studies suggest that green tea catechins may reduce the risk of cardiovascular diseases (CHD). The health benefit of green tea has been attributed to its antioxidant and anti-inflammatory properties; however, considerable evidence suggests that green tea and its catechins may reduce the risk of CHD by lowering the plasma levels of cholesterol and triglyceride. Although the mechanism underlying such effect of green tea is yet to be determined, it is evident from in vitro and in vivo studies that green tea or catechins inhibit the intestinal absorption of dietary lipids. Studies in vitro indicate that green tea catechins, particularly EGCG, interfere with the emulsification, digestion, and micellar solubilization of lipids, critical steps involved in the intestinal absorption of dietary fat, cholesterol, and other lipids. Based on the observations, it is likely that green tea or its catechins lower the absorption and tissue accumulation of other lipophilic organic compounds. The available information strongly suggests that green tea or its catechins may be used as safe and effective lipid-lowering therapeutic agents.

Keywords

intestinal absorption; lipids; green tea; (−)-epigallocatechin gallate

1. Introduction

Green tea is a popular beverage, derived from the tea plant, *Camellia sinensis*. Its peculiar green color results from the inactivation of polyphenol oxidase by treating fresh tea leaves with hot steam and air [1]. The major polyphenols in green tea are catechins constituting about one third of its total dry weight. The major catechins present in green tea (Figure 1) are (−)-epigallocatechin gallate (EGCG), (−)-epicatechin gallate (ECG), (−)- epigallocatechin (EGC) and (−)-epicatechin (EC).

Evidence from animal studies indicates that green tea and its catechins retard the development or progression of atherosclerosis in apoE-deficient mice [2,3] and hypercholesterolemic hamsters [4,5]. Epidemiological studies have shown an inverse association between coronary heart disease (CHD) risk and green tea consumption in humans [6–11].

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Studies have shown that catechins possess antioxidant activities and effectively inhibit low-density lipoprotein (LDL) oxidation and lipid peroxidation in vitro [12–17]. At present, it remains debatable whether the reduction in CHD risk in humans associated with green tea consumption is attributable to the prevention of LDL oxidation or to the antioxidant potential of green tea or its catechins [18,19]; however, evidence from animal studies clearly indicates that green tea or its catechins lower the blood levels of cholesterol in cholesterol-fed rats [20, 21], mice [22], and hamsters [23], as well as the plasma levels of triglyceride in hamsters fed a high fat diet [23] and in rats fed a high-fructose diet [24].

Green tea catechins - particularly the principal green tea catechin, EGCG - are not readily absorbed, with small percentages of orally ingested catechins appearing in the blood in rats [25] and humans [26,27]. Due to rather poor absorption and greater availability of green tea catechins in the intestinal lumen, it is likely that the lipid-lowering effect of green tea and catechins is mediated largely via their influence on the intestinal processes involved in digestion and absorption of lipids [28–30]. Available information suggests that green tea and its catechins interfere with or inhibit the luminal emulsification, hydrolysis, and micellar solubilization of lipids. The possibility also exists that green tea or catechins may influence the uptake and intracellular processing of lipids and assembly and secretion of chylomicrons.

