The effect of bioactive compounds in tea on lipid metabolism and obesity through regulation of peroxisome proliferator-activated receptors

Sung-Joon Lee[a,b] *and Yaoyao Jia*[a,b]

Purpose of review
The hypolipidemic and antiobesogenic effects of tea intake have been associated with bioactive compounds that regulate peroxisome proliferator-activated receptors (PPARs). This review describes the recent research on two of these compounds, (−)-epigallocatechin gallate (EGCG) and linalool.

Recent findings
Catechins (specifically EGCG) are key bioactive compounds found in tea, and a recent study has shown that linalool may also be an active tea compound. These compounds act on lipid metabolism by regulating PPAR subtypes. EGCG inhibits the key adipogenic transcription factor PPARγ while activating PPARα, whereas linalool is a PPARα agonist activating hepatic fatty acid uptake and subsequent oxidation to reduce plasma triglyceride levels.

Summary
The collective activities of EGCG and linalool in tea may exert hypolipidemic and antiobesogenic effects by regulating PPARs. The research summarized in this review expands our understanding of the biological and physiological mechanisms of the bioactive compounds found in tea.

Keywords
(−)-epigallocatechin gallate, linalool, lipid metabolism, peroxisome proliferator-activated receptors, tea

INTRODUCTION

Tea is produced from the leaves of the *Camellia sinensis* L. species of the Theaceas family. It is one of the most popular beverages worldwide and its consumption is increasing continuously [1▪]. Habitual tea consumption has been associated with antioxidative activity, improved lipid metabolism, and reduced body fat accumulation [2–4]. These effects are likely mediated by the bioactive compounds found in tea leaves, including catechin polyphenols [e.g., (−)-epigallocatechin gallate (EGCG)] and aroma terpenoids (e.g., linalool).

Tea is a source of various flavonoids including the flavon-3-ol called catechins, which are potent antioxidants that terminate lipid peroxidation and activate cellular antioxidant signaling pathways and are associated with the prevention of lifestyle-related diseases [5]. Among the catechins, EGCG has been suggested as the major active compound in tea because of its potency and relative quantity [6,7]. Green tea contains the highest concentration of EGCG among tea types [8]; thus, black tea, which is the most widely consumed tea worldwide, has lesser effects on lipid metabolism and antiobesogenic activity [9,10]. However, catechins or EGCG alone cannot explain the biological effects of tea on lipid metabolism as human trials with tea catechins or EGCG alone showed mixed results, suggesting the potential involvement of alternative bioactive tea components. Recently, linalool, a terpenoid aroma compound with antioxidant activity found in green tea, has been shown to have effects on lipid metabolism [11,12▪]. Therefore, it is possible that tea catechins together with linalool may be responsible for the hypolipidemic and antiobesogenic effects of tea.

[a]Department of Biotechnology, Graduate School of Life Sciences & Biotechnology and Brain Korea 21-PLUS Program and [b]Department of Food Biosciences and Technology, College of Life Sciences and Biotechnology, Korea University, Seoul, Republic of Korea

Correspondence to Sung-Joon Lee, Department of Biotechnology, Graduate School of Life Sciences & Biotechnology, Korea University, Seoul 136-713, Republic of Korea. Tel: +82 2 3290 3029; fax: +82 2 3290 3653; e-mail: junelee@korea.ac.kr

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KEY POINTS

- Recent studies investigating the hypolipidemic and antiobesogenic effects of tea intake have shown that these effects are associated with the regulation of PPARs in the liver and adipose tissues. This suggests that there is a collective biological effect of more than one tea compound.
- EGCG, a major bioactive compound found in tea, suppresses PPARγ in adipose tissues, while inducing PPARα expression in the liver.
- Linalool, an aromatic terpenoid found in teas, interacts directly with PPARα by inducing transactivation, ultimately regulating the expression of genes and proteins involved in fatty acid oxidation. This effect alters the transcriptome and metabolome, resulting in net hypotriglyceridemic effects *in vivo*.

Regulation of peroxisome proliferator-activated receptors (PPARs) by these compounds has been suggested as a potential mechanism of hypolipidemic and antiobesogenic effects. PPARs are nuclear hormone receptors that function as transcription factors [13]. There are three PPAR subtypes, alpha (α), delta/beta (δ/β), and gamma (γ) exist, which have different tissue distributions and pharmacological profiles. PPARα is expressed mainly in the liver and muscle, and regulates the genes involved in triglyceride metabolism and fatty acid oxidation. PPARγ is found in the muscle and adipose tissues, and is involved in the expression of genes associated with adipogenesis and insulin sensitivity. PPAR δ/β is ubiquitously expressed in various tissues and regulates genes involved in energy metabolism and thermogenesis. All three receptors act on lipid metabolism [14] and are thus well defined molecular targets for the development of drugs for hypertriglyceridemia, type II diabetes, and obesity.

