

## REVIEW

# Mechanisms of body weight reduction and metabolic syndrome alleviation by tea

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Tea, a popular beverage made from leaves of the plant *Camellia sinensis*, has been shown to reduce body weight, alleviate metabolic syndrome, and prevent diabetes and cardiovascular diseases in animal models and humans. Such beneficial effects have generally been observed in most human studies when the level of tea consumption was three to four cups (600–900 mg tea catechins) or more per day. Green tea is more effective than black tea. In spite of numerous studies, the fundamental mechanisms for these actions still remain unclear. From a review of the literature, we propose that the two major mechanisms are: (i) decreasing absorption of lipids and proteins by tea constituents in the intestine, thus reducing calorie intake; and (ii) activating AMP-activated protein kinase by tea polyphenols that are bioavailable in the liver, skeletal muscle, and adipose tissues. The relative importance of these two mechanisms depends on the types of tea and diet consumed by individuals. The activated AMP-activated protein kinase would decrease gluconeogenesis and fatty acid synthesis and increase catabolism, leading to body weight reduction and metabolic syndrome alleviation. Other mechanisms and the health relevance of these beneficial effects of tea consumption remain to be further investigated.

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## 1 Introduction

Tea, made from leaves of the plant *Camellia sinensis*, has been used in ancient days for medicinal purposes and now as a popular beverage. Cultivated in more than 30 countries, more than 4 million metric tons of tea are produced annually. Depending on the processing of the tea leaves, tea is classified into two major types: green tea and black tea. While black tea

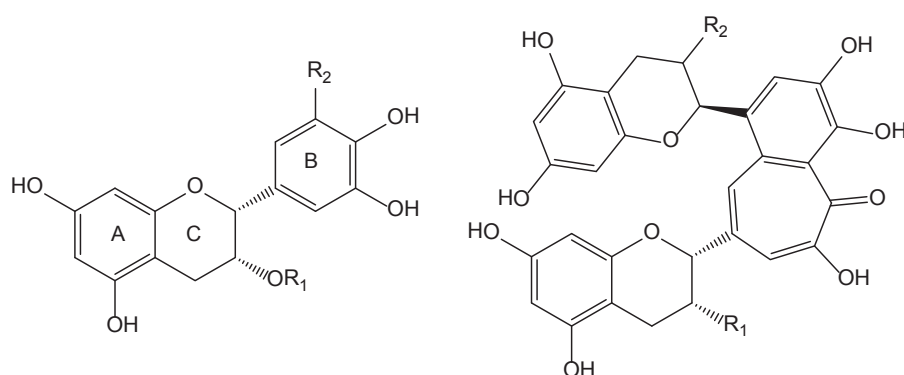
is the major type of tea produced and consumed worldwide, green tea is more popular than black tea in China and Japan.

For the past three decades, tea has been studied for its beneficial health effects. These include the reduction of body weight, alleviation of metabolic syndrome (MetS), prevention of cardiovascular diseases (CVDs) and cancer, and protection against neurodegeneration (reviewed in [1]). Overweight, obesity, and diabetes are emerging as major global health issues, and the closely related MetS also predisposes individuals to CVDs. If tea could prevent or delay the development of these diseases, then the public health implications would be tremendous. Many laboratory and epidemiological studies have shown that tea and tea polyphenols can decrease body weight, markers for MetS, and risk for diabetes and CVDs (reviewed in [1–4]). However, such beneficial effects have been observed only in some human studies, when the level of tea consumption was three to four cups or higher per day. Most of the observed beneficial effects are believed to be due to the polyphenols in tea, although caffeine also contributes to some of the effects. In spite of the many published studies, the underlying molecular mechanisms are still not fully understood. The dose–response relationship between

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**Abbreviations:** AMPK, AMP-activated protein kinase; BTE, black tea extract; CPT-1, carnitine palmitoyltransferase 1; COMT, catechol-*O*-methyltransferase; CVDs, cardiovascular diseases; EGCG, (–)-epigallocatechin gallate; FAS, fatty acid synthase; G-6-Pase, glucose-6-phosphatase; GLUT4, glucose transporter type 4; GTE, green tea extract; HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; i.g., intragastric; IRS, insulin receptor substrate; MetS, metabolic syndrome; PPAR, peroxisome proliferator activated receptor; RCTs, randomized controlled trials; ROS, reactive oxygen species

EGCG:  $R_1$ =Galloyl;  $R_2$ =OHEC:  $R_1$ = $R_2$ =HEGC:  $R_1$ =H;  $R_2$ =OHECG:  $R_1$ =Galloyl;  $R_2$ =HTheaflavin (TF):  $R_1$ = $R_2$ =OHTF-3-gallate:  $R_1$ =Galloyl;  $R_2$ =OHTF-3'-gallate:  $R_1$ =OH;  $R_2$ =GalloylTFn-3,3'-digallate:  $R_1$ = $R_2$ =Galloyl

**Figure 1.** Chemical structures of major tea polyphenols: catechins and theaflavins. EGC, (–)-epigallocatechin; ECG, (–)-epicatechin-3-gallate; EC, (–)-epicatechin.

tea consumption and health effects remains to be further substantiated.