2. Inhibition of Intestinal Lipid Absorption by Green Tea and Catechins

Using ovariectomized rats with mesenteric lymph-duct cannula, Löest et al. [28] showed that fresh green tea extract, intraduodenally infused at the doses equivalent to 1–2 cups of tea, significantly lowered the lymphatic absorption of cholesterol in a dosedependent manner in rats with mesenteric lymph-duct cannula. Similarly, green tea extracts profoundly inhibited the absorption of α-tocopherol, another lipid of extreme hydrophobicity; however, the absorption of fat (fatty acids) was altered in a biphasic fashion, with a significant increase at a low dose [of ECGC?] and a moderate decrease at a higher dose. Ikeda et al. [29] demonstrated that mixtures of catechins extracted from Japanese green tea lowered the absorption of cholesterol and triglyceride in rats with thoracic lymph-duct cannula. The investigators observed that a mixture of EGCG and ECG were more effective than a mixture of EC and EGC in lowering the absorption of cholesterol, suggesting that the gallate esters of green tea catechins were more potent inhibitors of cholesterol absorption. In another study [30], Ikeda et al. observed that heat-treated catechins high in gallocatechin gallate and catechin gallate were more effective in inhibiting cholesterol absorption than a catechin mixture high in EGCG and ECG. It appears that tea catechins are less effective in inhibiting fat absorption. USing the fecal isotope ratio method, Raederstorff et al. [31] found that EGCG lowered the absorption of cholesterol in a dose-dependent manner in rats, whereas it decreased fat absorption only moderately even at a high dose. This finding is consistent with the observation of Ikeda et al. [29] that the inhibition of fat absorption by catechins was both moderate and dependent on the types of fat incorporated into lipid emulsions.

3. Inhibition of Luminal Lipid Hydrolysis by Green Tea and Catechins

Studies in vitro have shown that green tea and catechins inhibit pancreatic lipase activity. Juhel et al. [32] first reported that a green tea extract significantly inhibited gastric and pancreatic lipase activities, as determined by using a relatively high level of catechins under gastric and duodenal conditions in vitro. The addition of the green tea extract at 60 mg/g triolein prevented the emulsification of fat in the presence of bile acids. Similarly, Ikeda [33] demonstrated that a mixture of catechins high in EGCG and ECG dose-dependently inhibited pancreatic lipase in vitro and suppressed the postprandial rise in serum triglyceride.

A recent study by Shishikura et al. [34] examined the effect of green tea catechins on lipid emulsification using a model emulsion consisting of olive oil, phosphatidylcholine (PC), and

bile salt. Green tea catechins, particularly EGCG, at the levels achievable by typical daily intake, markedly altered the physicochemical properties of a lipid emulsion by increasing its particle size and reducing the surface area [34]. Such changes likely slow the rate of hydrolysis of fat, as pancreatic lipase activity decreases with increasing emulsion droplet size and decreasing surface area [35]. Of particular interest is the finding that among the green tea catechins, EGCG was the main compound present on the lipid phase of the emulsion, indicating that EGCG is the principal catechin responsible for the changes in emulsion properties. This finding is consistent with the observation that EGCG is more effective than other catechins in lowering intestinal lipid absorption [29,36]. The investigators [34] proposed that the hydroxyl moieties of EGCG interact with the hydrophilic head group of PC at the exterior of a lipid emulsion by forming hydrogen bonds. Such interactions may lead to formation of cross links followed by coalescence of the emulsion droplets.

Consistent with the above findings, our recent study [36] showed that green tea catechins also inhibit pancreatic phospholipase A_2 (PLA_2), as determined under in vitro conditions. Among the major catechins, EGCG was most effective in inhibiting PLA_2 activity. The degree of PLA_2 inhibition by catechins, at 0.6 μmol, increased in the order of EC, EGC, ECG and EGCG. When labeled PC was infused intraduodenally along with EGCG in rats with mesenteric lymph cannula, a significant amount of PC remained unhydrolyzed in the small intestinal lumen and the cecum, with a marked decrease in the lymphatic output of the labeled tracer. Our findings from this study provide strong evidence that the decreased absorption of lipids by green tea catechins, particularly EGCG, is partly attributable to the inhibition of PLA_2 activity. As proposed by Shishikura et al. [34], it is possible that EGCG may form complexes with the surface PC of a lipid emulsion, hindering access to the substrate by PLA_2 or directly with the enzyme protein altering its conformation and catalytic activity [1,37,38].