This review summarizes the recent research related to the hypolipidemic and antiobesogenic activities of EGCG and linalool in tea, as it relates to their regulation of PPARα and PPARγ.

HYPOLIPIDEMIC AND ANTIOBESOGENIC ACTIVITIES OF TEA

Epidemiologic studies have found that consumption of tea, especially green tea, was inversely associated with serum levels of cholesterol [15,16] and obesity [17,18]. Numerous human clinical trials have revealed that plasma and LDL cholesterol levels, as well as body weight gain, were reduced as a result of tea intake. Epidemiologic studies suggested inverse association between green tea intake and the risk of coronary artery disease as well. Hirano *et al.* [19] showed that a green tea intake of at least 1 cup per day was found to be inversely associated with recurrent myocardial infarction in Japanese patients and Wang *et al.* [20] also reported inverse association between green tea intake and the risk of coronary artery disease. In the study, the adjusted odds ratio (OR) was 0.36 (0.17–0.73) in male patients consuming at least 250 g of dried tea leaves per month compared with nontea drinkers. In the Zutphen elderly study, intake of tea consumption was also inversely associated with the risk of coronary heart disease, showing the adjusted OR of 0.38 (0.18–0.82) in persons consuming 251–500 ml of tea per day compared to nontea drinkers [21].

Tea can be classified into three types based on the fermentation levels: fully fermented black tea, partially fermented oolong tea, and unfermented green tea [22,23]. Black tea has the highest consumption rate in North Africa at approximately 75% and is the primary tea consumed in Europe and North America. Green tea is the most popular in Asia, which consumes approximately 23% green tea and less than 2% oolong [24]. Epidemiologic studies and controlled trials have been performed primarily with green tea and black tea. Black tea consumption was associated with reduced risk of coronary heart disease in several studies, but not in recent meta-analysis [10]. In contrast, the consumption of green tea was associated with a lower risk of coronary heart disease among Asian and Dutch populations [19–21], although further confirmation requires additional prospective studies. An increase in green tea consumption of 1 cup per day was associated with a 10% decrease in the risk of developing coronary artery disease [10]. In a meta-analysis of 14 randomized clinical trials, intake of green tea, either as a beverage or a capsule form, significantly reduced total and LDL cholesterol concentrations but not HDL cholesterol and triglyceride levels. Collectively, these results suggest that green tea has greater hypolipidemic activity than black tea, although the hypolipidemic effect of black tea has not yet been confirmed in clinical trials.

The role of tea intake, especially green tea, has been intensively investigated in various experimental conditions during the last decade. Currently, it is widely accepted that green tea EGCG has an antiobesogenic effect on fat homeostasis by reducing adipogenesis and increasing thermogenesis. Although human clinical trial data published to date are inconsistent, several clinical trials revealed positive effects of green tea intake on obesity. For example, a randomized controlled trial examined the effect of green tea on body fat distribution in overweight and obese adults during exercise-induced

weight loss. The results showed that a 12-week supplementation of green tea showed a trend of body weight reduction (−1.2 kg, $P = 0.079$) toward a greater loss of body weight in the catechin group (624.7 mg catechins, 39 mg caffeine) compared with the control group (no catechins, 39 mg caffeine). The percentage changes in the total abdominal fat area [−7.7 (−11.7, −3.8) vs. −0.3 (−4.4, 3.9); $P = 0.013$], subcutaneous abdominal fat area [−6.2 (−10.2, −2.2) vs. 0.8 (−3.3, 4.9); $P = 0.019$], and fasting serum triglyceride −11.2 (−18.8, −3.6) vs. 1.9 (−5.9, 9.7); $P = 0.023$] were greater in the catechin group, which suggest that green tea catechin consumption enhances exercise-induced changes in abdominal fat and serum triglyceride [25]. In another double-blinded controlled trial, the effects of tea catechins were investigated on body fat among healthy Japanese. Results showed that body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area were significantly lower in the green tea extract group (690 mg of catechins per day) than in the control group. These suggested that daily consumption of tea containing catechins for 12 weeks reduced body fat, which suggests that the ingestion of green tea might be useful in the prevention and improvement of obesity [26].