This article reviews the evidence and discusses the molecular mechanisms for the mitigation of overweight and MetS, as well as related prevention of diabetes and CVDs by different types of tea. Based on this information, the possible human relevance of the published health effects will be evaluated. Because of the large number of publications on this topic, information from recently published meta-analyses and systematic reviews is used to help assess the relative strengths of the existing publications. It is hoped that this article will enhance our understanding of the health effects of tea consumption and stimulate future research.

## 2 Chemistry and biological actions of tea constituents

### 2.1 Major constituents of different types of tea

In the manufacturing of green tea, the tea leaves are heated to inactivate the enzymes, rolled, and then dried. This process prevents the autolysis of the leaves and the oxidation of the constituents. The drying of the tea leaves also helps to stabilize the tea constituents during storage. Green tea contains characteristic polyphenolic compounds known as catechins, which include: (–)-epigallocatechin gallate (EGCG), (–)-epicatechin gallate, (–)-epigallocatechin, and (–)-epicatechin (Fig. 1). Catechins account for about 30–42% of the dry weight of brewed green tea, and EGCG is the major form of tea catechin. Tea leaves also contain lower quantities of other polyphenols, such as quercetin, kaempferol, and myricetin as well as alkaloids, such as caffeine and theobromine. A typical brewed green tea beverage (e.g., 2.5 g tea leaves in

250 mL of hot water) contains 240–320 mg of catechins, of which 60–65% is EGCG, and 20–50 mg of caffeine [5, 6].

Black tea is commonly referred to as “fermented tea,” but it does not involve fermentation by microorganisms. In its manufacturing, the tea leaves are withered, crushed, and allowed to undergo enzyme-mediated oxidation. During this process, most of the catechins are oxidized, dimerized to form theaflavins and polymerized to form thearubigins [5, 6]. Theaflavins are produced from the dimerization of two catechin molecules and exist in four major forms (theaflavin, theaflavin-3 gallate, theaflavin-3'-gallate, and theaflavin-3,3'-digallate), which contribute to the red-orange color and characteristic taste of black tea. Thearubigins are mixtures of heterogeneous polymers with red-brown color and the structures are poorly understood [6]. In brewed black tea, catechins, theaflavins, and thearubigins each account for 3–10%, 2–6%, and >20% of the dry weight, respectively. The caffeine contents in black tea are the same as those in green tea.

Oolong tea is manufactured by mildly crushing the leaves and limiting fermentation to a specified period of time to produce specific flavors and tastes of the tea. Generally, Oolong tea contains catechins, theaflavins, and thearubigins as well as some characteristic components such as epigallocatechin esters, theasinensins, dimeric catechins, and dimeric proanthocyanidins [6]. Two specialized teas, “white tea” and “dark tea,” have also received much recent attention for their possible beneficial health effects [7–10]. White tea is usually made from younger leaves with less extensive processing than green tea, but its composition is probably within the range of different varieties of green tea. Dark tea (such as Pu-erh tea) is made by fermentation with microorganisms, which converts catechins to many new compounds. The overall composition is not well characterized and varies in different brands and preparations of dark tea.

## 2.2 Biochemical properties and bioavailability of tea polyphenols

The health effects of tea depend on the biochemical properties and bioavailability of the constituents in tea. Tea catechins, especially EGCG, have received most of the attention. It is commonly recognized that tea catechins are strong antioxidants, efficiently scavenging free radicals and also preventing the formation of reactive oxygen species (ROS) by chelating metal ions (reviewed in [6]). In vivo, EGCG (and perhaps other catechins) may also cause the formation of ROS in the mitochondria [11, 12]. The ROS may activate nuclear factor erythroid 2-related factor 2 (Nrf2) mediated antioxidant and other cytoprotective enzymes [13–15], and this may be referred to as an “indirect antioxidant” effect. EGCG is also known to undergo superoxide-catalyzed auto-oxidation in vitro to produce ROS [16]. Nevertheless, such auto-oxidation of EGCG is unlikely to occur in internal organs because of the lower oxygen partial pressure (than in solution in vitro) and the presence of antioxidant enzymes in animal tissues. Therefore, results on EGCG obtained from cell culture studies need to be interpreted with caution.

The phenolic groups in catechins can be donors for hydrogen bonding; the multiple H-bonds enable tea polyphenols to bind strongly to proteins, lipids, and nucleic acids. The binding of EGCG to many proteins, such as 67-kDa laminin receptor [17] and prolyl *cis/trans* isomerase [18], has been proposed to be a key mechanism for its anticancer activities (reviewed in [19]). Black tea polyphenols may bind to biomolecules and biomembranes with even higher affinity than EGCG.