The potent inhibitory effect of EGCG on pancreatic PLA_2 activity may be largely responsible for the decreased absorption of lipids because luminal PC hydrolysis is critical to facilitating intestinal lipid digestion and absorption as evidenced from studies in vitro [39–43] and in vivo [44]. Many studies in vitro demonstrated that if PC present on the exterior of a lipid emulsion remains intact, it interferes with the hydrolysis of the core triglyceride by pancreatic lipase. Pancreatic lipase/colipase was shown to be ineffective in hydrolyzing triglyceride incorporated into PC-containing lipid emulsions and the initial hydrolysis of the surface PC by pancreatic PLA_2 significantly increased the hydrolysis of triglyceride by pancreatic lipase/colipase [39, 42,43,45]. In addition, a study with intestinal cells [44] showed that a minimal hydrolysis of triglyceride was required for stimulation of the cell uptake of other extremely hydrophobic lipids such as cholesterol. Thus, the initial action of pancreatic PLA_2 is critical to the hydrolysis of triglyceride by lipase, formation of mixed micelles and subsequent transfer of micellar lipids to the enterocyte through the unstirred water layer [46,47].

In our study [36], α-tocopherol was included in a lipid emulsion as another marker of extremely hydrophobic lipids and retinol as a relatively less hydrophobic lipid to determine whether EGCG differentially inhibits the absorption of lipids differing in hydrophobicity in rats. Data showed that EGCG lowered the lymphatic output of α- tocopherol to 46% of the controls, whereas it did not affect the lymphatic absorption of retinol and lowered fat (fatty acid) absorption only moderately (by less than 9%). These findings are in keeping with those of Homan and Hamelehle [48] that the presence of PC in bile salt micelles markedly reduced the uptake of cholesterol, whereas it did not interfere with the cell uptake of less hydrophobic lipids such as retinol, oleic acid, and monoacylglycerol. Thus, the inhibition of luminal PC hydrolysis by EGCG may explain the rather marked inhibition of the lymphatic absorption of cholesterol and α-tocopherol of extreme hydrophobicity and the moderate or no effect of EGCG on less hydrophobic compounds such as retinol and fatty acid [36].

In view of the above findings, it would be of interest to determine whether EGCG interferes with the absorption of non-nutrient lipophilic compounds, including persistent organic pollutants (POPs). Previously, it has been shown that green tea profoundly lowered the absorption of POPs, including polychlorinated biphenyls (PCBs), thus decreasing the tissue burden of the POPs [49]. Attention should be directed to determining whether green tea or catechins can be used as an effective dietary means of reducing the absorption and tissue accumulation of certain environmental lipophilic POPs.

4. Influence of Green Tea and Catechins on the Intestinal Uptake and Intracellular Processing of Lipids

A critical step for the uptake and absorption of lipids by the enterocyte is the micellar solubilization of hydrolyzed lipids, which facilitates the transfer of lipids via the unstirred water layer to the enterocyte for uptake. Studies have shown that EGCG is more effective than other green tea catechins in precipitating cholesterol from bile salt micelles [29,30] but that it does not significantly affect the micellar solubility of fatty acids and monoacylglycerol, products of triglyceride hydrolysis by pancreatic lipase. The observations are in keeping with the findings that EGCG is a potent inhibitor of cholesterol absorption but has little or moderate inhibitory effect on fatty acid (fat) absorption [29,31].

Increasing evidence suggests that uptake of lipids by the enterocyte is partly mediated by specific transporters on the brush border membrane (BBM). The possibility exists that green tea catechins may interact with proteins implicated in the uptake and efflux of lipids. For example, the transport of cholesterol across the BBM is modulated by proteins such as multidrug resistance P-glycoprotein 1 (MDR1) [50], ATP-binding cassette (ABC) proteins [51,52], B type-1 scavenger receptors [53,54], and Niemann Pick C1-like 1 protein [55]. As stated above, ingested catechins may form complexes with BBM proteins through hydrophobic interactions and hydrogen bonding. This possibility is supported by the findings that certain flavonoids modulate the activities of MDR glycoproteins by interacting with the ATP-binding site and steroid-interacting region [56,57]. Thus, it is probable that green tea catechins may influence the uptake of cholesterol and other lipids by the enterocyte through interaction with transporters, particularly those exposed to the intestinal lumen. At present, it remains unknown whether green tea or its constituents influence their expression in the enterocyte.

