

## Review

# Anti-obesity effects of green tea: From bedside to bench

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During the last decade, the traditional notion that green tea consumption benefits health has received significant scientific attention and, particularly, the areas of cardiovascular disease and cancer were subject to numerous studies. Due to the ever-growing obesity pandemic, the anti-obesity effects of green tea are being increasingly investigated in cell, animal, and human studies. Green tea, green tea catechins, and epigallocatechin gallate (EGCG) have been demonstrated in cell culture and animal models of obesity to reduce adipocyte differentiation and proliferation, lipogenesis, fat mass, body weight, fat absorption, plasma levels of triglycerides, free fatty acids, cholesterol, glucose, insulin and leptin, as well as to increase beta-oxidation and thermogenesis. Adipose tissue, liver, intestine, and skeletal muscle are target organs of green tea, mediating its anti-obesity effects. Studies conducted with human subjects report reduced body weight and body fat, as well as increased fat oxidation and thermogenesis and thereby confirm findings in cell culture systems and animal models of obesity. There is still a need for well-designed and controlled clinical studies to validate the existing and encouraging human studies. Since EGCG is regarded as the most active component of green tea, its specific effects on obesity should also be investigated in human trials.

**Keywords:** Adipose tissue / Epigallocatechin gallate / Green tea / Human / Obesity

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## 1 Introduction

In Asia, green tea is a widely consumed beverage and, for centuries, has been regarded to possess significant health-promoting effects [1]. The legendary Chinese emperor, Shen Nung, discovered the detoxifying and health-maintaining effects of green tea around 2700 BC. Traditionally, green tea was used to improve blood flow, eliminate alcohol and toxins, improve resistance to disease, relieve joint pain,

and to clear urine and improve its flow [1]. Chen Zang, a famous pharmacist of the Tang Dynasty (618–907), highlighted the broad range of health-promoting effects: “Every medicine is the only medicine for a specific disease, but tea is the medicine for all diseases.” According to the pharmacist Wang Ang (1615–1695), drinking green tea for a long time can eliminate fat. In recent years, research has mainly focused on effects of green tea related to the prevention of cancer [2] and cardiovascular disease [3]. Furthermore, the anti-inflammatory [4], antiarthritic [5, 6], antibacterial [7], antiangiogenic [8, 9], antioxidative [10, 11], antiviral [12, 13], neuroprotective [14], and cholesterol-lowering effects [15, 16] of green tea and isolated green tea constituents are under investigation.

The health-promoting effects of green tea are mainly attributed to its polyphenol content. Green tea is a rich source of polyphenols, especially of flavanols and flavonols, which represent approximately 30% of dry weight of the fresh leaf [1]. Catechins are the predominant form of the flavanols and mainly comprised epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC) [17]. Recently, many of the aforementioned beneficial effects of green tea were attributed to its most abundant catechin, EGCG [18–24].

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**Abbreviations:** BAT; brown adipose tissue; cAMP, cyclic adenosine monophosphate; Cdk2, cyclin-dependent kinase 2; C/EBP $\alpha$ , CCAAT/enhancer binding protein alpha; C/EBP $\beta$ , CCAAT/enhancer binding protein beta; C/EBP $\delta$ , CCAAT/enhancer binding protein delta; ECG, epicatechin gallate; EGC, epigallocatechin; EGCG, epigallocatechin gallate; ERK1, extracellular signal-regulated kinase 1; ERK2, extracellular signal-regulated kinase 2; GTE, green tea extract; IBMX, isobutyl-1-methylxanthine; i.p., intraperitoneal; i.v., intravenous; NA, noradrenaline; PPARY, peroxisome proliferator activated receptor gamma 2; SCD1, stearoyl-coenzyme A desaturase 1; T2DM, type 2 diabetes mellitus; UCP-2, uncoupling protein 2

Even though awareness of the association between obesity and health problems is longstanding, the prevalence of obesity has grown to epidemic proportions during the last few decades [25–27]. Obesity is considered the most important risk factor for the onset of type 2 diabetes mellitus (T2DM) [28]. Moreover, even being moderately overweight is closely associated with the onset of T2DM. Among all other risk factors, obesity has the strongest impact on cardiovascular risk profile [29] and causes significant mortality [30]. Weight loss is known to reduce blood pressure, lipid levels, and the incidence of T2DM [31]. Thus, the treatment or prevention of obesity would reduce the prevalence of a variety of chronic diseases and acute adverse events.

As the long-term consumption of green tea is traditionally regarded to cause weight loss, and as obesity is becoming one of the most severe health threats, there is increasing interest in this particular feature of green tea. A number of cell, animal, and human studies were, and are currently, being performed to investigate the anti-obesity effects of green tea. As of today, a body of evidence has accumulated, which scientifically supports the traditional notion that green tea reduces body weight by “eliminating fat”. Thus, there has been a reverse “from bedside to bench” approach, starting with an effect discovered in ancient times and imprinted in today's common knowledge in Asia, leading to tremendous efforts to scientifically demonstrate and prove those effects. This review focuses on cell, animal, and human studies investigating the anti-obesity effects of green tea and isolated green tea components and exploring the underlying mechanisms.