The bioavailabilities of tea polyphenols follow the prediction of “Lipinski’s Rule of 5” [20] (reviewed in [21, 22]). Both human and animal studies have shown that the bioavailabilities of epicatechin and catechin (molecular weight 290 and five phenolic groups) are higher than that of EGCG (molecular weight 458 and eight phenolic groups). The plasma bioavailability of EGCG in mice following intragastric (i.g.) administration of EGCG (75 mg/kg) was low, with more than 50% of EGCG existing as glucuronide conjugates. Levels of EGCG in the small intestine and colon were 20.6 and 3.6 ng/g, respectively [21]. In humans, following oral administration of the equivalent of two or three cups of green tea, the peak plasma levels of tea catechins (including the conjugated forms) were usually 0.2–0.3  $\mu\text{M}$  [22]. With high pharmacological oral doses of EGCG, peak plasma concentrations of 2–9 and 7.5  $\mu\text{M}$  were reported in mice and humans, respectively [21]. On the other hand, theaflavin and theaflavin-3,3'-digallate (molecular weights of 564 and 868 and containing 9 and 14 phenolic groups, respectively) have extremely low or no bioavailabilities when administered orally [6, 23]. It was reported that following consumption of 700 mg of pure theaflavins mixture, equivalent to about 30 cups of black tea by an individual, the maximum concentrations of theaflavin in plasma and urine were only 1  $\mu\text{g/L}$  (1.8 nM) and 4.2  $\mu\text{g/L}$ , respectively, [23]. Apparently, gallated theaflavins were not detected. The bioavailability of many polypheno-

lic compounds is regulated by active efflux. The multidrug resistance-associated protein 2, located on the apical surface of the intestine and liver, mediates the transport of some polyphenolic compounds to the lumen and bile, respectively. Therefore, EGCG is predominantly effluxed from the enterocytes into the intestinal lumen, or to be effluxed from the liver to the bile and excreted in the feces, with little or no EGCG excreted in the urine.

EGCG and other tea catechins undergo extensive biotransformation [6]. They are readily methylated by catechol-O-methyltransferase (COMT), glucuronidated by UDP-glucuronosyltransferases, and sulfated by sulfotransferases [6]. Tea catechins can be degraded in the intestinal tract by microorganisms to form ring fission metabolites 5-(3',4',5'-trihydroxyphenyl)- $\gamma$ -valerolactone, 5-(3',4'-dihydroxyphenyl)- $\gamma$ -valerolactone and 5-(3',5'-dihydroxyphenyl)- $\gamma$ -valerolactone, which can be found in urine and plasma samples [6, 24]. These compounds can undergo further degradation to phenylacetic and phenylpropionic acids. The biological activities of these metabolites are lower than their parent compounds.

## 3 Reduction of body weight, alleviation of MetS, and prevention of related diseases

Overweight, obesity, and type 2 diabetes are emerging as major health issues in the United States and many other countries. MetS is a complex of symptoms that include elevated waist circumference and two or more of the following: elevated serum triglyceride, dysglycemia, elevated blood pressure, and reduced high-density lipoprotein-associated cholesterol [25]. Therefore, beneficial effects of tea consumption on body weight reduction and MetS alleviation could have huge public health implications.

### 3.1 Decrease of body weight and alleviation of MetS and fatty liver in animal models

The effects of tea and tea polyphenols on body weight and MetS have been studied extensively in animal models (reviewed in [1–3]). Most of the studies showed that the consumption of green tea extracts (GTE) or EGCG significantly reduced the gaining of body weight and/or adipose tissue weight, lowered blood glucose or insulin levels, and increased insulin sensitivity or glucose tolerance. These studies used rodents on high-fat diets or genetically obese/diabetic animal models. For example, in mice fed with a high-fat (60% of the calories) diet, we found that dietary EGCG treatment (0.32 % in diet) for 16 wk significantly reduced body weight gain, body fat, and visceral fat weight compared to mice without EGCG treatment [26]. These results were also reproduced in a second study using a high-fat/Western style diet [27]. EGCG treatment also attenuated insulin resistance, plasma

cholesterol, and monocyte chemoattractant protein concentrations in mice on the high-fat diet [26, 27]. Similar results were also observed in several recent studies [28–30]. For example, treatment of male Swiss mice with GTE (50 mg/kg, i.g., daily) for 8 wk decreased body weight and white adipose tissue weight [28]. In another study, EGCG administration (20 mg/kg, i.p., 3 times weekly) to C57BL/6b mice that were fed a high-fat diet significantly reduced body weight and liver fat accumulation at 42 and 66 wk [29]. In a genetic diabetes model, the *db/db* mice, dietary supplementation of EGCG (1% in diet) prevented the progression of glucose intolerance and reduced the number of pathologically altered islets of Langerhans [30]. A recent study in diabetic mice showed that both GTE and black tea extract (BTE), administered at 0.01% in drinking water, lowered blood glucose levels, and GTE was more efficacious [31]. GTE was also more effective in lowering body weight gain and histological liver deterioration, but only BTE significantly elevated serum insulin levels [31]. The doses of GTE and BTE used in this study were very low and the mechanism of BTE action is unknown.