Several meta-analyses reported the antiobesogenic effects of tea on metabolic and anthropometric variables [27–30]. Two meta-analyses reported that green tea catechin significantly decreased body weight by 1.31 and 1.38 kg, respectively [28,30]. More recently, meta-analysis published by Hursel *et al.* [27] showed catechin and caffeine rich tea increased energy expenditure by more than 400 kJ over 24 h, an increase of approximately 5% of total daily energy expenditure. In the analysis, calculations showed that catechin and caffeine rich tea stimulate daily energy expenditure in a dose-dependent manner by 0.4–0.5 kJ/mg administered. Jurgens *et al.* [29] also analyzed clinical trials performed in or outside Japan separately, because of the degree of heterogeneity among studies. Japanese studies revealed a significant mean weight loss of −1.44 kg; however, the studies included in the analysis were highly heterogeneous; therefore, it was concluded that green tea had only a minor, nonsignificant effect on weight loss. This conclusion does not appear to be in line with the previous meta-analyses. However, many human studies have suggested that intake of green tea resulted in a small improvement in anthropometric variables, including body weight, BMI, fat mass, and waist-to-hip ratio [25,31–34].

Regulation of PPARs by compounds found in tea has been suggested as a potential mechanism underlying the hypolipidemic and antiobesogenic effects of tea intake. Current reports suggest that tea or tea extracts regulate the expression of PPARs by activating PPARα and inhibiting PPARγ. Inhibition of adipocyte proliferation and adipogenesis by PPARγ suppression has been suggested as one of the antiobesogenic mechanisms of tea consumption; activation of PPARα could contribute to the amelioration of hypolipidemia in both liver and adipose tissues [35]. A study in cultured hepatocyte showed green tea catechins decreased apolipoprotein B-100 secretion [36], and human studies showed that tea consumption decreased plasma triglyceride concentrations [32], as well as postprandial lipemia [37], although a meta-analysis did not confirm the reduction of plasma triglyceride concentrations [38]. Green tea extract induced PPARα transactivation using a full-length PPARα reporter gene assay [39], thus upregulating several PPARα responsive genes involved in fatty acid β-oxidation, including acyl-CoA oxidase-1 and carnitine palmitoyl transferase-1, to increase the rate of fatty acid oxidation [40,41]. In addition, green tea has been shown to inhibit a number of lipogenic enzymes, including acetyl-CoA carboxylase [42], fatty acid synthase [43], and PPARγ coactivator 1-α [44]. These results suggest that tea compounds differentially regulate PPARα and PPARγ to mediate hypolipidemic and antiobesogenic effects. The next two sections of this review will discuss the recent research on the specific effects of the tea compounds EGCG and linalool on lipid metabolism.

EFFECTS OF (−)-EPIGALLOCATECHIN GALLATE ON LIPID METABOLISM THROUGH ACTIVATION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR α AND INHIBITION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR γ EXPRESSION

EGCG is the major polyphenol found in tea. A number of in-vitro and in-vivo studies have reported hypolipidemic effects of EGCG on lipid metabolism, including the expression of PPARα and its target genes at both gene and protein levels. PPARα transactivation by tea catechins, including EGCG, has been examined using a Gal4/UAS reporter gene assay. Results showed moderate inductions of PPARα, leading to the conclusion that EGCG may not be a direct ligand of PPARα [45] and may activate PPARα by an indirect mechanism. EGCG inhibits nuclear transcription factor κB (NF-κB) activation by blocking the phosphorylation of inhibitor of κB (IκB) [46]. This action of EGCG may prevent NF-κB from inhibiting PPARs to induce mRNA expression of

lipid-metabolizing enzymes and enhance fatty acid oxidation.

Recent animal studies demonstrated that EGCG significantly reduced plasma triglyceride and LDL cholesterol concentrations and body fat mass in animals (41,47). For example, C57BL/6J mice fed a high-fat diet containing EGCG (0.32%, added to the diet) for 16 weeks had upregulated mRNA expression of PPARα and its target genes, including uncoupling protein 3, in the liver. This in turn reduced hepatic lipid accumulation and induced mitochondrial fatty acid oxidation in skeletal muscle [47]. In addition, other report demonstrated that EGCG activates PPARα and its targets including carnitine palmitoyl transferase-I, uncoupling protein 2, hormone sensitive lipase, lipoprotein lipase and inhibits sterol regulatory element-binding protein (SREBP)-1c, fatty acid synthase, and acetyl CoA carboxylase in rats fed high-fat diet [41]. These results suggest PPARα to be a key modulator of EGCG in hepatic fatty acid oxidation, ultimately resulting in the amelioration of hyperlipidemia.