## 2 Anti-obesity effects of green tea *in vitro*

### 2.1 Effects on adipocyte differentiation

In cultured adipocyte models, green tea catechins robustly inhibit adipocyte differentiation. It was recently reported that EGCG (TEAVIGO™, DSM Nutritional Products) dose-dependently inhibited adipogenesis induced by the classic adipogenic mixture of insulin, dexamethasone, and 3-isobutyl-1-methylxanthine (IBMX) in C3H10T1/2 cells (Fig. 1) [32]. Similarly, Furuyashiki *et al.* [33] demonstrated that catechin, CG, EGC, ECG, and EGCG at 5  $\mu$ M suppressed lipid accumulation induced by the same mixture in another adipocyte model, 3T3-L1 cells. In a time-course experiment, CG and EGC attenuated lipid accumulation starting from day 3 and the amount of lipid was reduced to 50% compared to the control at day 8, suggesting that catechins inhibit both early-stage and late-stage differentiation programs. In addition, Hung *et al.* [34] found that green tea catechins dose-, time-, and phase-dependently inhibited proliferation of 3T3-L1 preadipocytes. Two cell cycle control kinases, ERK and cyclin-dependent kinase 2 (Cdk2), are required

for these inhibitory effects. Total amounts of extracellular signal-regulated kinase 1 (ERK1) and extracellular signal-regulated kinase 2 (ERK2) were not altered by EGCG; however, EGCG at 50  $\mu$ M significantly reduced phospho-ERK1 and phospho-ERK2, the active forms of ERK. Another key regulator of the cell cycle, Cdk2, was reduced by EGCG at both the protein level and activity level after 4, 24, or 48 h treatment. Among tested catechins, EGCG had more potent antimitogenic properties than EC, ECG, or EGC and arrested preadipocytes at the G0/G1 phase.

It is well-known that obesity is the result of both increased adipocyte size (hypertrophy) and increased adipocyte number (hyperplasia) [35]. Aforementioned data point to the fact that green tea catechins inhibit not only adipocyte differentiation but also proliferation, the two contributors to increased adipose mass. Adipocyte differentiation is tightly regulated by several transcription factors, such as CCAAT/enhancer binding protein beta (C/EBP $\beta$ ), CCAAT/enhancer binding protein delta (C/EBP $\delta$ ), peroxisome proliferator activated receptor gamma 2 (PPAR $\gamma$ 2), and CCAAT/enhancer binding protein alpha (C/EBP $\alpha$ ) [36]. It is initiated by C/EBP $\beta$  and C/EBP $\delta$ , which can be induced by IBMX and dexamethasone, respectively. C/EBP $\beta$  and C/EBP $\delta$  act together to induce PPAR $\gamma$ 2, a key regulator for adipogenesis, and C/EBP $\alpha$  [37, 38]. C/EBP $\alpha$  and PPAR $\gamma$  together promote adipocyte differentiation by activating expression of adipose-specific genes and are also crucial for maintenance of each other's expression at high levels.

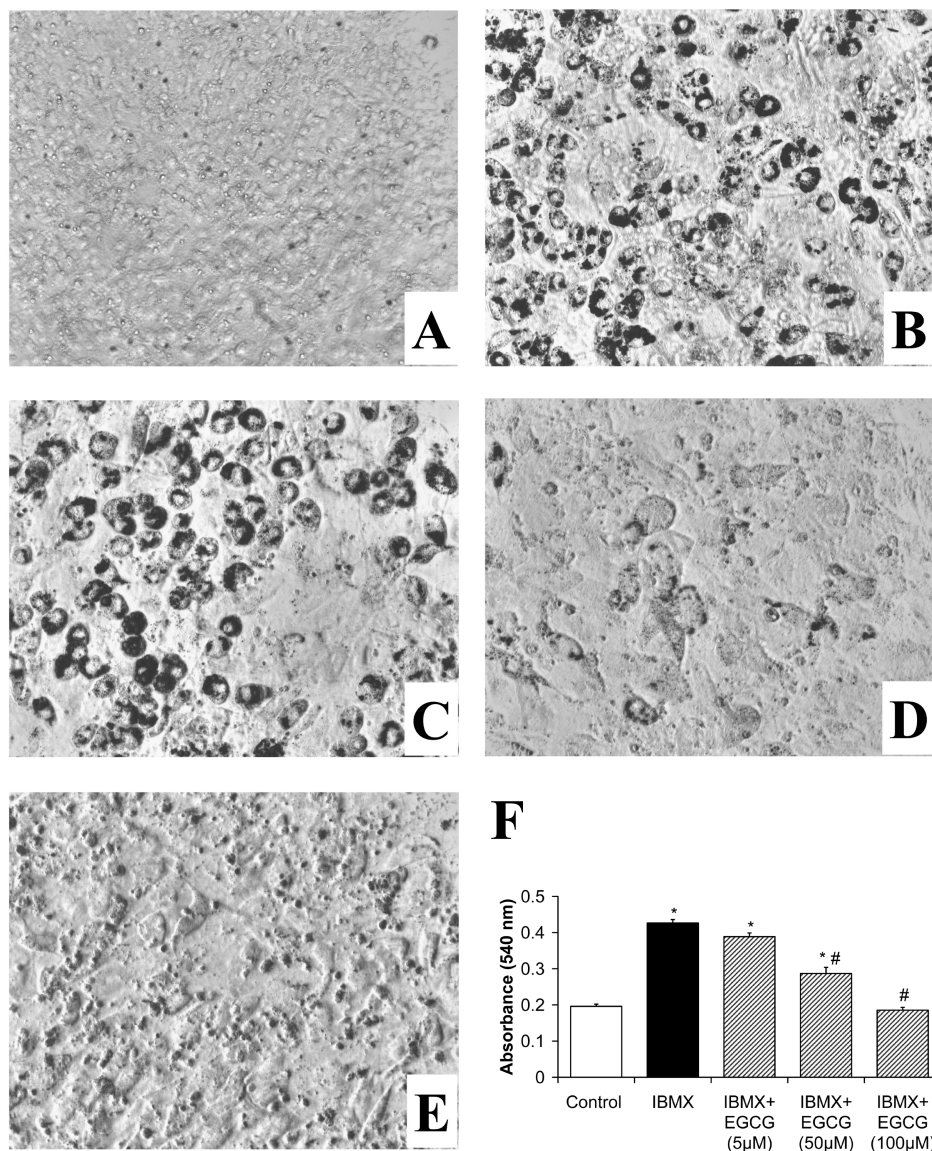
CG and EGC at 30  $\mu$ M and EGCG at 10 and 30  $\mu$ M significantly down-regulate expression of PPAR $\gamma$ 2 and C/EBP $\alpha$  during adipocyte differentiation [33]. Thus, the antiadipogenic effects of green tea catechins are mediated, at least partially, *via* the inhibition of PPAR $\gamma$ 2 and C/EBP $\alpha$ . However, the direct molecular targets of action remain to be identified.