After lipids are taken up by the entrocyte, green tea may alter the intracellular processing and packaging of lipids including their reacylation or resynthesis of lipids. In our previous study [28], we observed a transient but significant decrease in the relative amount of esterified cholesterol appearing in lymph when a lipid emulsion was luminally infused with green tea extract, suggesting that green tea may inhibit intestinal acyl CoA:cholesterol acyltransferase in the enterocyte. Evidence indicates that flavonoids such as quercetin and naringenin inhibit the activity of diacylglycerol acyltransferase and the lipidation of ApoB-containing lipoproteins by microsomal triglyceride transfer protein in Caco-2 cells [58] and HepG2 cells [59]. Thus, it is possible that green tea catechins may influence critical steps involved in the assembly and secretion of chylomicrons from the enterocyte into the lymphatics. Further studies are warranted to determine whether green tea or its constituents alter the expression of genes involved in regulating these processes.

5. Summary and Conclusion

Based on the information available thus far, it is evident that green tea and its catechins effectively lower the intestinal absorption of lipids. Among the green tea catechins, EGCG is the most potent inhibitor of lipid absorption. The potent inhibitory effect of EGCG appears to be associated with its ability to form complexes with lipids and lipolytic enzymes, thereby

interfering with the luminal processes of emulsification, hydrolysis, micellar solubilization, and subsequent uptake of lipids. EGCG appears to be more effective in lowering the absorption of lipids of extreme hydrophobicity, such as cholesterol and α-tocopherol, with little or a moderate effect on less hydrophobic lipids such as retinol and fatty acid. It is probable that green tea or it constituents lower the absorption of other lipophilic compounds such as POPs. Further studies are warranted to define the mechanisms underlying the inhibition of lipid absorption by green tea and its catechins.

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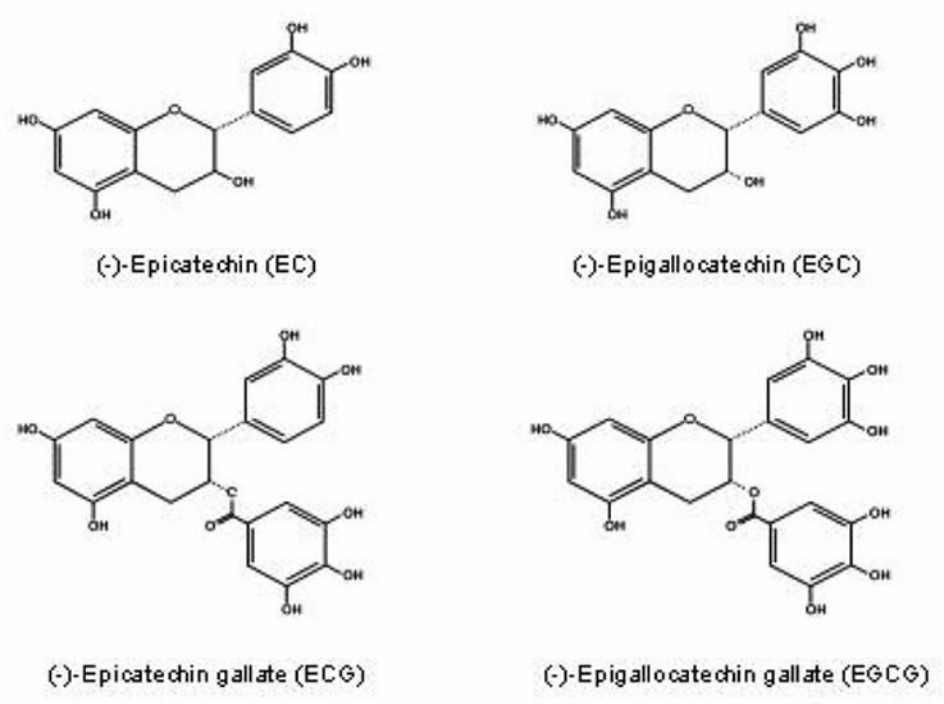

Fig. 1.
Structures of major green tea catechins