The possibility of direct binding of EGCG to PPARα ligand-binding domain with moderate affinity cannot be excluded, as a cell-based reporter gene assay detected both direct and indirect activation. The PPARs have a relatively large ligand-binding pocket compared with other nuclear receptors, which could accommodate diverse natural compounds [48]. Thus, EGCG might have a direct effect on PPARα and its target gene expression. This possibility should be investigated in future studies.

Antiobesogenic effects of EGCG mediated by PPARγ suppression have been reported in many in-vitro and in-vivo studies [49]. EGCG inhibited the proliferation and differentiation of adipocytes in 3T3-L1 proadipocyte cell lines. Adipocyte differentiation is precisely controlled by several transcription factors, of which PPARγ, a key regulator of late-stage adipogenesis, and CCAAT enhancer-binding protein-α are the key regulators [50]. Levels of both PPARγ and CCAAT enhancer-binding protein-α were reduced in cells stimulated with EGCG at both mRNA and protein levels, thus blocking differentiation [51,52]. These in-vitro results have been supported by in-vivo experiments with diet-induced obese mice fed EGCG. [53].

A potential mechanism of the inhibitory effect of EGCG on PPARγ has been suggested recently [54▪]. EGCG stimulation of 3T3-L1 during adipogenesis upregulated the wingless-type MMTB integration site (WNT)–β-catenin pathway inducing β-catenin expression, whereas suppressing the major genes in the adipogenesis, including PPARγ, CCAAT enhancer-binding protein-α, fatty-acid-binding protein-4, and fatty acid synthase. In that study, knockdown of the β-catenin gene by small interfering RNA attenuated the inhibitory effects of EGCG on intracellular lipid accumulation and the suppression of adipogenic genes. The DNA-binding activity of PPARγ was reduced by EGCG, and this inhibition was reversed by β-catenin gene knockdown. These results suggest that inhibition of PPARγ is carried out at least in part by activation of the WNT/β-catenin pathway.

Therefore, activation of PPARα and inhibition of PPARγ could lead to body fat consumption and subsequent weight reduction (Fig. 1); however, human trials with EGCG revealed mixed results in terms of body weight. Green tea extract prevented weight gain [34] and intake of a 150-mg capsule of EGCG twice daily for 12 weeks significantly reduced waist circumference, total body fat, abdominal fat, and intra-abdominal adipose tissue in overweight or obese postmenopausal women [55]. However, a more recent study reported that dietary supplementation with EGCG (300 mg/day) for 12 weeks in obese Caucasian women did not significantly affect body weight [56]. These studies suggest that an additional tea compound may have synergistic effects with EGCG on lipid metabolism and weight control.

THE EFFECTS OF LINALOOL ON LIPID METABOLISM THROUGH THE REGULATION OF SREBP-2 AND PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR α

Linalool, a major aromatic monoterpene in Lamiaceae plants [57], is also found in tea [58]. Linalool showed strong antioxidant activity by reducing the oxidation of LDL particles [59] and has hypocholesterolemic activity [11]. Oral administration of linalool to mice for 6 weeks significantly lowered total and LDL cholesterol levels. These reductions were primarily a result of a reduction in 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase protein level through both transcriptional and post-transcriptional mechanisms. Linalool inhibited the nuclear translocation of SREBP-2, which is required for the downregulation of HMG-CoA reductase transcription, and induced HMG-CoA reductase protein degradation by ubiquitin-dependent proteolysis (Fig. 1).

More recently, the hypotriglyceridemic mechanism of action of linalool in tea and its regulation of PPARα have been demonstrated (Fig. 1) [12▪]. *In vitro*, PPARα activity was assessed with a full-length PPARα reporter gene assay, and the results showed a dose-dependent induction of PPARα transactivation. In a nuclear receptor such as PPARα, agonist binding alters protein confirmation and