In 2004, Tachibana *et al.* [39] cloned a receptor from a cancer cell line, a 67 KDa laminin receptor, which binds EGCG with a very low  $K_d$  value. However, it is not clear yet whether this receptor is expressed in adipocytes and if it is involved in mediating EGCG-induced signaling.

Thus, it has clearly been demonstrated that the most abundant green tea catechin, EGCG, inhibits adipocyte proliferation and differentiation, which are at least partially mediated *via* inhibition of phospho-ERK1, phospho-ERK2, Cdk2, PPAR $\gamma$ 2, and C/EBP $\alpha$ .

### 2.2 Effects on brown adipose tissue (BAT) thermogenesis

Dulloo *et al.* [40] demonstrated that green tea extract (GTE) stimulates BAT thermogenesis to a much greater



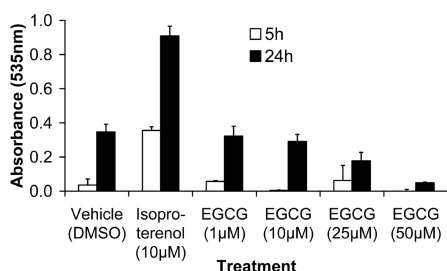
**Figure 1.** Adipocyte differentiation of C3H10T1/2 cells, as indicated by Oil Red O incorporation (magnification 100-fold). (A) Untreated control cells. (B) Cells treated with differentiation mix. (C) Cells treated with differentiation mix and 5  $\mu$ M EGCG. (D) Cells treated with differentiation mix and 50  $\mu$ M EGCG. (E) Cells treated with differentiation mix and 100  $\mu$ M EGCG. (F) Absorbance of Oil Red O at 540 nm, as an indicator of adipocyte differentiation of C3H10T1/2 cells. Untreated control cells and cells treated with differentiation mix, with or without EGCG at concentrations of 5, 50, 100  $\mu$ M. Data are shown as mean  $\pm$  SEM. \* significantly different from untreated control cells ( $p < 0.05$ ), # significantly different from cells treated with differentiation mix without EGCG ( $p < 0.05$ ) (adapted from Wolfram *et al.*, 2005).

extent than the corresponding amount of caffeine alone. The study suggests that the interaction between catechins and caffeine together with sympathetically released norepinephrine (NA) is responsible for the pronounced effect of GTE on BAT thermogenesis. When EGCG was added to a combination of caffeine and ephedrine, a synergistic stimulation of thermogenesis was observed. The authors speculated that the action of catechins and caffeine at different control points of the NA-cyclic adenosine monophosphate

(cAMP) axis may mediate the observed synergistic effects. EGCG directly inhibits COMT (catechol-*O*-methyl-transferase), an enzyme that degrades NA, thus prolonging the action of sympathetically released NA. Caffeine inhibits phosphodiesterase activity, an enzyme that breaks down cAMP, a second messenger released in response to NA. Thus, EGCG and caffeine may synergistically increase the level of intracellular cAMP and thereby mediate the pronounced thermogenic effect of GTE.

## 2.3 Effects on lipolysis

Adipose tissue is the largest energy store in the body. The breakdown of triglycerides to fatty acids and glycerol in adipocytes supplies fuel to other organs, and also provides an important regulation of adipose mass. Catecholamines are the major hormones stimulating lipolysis in humans. Polymorphisms in catecholamine receptor signaling pathways are associated with risk of the development of obesity. Natural compounds, such as conjugated linoleic acid and forskolin, induce lipolysis in adipocyte models [41, 42]. Therefore, we investigated the lipolytic function of EGCG in differentiated adipocytes (Ying Wang, 2005, unpublished data). Preadipocyte cultures, C3H10T1/2, were differentiated as previously described [32]. Differentiated adipocytes were treated with either EGCG at 1, 10, 25, or 50  $\mu\text{M}$  or isoproterenol, a  $\beta$ -adrenergic compound, at 10  $\mu\text{M}$ . Cell supernatants were collected after 5 or 24 h, and free glycerol contents were assayed using a Sigma triglyceride determination kit (Sigma TR0100). Isoproterenol robustly induced lipolysis and the lipid droplets started to disappear after 3-h incubation, as determined by microscopic observation. Absorbance measurement at 535 nm demonstrated a significant increase in glycerol content compared to the control samples, after both short- and long-term incubation, whereas EGCG at tested dosages had no obvious effect on the lipolysis process (Fig. 2). Therefore, these data indicate that the anti-obesity effects of green tea catechins, such as EGCG, are not mediated *via* increased lipolysis.



**Figure 2.** C3H10T1/2 cells were differentiated with insulin, dexamethasone, and IBMX and then treated with either isoproterenol (10  $\mu\text{M}$ ) or EGCG (1, 10, 25, or 50  $\mu\text{M}$ ). Free glycerol in the supernatant was determined after 5 or 24 h, using a Sigma triglyceride determination kit. Isoproterenol robustly induced both short-term and long-term lipolysis (9- vs. 3-fold). At the tested concentrations, EGCG had no effect on lipolysis (Ying Wang, 2005, unpublished data).

## 2.4 Effects on nutrient absorption

There are several studies which focused on nutrient absorption in relation to the anti-obesity properties of green tea catechins. It was demonstrated that ECG inhibited glucose uptake in Caco-2 cells [43]. In brush border membrane vesicles, ECG inhibited the sodium/glucose cotransporter 1

(SGLT1) in a competitive manner. Green tea catechins reduced  $\alpha$ -amylase and sucrase activities in rat intestine [44]. A more detailed investigation of this phenomenon revealed that EGCG exerts only a minor inhibitory effect on sucrase activity and that theaflavins, found to a larger extent in black tea, are far more potent [45]. EGCG reduced the glucose uptake from rat intestine and inhibited the sodium-dependent glucose transporter significantly, but was less potent than ECG [46]. A GTE was found to inhibit gastric and pancreatic lipase activities, which was suggested to lead to reduced fat digestion in humans, thus contributing to the anti-obesity effects of green tea [47]. Therefore, presently available *in vitro* data suggest that green tea could reduce glucose and fat absorption by inhibiting gastrointestinal enzymes involved in nutrient digestion. The precise contribution of these effects to the observed *in vivo* anti-obesity effects of green tea, green tea catechins, and EGCG remains to be determined.

## 2.5 Summary

In summary, *in vitro* data suggest that the anti-obesity effects of green tea are at least partially mediated *via* inhibition of adipocyte differentiation and proliferation. Furthermore, green tea could potentially reduce carbohydrate and fat absorption by inhibition of various digestive enzymes. The precise contribution of these mechanisms to the anti-obesity effects of green tea remains to be determined. Additionally, other target organs, such as liver and skeletal muscle, may also contribute to the anti-obesity effects of green tea, green tea catechins, and EGCG (see other sections).

## 3 Anti-obesity effects of green tea *in vivo*

### 3.1 Anti-obesity effects of green tea

Yang *et al.* (2000) [48] studied the effects of drinking green tea, oolong tea, and black tea in a rat model of hyperlipidemia induced by feeding of a high-sucrose diet. Even though this model is not suitable for the study of obesity, it provides valuable insights into lipid metabolism. Green tea consumption resulted in decreased levels of total plasma triglycerides and cholesterol, with the shortest onset and greatest magnitude, compared to oolong tea and black tea. The levels of HDL cholesterol were not changed by any of the treatments. In liver and heart, green tea prevented the lipotropic effects of the high-sucrose diet. Green tea did not modify protein absorption, bile acid concentration, and daily bile acid excretion but slightly, however significantly, reduced fat absorption. The authors concluded that the effects of green tea on lipid metabolism are stronger than the effects of oolong tea and black tea. This study provided information on the pronounced effects of green tea on lipid

metabolism and, thereby, the rationale for investigating green tea in obesity models.

In Sprague–Dawley rats fed a high-fat diet, consumption of a water extract of green tea for 2 wk resulted in decreased body fat accumulation [49]. This effect appeared to be mediated by increased energy expenditure and a slight, but statistically significant, reduction in food digestibility whereas food intake was not changed. Furthermore, the protein content of interscapular BAT was increased by consumption of green tea, which is indicative of an increased thermogenic capacity. Beta-adrenoreceptor blockade by propranolol partially abolished the decrease in body fat and the increases in energy expenditure and brown fat protein content caused by green tea, while the reduction of digestibility was not affected. Therefore, it can be concluded that green tea reduces body fat and increases energy expenditure, which is partially mediated *via* beta-adrenoreceptor activation.

In ICR mice, the effects of different green tea components were investigated [50]. Caffeine and theanine suppressed body weight and body fat, while catechins did not change these parameters but reduced serum triglycerides and free fatty acids. However, these findings are at variance with the results of other studies investigating the anti-obesity effects of green tea catechins (see Section 3.2). The authors speculated that the relatively low dosage of catechins (0.3% w/w of diet) and possibly the study duration of 16 wk, which was shorter compared to another study [51], influenced the results. Moreover, ICR mice are outbred and genetically heterogeneous mice, which are commonly not used for studies in obesity research. Additionally, it appears that the mice were fed a regular, low-fat diet, which in most mouse models does not lead to the development of obesity, especially when given at a young age as in the described study [50]. Therefore, the animal model chosen in this study might not be appropriate for investigation of anti-obesity effects. However, the study highlighted the fact that green tea is likely to contain more than one weight-suppressing ingredient and that combinations of those ingredients, especially of caffeine and catechins, might synergistically decrease body weight and body fat.

In Zucker rats, a 10-day administration of powdered green tea dissolved in water resulted in significantly attenuated body weight gain and decreased adipose tissue weight while food intake was not affected [52]. Liver weight and plasma cholesterol levels were significantly reduced by consumption of green tea.

Young Wistar rats drinking green tea for 3 wk displayed significantly reduced adipose tissue weight compared to controls drinking water [53]. Body weight, food intake, and fluid intake were not changed by green tea. Plasma levels of free fatty acids and of total cholesterol were reduced and

the low density lipoprotein LDL/HDL ratio also decreased, which indicates that green tea beneficially modified the lipid profile. Furthermore, glucose uptake of skeletal muscle was significantly increased, while glucose uptake of adipose tissue was significantly decreased. These effects were likely to be mediated *via* increased GLUT4 translocation in skeletal muscle and decreased GLUT4 translocation in adipose tissue. Interestingly, the protein expression of PPAR $\gamma$ , a key regulator of adipocyte differentiation, was decreased in adipose tissue.

### 3.2 Anti-obesity effects of green tea catechins

Murase *et al.* (2002) [51] investigated the effects of GTE, with relatively low caffeine and high catechin contents, in C57BL/6J mice fed a high-fat diet for 11 months. It was found that supplementation with green tea catechins dose-dependently reduced body weight, adipose tissue mass, and liver fat content. Plasma levels of cholesterol, glucose, insulin, and leptin were dose-dependently decreased by intake of green tea catechins. In the liver, beta-oxidation determined by [ $^{14}$ C]-palmitic acid oxidation activity was increased by GTE, whereas in intestine, BAT, and skeletal muscle no changes were detected. Furthermore, acyl-CoA oxidase and medium-chain acyl-CoA dehydrogenase mRNA expression increased in the liver, indicative of increased lipid oxidation.