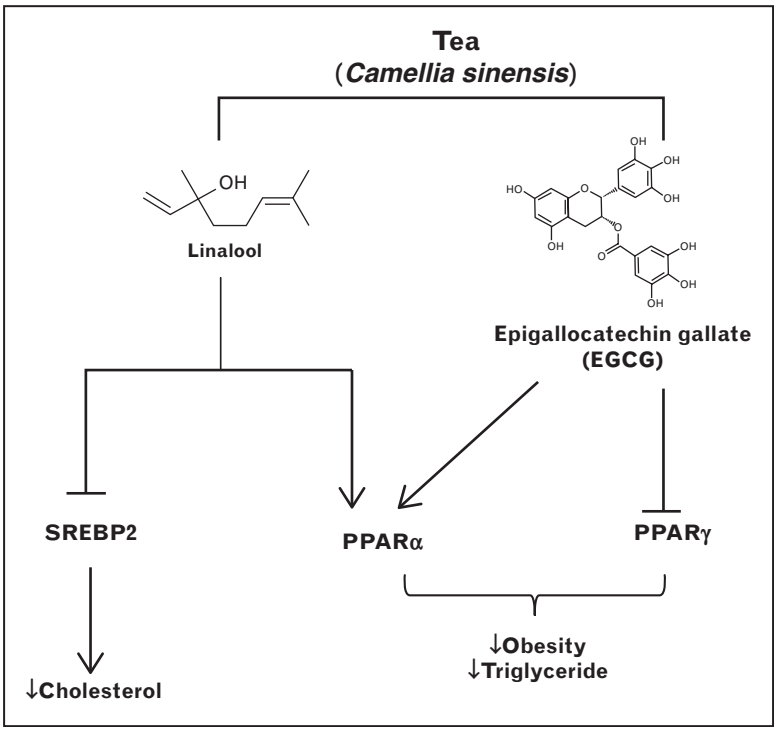

FIGURE 1. Effects of the tea compounds, EGCG and linalool, on lipid metabolism regulated by PPARα and PPARγ. EGCG indirectly regulates PPARs and activates hepatic PPARα, whereas inhibiting adipocyte PPARγ. Inhibition of NF-κB leads to PPARα activation, and the induction of WNT–β-catenin signaling inhibits PPARγ expression in adipocytes. Linalool directly interacts with PPARα to induce transactivation and target gene expression involved in fatty acid oxidation and fatty acid synthesis. Linalool has hypocholesterolemic effects by reducing gene and protein expression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by inhibition of nuclear translocation of SREBP2 and induction of ubiquitin-dependent sterol regulatory element-binding protein-2 (SREBP2) degradation. EGCG, epigallocatechin gallate; NF-κB, nuclear transcription factor κB; PPARs, peroxisome proliferator-activated receptors.

recruits a coactivator peptide. Results from a PPAR coactivator recruitment assay revealed that linalool activated PPARα and allowed the recruitment of the PPARα coactivator 1-α coactivator peptide, a coactivator of PPARα, demonstrating that linalool may act as an agonist and directly interact with the PPARα ligand-binding domain. The activity of other PPAR subtypes was unaltered. In cultured hepatocytes, linalool stimulation decreased intracellular lipid accumulation, regulating PPARα target genes and significantly elevating the rate of fatty acid oxidation. In two experiments in mice, oral administration of linalool for 3 weeks reduced plasma triglyceride concentrations in Western-diet-fed C57BL/6J mice by 31% ($P < 0.05$) and human apolipoprotein E2 transgenic mice by 50% ($P < 0.05$), and modulated PPARα target genes and proteins. Importantly, silencing PPARα in cultured hepatocytes and PPARα-deficient mice did not show such effects. These findings confirmed that the hypotriglyceridemic effects of linalool are PPARα dependent. Furthermore, hepatic transcriptome and plasma metabolome analyses demonstrated that linalool changed the gene expression and metabolome profiles from hyperlipidemic conditions to those of wildtype controls. Notably, the concentrations of saturated fatty acids were significantly reduced in linalool-fed mice. These findings suggest that the intake of a natural aromatic compound such as linalool in tea might exert beneficial metabolic effects by regulating a cellular nutrient sensor. An investigation of the long-term effects of linalool on body weight gain or maintenance would be of interest as a future study.

CONCLUSION

The hypolipidemic effects of tea may be due to the regulation of PPAR subtypes by more than one compound. Research suggests that EGCG and linalool in tea regulate PPARs in liver and adipose tissues, exerting hypolipidemic and antiobesogenic effects. Although the exact molecular mechanisms have not yet been clearly described, the recent advances in tea research described in this review suggest that the hypolipidemic effects of tea may

involve the differential regulation of PPAR subtypes. A variety of studies have shown that EGCG inhibits the key adipogenic transcription factor PPARγ while activating PPARα, whereas linalool independently activates PPARα while inhibiting SREBP2. The interactions of specific tea compounds with PPARs should be investigated in future research.

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Conflicts of interest

None.

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