Recently, it was demonstrated by indirect calorimetry that consumption of green tea catechins over a period of 10 wk, in addition to endurance training, stimulates fat oxidation in BALB/c mice [54]. Beta-oxidation in the gastrocnemius muscle of mice fed green tea catechins was elevated and exercise capacity was increased. Furthermore, the effects of the most abundant green tea catechin, EGCG, were also assessed in this study. Consumption of EGCG (TEAVIGO<sup>TM</sup>, DSM Nutritional Products), in addition to endurance training, dose-dependently increased exercise capacity, as well as beta-oxidation and the expression of fatty acid translocase/CD36 mRNA in skeletal muscle. This study provides evidence that endurance exercise in addition to long-term consumption of green tea catechins, or of EGCG alone, improves exercise capacity and stimulates lipid metabolism in mice. If the same effects are demonstrated in clinical studies, the habitual consumption of green tea catechins or EGCG holds potential for endurance athletes to improve their exercise capacity.

### 3.3 Anti-obesity effects of EGCG

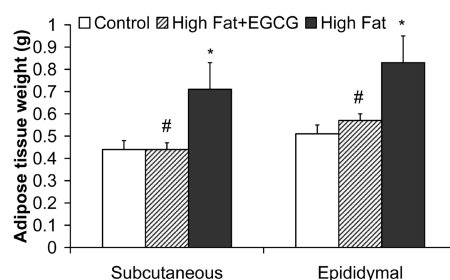
In a study by Kao *et al.* [55], in which EGCG (85 mg/kg) was injected intraperitoneal (i.p.) into lean and obese Zucker rats, the anti-obesity effects of EGCG were investi-

gated. Marked decreases in food intake, body weight, blood glucose, and insulin levels were observed. However, i.p. and intravenous (i.v.) administration of EGCG results in suprapharmacologic plasma concentrations in rodents [55–57]. After i.p. injection of 100 mg/kg EGCG to Sprague–Dawley rats, a maximum plasma concentration ( $C_{\max}$ ) of 24  $\mu\text{mol/L}$  of free EGCG was observed [55]. In comparison, oral administration of 75 mg/kg EGCG to Sprague–Dawley rats resulted in a  $C_{\max}$  of 0.043  $\mu\text{mol/L}$  of free EGCG [56], which is approximately a 558-fold lower concentration. In a pharmacokinetic study in mice, this pronounced difference in  $C_{\max}$  of free EGCG (*via* a comparison between i.v. and oral administration) was confirmed [57]. Not only are the plasma concentrations of EGCG several-fold lower following oral administration, as compared to i.v. or i.p. administration, but there is also a larger proportion of EGCG circulating in a glucuronidated form. Pharmacokinetic data obtained in humans [58] indicate that even an EGCG dosage of 1 600 mg *per* human does not result in plasma levels that would be comparable to rodents administered EGCG i.v. or i.p. However, oral administration of 75 mg/kg to mice results in plasma levels of total EGCG that are similar to humans consuming 50 mg of EGCG, an amount that is present in a cup of green tea. Nevertheless, there is still an apparent difference in the levels of free EGCG, which are lower in rodents due to the extensive glucuronidation. Therefore, the relevance of the decrease in food intake, body weight, blood glucose, and insulin levels caused by i.p. injection of EGCG, as observed in the study by Kao *et al.* [55], remains to be determined. Furthermore, it is unclear whether these observations were due to a direct effect on adipose tissue or an anorectic effect caused by the injections of EGCG. Notably, the pronounced decrease in food intake was not observed when a similar dosage of EGCG (81 mg/kg) was applied orally.

In two recent studies, the anti-obesity effects of EGCG (TEAVIGO™, DSM Nutritional Products) were investigated [32, 59]. TEAVIGO™ is an extract from green tea, which contains more than 94% EGCG but less than 0.1% caffeine. Dietary supplementation with EGCG prevented the increase in body weight and adipose tissue mass induced by feeding a high-fat diet to C57BL/6J mice [32]. This was accompanied by reduced expression of acetyl-coenzyme A carboxylase-1, fatty acid synthase, and glycerol-3-phosphatase acyltransferase mRNA in epididymal adipose tissue, suggesting that EGCG reduces lipogenesis in adipose tissue. In obese Sprague–Dawley rats, dietary supplementation with EGCG resulted in a significant weight loss within 4 wk. In both models, energy intake was not affected by EGCG supplementation. Treatment of differentiating adipocytes with EGCG resulted in a dose-dependent decrease in lipid incorporation, again supporting the hypothesis that EGCG directly reduces adipocyte lipogenesis and thereby decreases differentiation.

In New Zealand Black (NZB) mice EGCG supplementation resulted in a dose-dependent reduction of diet-induced obesity [59]. Determination of body composition by quantitative magnetic resonance revealed that the reduced body weight was exclusively due to a reduction in body fat. The respiratory quotient during the activity period (night, period of food intake) was reduced, suggesting that EGCG decreased lipogenesis and increased fat oxidation. Total food intake and food digestibility were not changed by EGCG supplementation. However, the energy content of the feces was slightly, but significantly, increased at the highest dosage of EGCG. This finding is in line with a recent investigation, in which EGCG caused a small, but statistically significant, reduction of fat absorption [15]. It remains to be investigated to which extent the slightly increased energy excretion contributes to the observed anti-obesity effects of EGCG. In liver and epididymal adipose tissue, stearoyl-coenzyme A desaturase 1 (SCD1) mRNA expression was significantly reduced by EGCG supplementation. SCD1 is a rate-limiting enzyme for the synthesis of monounsaturated fatty acids, and knockout of the gene results in protection from diet-induced obesity in mice [60]. Furthermore, malic enzyme, glucokinase, and pyruvate kinase mRNA expression were reduced, while UCP2 mRNA expression was increased, supportive of reduced hepatic lipogenesis and glucose oxidation and increased fat oxidation.

In summary, these data indicate that EGCG has pronounced anti-obesity effects and that such effects of EGCG are at least partially mediated *via* a direct impact on lipogenesis in adipose tissue.



**Figure 3.** Adipose tissue weights of C57BL/6J mice after 5 months of feeding a low-fat control diet, a high-fat diet containing 1% w/w EGCG, or a high-fat diet. Data are shown as mean  $\pm$  SEM. \* significantly different from control ( $p < 0.05$ ) (adapted from Wolfram *et al.*, 2005).

### 3.4 Summary

Green tea reduces adipose tissue weight in animal models of obesity and has a pronounced effect on lipid metabolism in hyperlipidemia models. The effects appear to be mediated *via* increased energy expenditure, increased and decreased glucose uptake by skeletal muscle and adipose

tissue, respectively, and a slight reduction in food digestibility. There is likely to be more than one active component in green tea and, in particular, the combination of caffeine and catechins deserves attention as this combination might be especially effective in reducing or preventing obesity (see also other sections). Green tea catechins were shown to prevent diet-induced obesity in a dose-dependent manner. Furthermore, the consumption of green tea catechins in combination with endurance exercise promoted beta-oxidation and enhanced exercise capacity in mice. Similarly, the most abundant green tea catechin, EGCG, prevents obesity, enhances beta-oxidation, and improves exercise capacity in a dose-dependent manner.

The precise molecular mechanisms of action of green tea, green tea catechins, or EGCG in animal models of obesity remain to be discovered. However, the discussed *in vivo* studies identified white adipose tissue and BAT, liver, skeletal muscle, and intestine as target organs and proposed the down-regulation of lipogenic enzymes and up-regulation of enzymes involved in beta-oxidation in adipose tissue and liver to be at least partly responsible for the observed anti-obesity effects. Further studies are necessary to dissect the molecular pathways of action of green tea, green tea catechins, or EGCG and to substantiate and confirm investigations implying, for example, a role for the key adipogenic trigger PPAR $\gamma$  or for the shift in GLUT4 translocation, which may decrease in adipose tissue and increase in skeletal muscle in response to green tea.

## 4 Anti-obesity effects of green tea in humans

### 4.1 Efficacy trials assessing the anti-obesity effects of green tea and GTE

The first studies in humans were performed using nonfermented or partially fermented leaves of the plant *camellia sinensis*, *i. e.*, green tea or oolong tea or their dried extracts, with high EGCG contents [61–68]. In 2003, Wu *et al.* [65] reported the results of an epidemiological study conducted with subjects from Taiwan. Subjects with habitual consumption of tea for more than 10 years were characterized by a lower percentage of total body fat, smaller waist circumference, and decreased waist-to-hip ratio. Approximately 4% of the habitual tea drinkers consumed black tea and 96% consumed green or oolong tea, which contain higher amounts of catechins compared to black tea. However, the use of a questionnaire for assessment of tea consumption did not enable quantification of catechin intake. Furthermore, the effect of the duration of tea consumption on obesity was stronger than the effect of the amount of tea consumed, thus not allowing conclusions to be drawn with respect to a dose-response relationship. Even though this study provided valuable information that a long duration of

habitual tea consumption may decrease body fat, it is important to focus on intervention studies in order to determine the effective amount of green tea or green tea catechins, as well as the duration of intake, necessary to observe the anti-obesity effects.

Chantre and Lairon [62] investigated the effects of encapsulated GTE in moderately overweight subjects. They observed a 4.6% decrease in body weight, compared to baseline, and a reduction in waist-to-hip ratio at a magnitude of 4.5%, the latter being similar to that reported for anti-obesity drugs. However, this study was an open, uncontrolled study (*e.g.*, not blinded and lacking a control group). In contrast, Hase *et al.* [61] and Tsuchida *et al.* [63] performed studies testing the effects of beverages with different concentrations of green tea catechins. Both studies applied sophisticated techniques to measure body composition, in particular visceral fat, in moderately overweight subjects. Slight reductions in body weight and more pronounced decreases in body fat, especially visceral fat, were reported in both studies. Although these studies were not controlled for dietary intake and physical activity, the energy intake was recorded and no differences between the control and treatment groups over the study period of 3 months were reported. A different concept was used in the study by Nagao *et al.* [67]. They demonstrated that after a 12-wk treatment with green tea catechin-enriched oolong tea in overweight, but otherwise healthy subjects, the reduction in body weight and body fat was significant compared to the control group. In contrast to the studies mentioned above, subjects received 90% of their individual energy requirement. The objective of a study by Kovacs *et al.* [66] was to examine how green tea catechins might influence the regain of body weight after a weight loss program. During the first 4 wk the subjects consumed a very low-energy diet. Subsequently, the subjects consumed their habitual diet for 13 wk and the effects of GTE on body weight regain and body composition were studied. No beneficial effects of the GTE were found. The authors speculated that the magnitude of habitual caffeine intake may have adversely affected the effectiveness of green tea administration. This hypothesis was recently confirmed by the same group of investigators [68]. In this latter study, the same experimental setup was utilized; a very low-energy diet was consumed for 4 wk, followed by a maintenance period of 13 wk during which the subjects received GTE or placebo. However, in this study, subjects with a low habitual caffeine intake and subjects with a high habitual caffeine intake were investigated. Interestingly, during the weight maintenance period, subjects with low habitual caffeine intake, supplemented with GTE, continued to lose body weight and fat mass while all other groups regained weight. Furthermore, subjects with low habitual caffeine intake, supplemented with GTE, displayed significantly increased energy expenditure and a decreased respiratory quotient compared to all other

groups, indicating a higher fat oxidation during the weight maintenance period. Thus, it appears that the GTE exerted greater anti-obesity effects in subjects that generally consume less caffeine.

The dosage of total EGCG used in the various studies described above ranged from 115 mg/day in the study by Tsuchida *et al.* [63] to 323 mg/day in the study by Kovacs *et al.* [66], while the duration of the studies varied from 12 [61–63, 67] to 13 [66, 68] wk (see also Table 1).

The test items were administered either in the form of capsules containing GTE, at up to six capsules/day [69], or as green tea or oolong tea beverages at up to 1500 mL/day [70]. In all studies, one or more groups were administered capsules or beverages containing green tea catechins, with particularly high EGCG contents, and a control group was administered capsules containing a placebo or a beverage containing significantly smaller amounts of EGCG. Most of the experiments were performed in free-living subjects without strict control of energy and nutrient intake. Only the studies by Dulloo *et al.* [69] and Rumpler *et al.* [70],

**Table 1.** Effects of green tea or GTE, high in EGCG, on obesity in humans

Citations	Type of study	Population	Test components (daily dosage)	Duration of intake	Main outcomes Weight, kg Fat mass, kg BMI
Chantre and Lairon (2002)	Multicenter, open, uncontrolled	7 M, 63 F BMI: 28.9	<b>GTE</b> (375 mg catechins, of which 270 mg was EGCG)	12 wk	–3.5 Not reported Not reported
Hase <i>et al.</i> (2001) <sup>a)</sup>	Case control	23 M BMI: 24–25	<b>Control</b> (118.5 mg catechins, of which 32 mg was EGCG) <b>GTE</b> (483.0 mg catechins, of which 300 mg was EGCG)	12 wk	–0.5 –1.7 –0.6
Kovacs <i>et al.</i> (2004)	Randomized, parallel, placebo controlled	26 M and 78 F BMI: 25–35	<b>Control</b> (placebo) <b>GTE</b> (573 mg catechins, of which 323 mg was EGCG, and 104 mg caffeine)	13 wk	0.6 0.5 0.2
Nagao <i>et al.</i> (2005)	Double blind, controlled	35 M BMI: 24.9–25.0	<b>Control</b> (oolong tea containing 3 mg EGCG and 78 mg caffeine) <b>GTE</b> (690 mg catechins, of which 136 mg was EGCG, and 75 mg caffeine)	12 wk at low calorie diet	–1.1 <sup>b)</sup> –0.7 <sup>b)</sup> –0.4 <sup>b)</sup>
Tsuchida <i>et al.</i> (2002)	Randomized, double-blind, controlled	43 M and 37 F BMI: 25.9–26.5	<b>Control</b> (126.5 mg catechins, of which 25.2 mg was EGCG) <b>GTE</b> (588 mg catechins, of which 115 mg was EGCG)	12 wk	–1.25 <sup>b)</sup> –1.37 <sup>b)</sup> –0.49 <sup>b)</sup>
Westerterp-Plantenga <i>et al.</i> (2005) <sup>c)</sup>	Randomized, parallel, placebo controlled	23 M and 53 F BMI: 25–35	<b>Low habitual caffeine control</b> (placebo) <b>High habitual caffeine control</b> (placebo) <b>Low habitual caffeine GTE</b> (270 mg EGCG and 150 mg caffeine) <b>High habitual caffeine GTE</b> (270 mg EGCG and 150 mg caffeine)	13 wk	Low habitual caffeine –2.8 <sup>b)</sup> –2.1 <sup>b)</sup> –0.9 <sup>b)</sup> High habitual caffeine 0.3 0.1 0.2

Main outcomes = net effects of GTE (change corrected for change in control group), unless stated otherwise; M = male, F = female, BMI = body mass index.

a) Hase *et al.* reported changes as percentage of baseline. The authors of this article calculated the absolute figures by relating the percentages to the baseline values as reported by Hase *et al.*

b)  $p < 0.05$ .

c) The complete data set was provided by Westerterp-Plantenga. The authors of this article calculated the effects exerted by GTE *via* assessing the changes in the weight maintenance period and correcting for changes in the respective placebo group.



**Table 2.** Effects of caffeine, oolong tea, green tea or GTE, high in EGCG, on fat oxidation and thermogenesis in humans

Citations	Type of study	Population	Test components (daily dosage)	Duration of intake	Main outcomes
Dulloo <i>et al.</i> (1999)	Randomized, double-blind, placebo-controlled, cross-over	10 healthy M BMI: 25.1	<b>Control</b> (placebo) <b>GTE</b> (375 mg catechins, of which 270 mg was EGCG, and 150 mg caffeine)  <b>Caffeine</b> (150 mg)	1 day	<b>GTE:</b> 24 h energy expenditure increased by 4% ( $p < 0.01$ ), 24 h RQ decreased by 3.4% ( $p < 0.001$ ) due to increased fat oxidation (35%, $p < 0.001$ ), urinary norepinephrine increased by 40% ( $p < 0.05$ )
Komatsu <i>et al.</i> (2003)	Randomized, controlled, cross-over	11 healthy F BMI: 21.1	<b>Control</b> (water)  <b>Oolong tea</b> (81 mg EGCG and 77 mg caffeine)  <b>Green tea</b> (156 mg EGCG and 161 mg caffeine)	Single administration	<b>Control:</b> Cumulative increase in EE of $11.2 \pm 1.1$ kJ/2 h <b>Oolong tea:</b> Cumulative increase in EE of $110.7 \pm 17.7$ kJ/2 h ( $p < 0.05$ ) and no significant difference in RQ <b>Green tea:</b> Cumulative increase in EE of $49.5 \pm 0.4$ kJ/2 h ( $p < 0.05$ ) and no significant difference in RQ
Rumpler <i>et al.</i> (2001)	Randomized, cross-over	12 healthy M BMI: 25.9	<b>Control</b> (water) <b>Caffeine</b> (270 mg)  <b>Half-strength tea</b> (122 mg EGCG)  <b>Full-strength tea</b> (244 mg EGCG)	3 days	<b>Caffeine:</b> 24 h EE increased by 3.4% and fat oxidation by 8% above control <b>Half-strength tea:</b> 24 h EE increased by 0.5% and fat oxidation by 2% above control <b>Full-strength tea:</b> 24 h EE increased by 2.9% and fat oxidation by 12% above control

M = male, F = female, BMI = body mass index, EE = energy expenditure, RQ = respiratory quotient.

investigating the effects of GTE or oolong tea, respectively, on fat oxidation and thermogenesis, confined the subjects to a metabolic chamber and strictly controlled for energy intake (see Section 4.2 and Table 2).

All existing studies were designed to investigate the development of body weight and body fat in response to green tea catechins, with high EGCG contents. Most of the studies showed a significant decrease in body weight and body fat when compared to baseline. The change in body weight due to consumption of green tea catechins, corrected for the changes in the respective placebo groups, ranged from 0.6 [66] to  $-1.25$  kg [63], whereas the change in body fat ranged from 0.5 [66] to  $-1.7$  kg [61] (for more details see Table 1). Significant reductions in body weight and body fat due to green tea catechins, compared to the placebo group, were reported by Nagao *et al.* [67], where the study participants had a moderate energy restriction (90% of individual energy requirements), and by Tsuchida *et al.* [63], where the subjects maintained their regular dietary habits.

While plasma triglyceride levels were found to be unchanged in all studies, significant decreases in total cho-

lesterol and free fatty acids were reported by Hase *et al.* [61]. Furthermore, significant reductions were also reported for plasma insulin and glucose in the studies of Hase *et al.* [61] and Nagao *et al.* [67].

## 4.2 Human trials assessing underlying mechanisms

As mentioned in Sections 2 and 3, it is likely that several mechanisms and target tissues mediate the anti-obesity effects of green tea, GTE, and EGCG. However, the only mechanism of action studied in human trials so far is the effect of green tea catechins on thermogenesis and substrate oxidation [69–71] (see also Table 2).

Dulloo *et al.* [69] and Rumpler *et al.* [70] used a metabolic chamber for measuring energy expenditure and substrate oxidation in their study subjects during 24 h periods. Although the aims of the two studies were comparable, different types of administration were employed, *i.e.*, capsules or beverages, respectively. The study by Komatsu *et al.* appears to be hampered by methodological deficiencies,

including the duration of the test, which may have been too short, as well as the use of Douglas bags for gas analyses, which is less accurate than more modern methods.

All three studies demonstrated clear increases in energy expenditure; two of the studies, which included the state-of-the-art methodology and appropriate study designs, reported increases in energy expenditure of 2.9 and 4, respectively, and fat oxidation of 12 and 35%, respectively [69, 70].

### 4.3 Summary

To date there are only a limited number of trials studying the effects of green tea and GTE on obesity in humans. All reported studies showed a reduction in body weight and body fat in response to green tea and GTE, when compared to baseline. The effects are similar to those observed in animals, however to a lesser extent. Furthermore, these changes tended to be rather smaller when changes in the control groups were taken into account. Significant reductions in both parameters, compared to the placebo group, were reported in the studies by Nagao *et al.* [67] and by Tsuchida *et al.* [63]. The results of the human intervention studies do not indicate any specific relationship between the dosages of green tea or GTE and observed effects on body weight and body fat. Furthermore, it might be necessary to extend the length of the administration of green tea or green tea catechins to more than 12 wk. Most of the studies were performed in free-living subjects and not strictly controlled for energy intake and physical activity; thus, variations in such factors may have influenced the effects of the supplements. However, food intake was monitored in these studies and the results obtained suggest no significant difference in energy intake between groups.

No undesirable side effects of green tea or GTEs with high EGCG contents were reported. All studies indicated no significant effect on plasma triglyceride levels, while any effects on other cardiovascular and diabetic risk factors were inconsistent; not all, but some authors reported significant reductions in free fatty acids, total cholesterol, insulin, and glucose.

Some of the studies in humans suggest that the body fat-lowering effects may be associated with an increase in thermogenesis and fat oxidation. Three studies investigated changes in nutrient oxidation and thermogenesis; two of them were well controlled, including the use of a metabolic chamber, and both reported an increase in these parameters [69, 70]. A third study, using different equipment, found no significant differences when compared to the placebo [71].

EGCG is regarded as the most active catechin in green tea. However, until now, human trials have included a combination of catechins, together with caffeine, the latter being a

natural component of tea leaves. Caffeine *per se* is known to stimulate metabolism and increase fat oxidation [72–74]. The studies reported by Dulloo *et al.* [69] and Rumpler *et al.* [70] suggest a synergism between EGCG and caffeine. However, the experimental designs do not enable final conclusions to be drawn, since the type of tea and the method of delivery were different between the two studies.

Therefore, currently available data suggest that green tea, and GTEs with high EGCG contents, exert anti-obesity effects in humans. Additional studies that are well controlled for nutrient and energy intake, as well as for physical activity, are needed for confirmation of these findings. As for cardiovascular diseases and cancer, preclinical data on obesity suggest that EGCG is at least partly responsible for the anti-obesity effects of green tea. Thus, pure EGCG should be used in human trials to assess its long-term effects on obesity.

### 5 Conclusions

Green tea, green tea catechins, and EGCG are efficacious in cell and animal models of obesity. Decreased adipocyte differentiation and lipogenesis, increased beta-oxidation, and decreased lipid absorption are proposed modes of action. It is likely that green tea exerts its effects *via* different molecular mechanisms, which remain to be investigated in greater detail. To date, six studies have investigated the anti-obesity effects of green tea and green tea catechins in humans. Most of these studies reported decreased body weight and fat mass, of which two studies found those effects to be statistically significant compared to the control group. Three human studies assessed the mode of action of green tea and green tea catechins and demonstrated increased fat oxidation, which could contribute to the fat loss observed in response to these compounds. Thus, the anti-obesity effects of green tea, green tea catechins, and EGCG were demonstrated in both *in vitro* and *in vivo* models of obesity. However, there is still a demand for well-designed clinical studies to confirm the results of the initial and encouraging human trials. In general terms, it appears that the traditional knowledge about the anti-obesity effects of green tea can be confirmed and validated by scientific evidence.

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### 6 References

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