Green tea polyphenols also alleviate MetS in other insulin-resistant animals. For example, in insulin-resistant rats, treatment with green tea polyphenols significantly decreased blood glucose, insulin, triglycerides, total cholesterol, LDL cholesterol, and free fatty acids [32]. In insulin-resistant beagle dogs, oral administration of GTE (80 mg/kg daily, before the daily meal) for 12 wk also markedly increased insulin sensitivity index [33].

Diet-induced liver steatosis, which predisposes to liver cancer, is becoming a common disease, and its possible prevention by tea consumption warrants more investigation. We have shown that EGCG treatment reduces the incidence of hepatic steatosis, liver size (48% decrease), liver triglycerides (52% decrease), plasma alanine aminotransferase concentration (67% decrease), and liver pathology in mice fed with a high-fat diet [26, 27]. Tea catechins have been reported to also reduce hepatic steatosis and liver toxicity in rodents treated with ethanol, tamoxifen, or endotoxins, or rodents with liver ischemia/reperfusion injury (reviewed in [4]). These findings may have potential for practical applications.

### 3.2 Human studies on weight reduction and mitigation of MetS

The effects of tea consumption on body weight and biomarkers of MetS have been studied in many short-term randomized controlled trials (RCTs) during the past decade. Systematic reviews and meta-analysis covering more than 26 earlier RCTs indicated the beneficial effects of tea consumption in reducing body weight and alleviating MetS [34, 35]. Most of these studies used green tea or green tea extracts with caffeine, in studies for 8–12 wk, on normal weight or overweight subjects. Some of the more recent RCTs also showed that daily consumption of 458–886 mg of green tea catechins by moderately overweight Chinese subjects for 90 days reduced

body fat [36], and that intake of Polyphenon E capsules (containing 400 or 800 mg EGCG and lower amounts of other catechins, but negligible amounts of caffeine) daily for 2 months by postmenopausal women in the United States decreased blood levels of LDL cholesterol, glucose, and insulin [37]. In another study, GTE supplementation (379 mg per day) to obese patients for 3 months decreased body weight and waist circumference [38]. Improvements in lipid profiles, including the decrease in levels of total cholesterol, LDL cholesterol, and triglycerides were also observed in this study [38]. However, a recent RCT with obese Caucasian women, after an energy-restricted diet intervention, showed that supplementation with EGCG (200 mg daily) for 12 wk did not cause changes in body weight, fat mass, energy and fat metabolism, insulin resistance, total or LDL cholesterol levels, and other biomarkers [39]. The lack of beneficial effects of the supplement is possibly due to the relatively low dose of EGCG used, especially in subjects who were previously treated for weight reduction.

A recent metabolomic study with healthy male subjects demonstrated that green tea extract supplementation (1200 mg catechins and 240 mg caffeine daily) for 7 days increased lipolysis, fat oxidation and citric acid cycle activity under resting conditions without enhancing adrenergic stimulation [40]. The role of caffeine in these studies was inconsistent among the different studies. A meta-analysis of metabolic studies showed that both a catechin-caffeine mixture and caffeine alone dose-dependently stimulated daily energy expenditure, but only the catechin-caffeine combination significantly increased fat oxidation [41].

In contrast to the above-described beneficial effects, a recent study in English adults showed that daily supplementation with green tea (>560 mg EGCG) plus caffeine (0.28–0.45 mg) for 12 wk had no effects on fat absorption, resting energy expenditure, and body composition [42]. The reasons for these contradictory results are not known. The different populations, with different physiological and dietary conditions, could be contributing factors. The authors also discussed a time factor; that is, the increase in energy expenditure was observed in short-term (7–10 days) studies with catechins, but not in long-term studies [42]. This may be related to our previous observations in mice that the plasma levels of EGCG increased in the first several days of daily catechin administration, but the EGCG levels decreased gradually to ~13% of the maximal levels [43]. More research is needed on the time-dependent changes in bioavailability and health beneficial effects of catechins.

Two recent epidemiological studies also suggested the beneficial effects of green tea consumption on MetS [44, 45]. One study on elderly Taiwanese males in a rural community indicated that tea drinking, especially for individuals who drank 240 mL or more tea daily, was inversely associated with incidence of MetS [44]. The second, a cross-sectional study of US adults, showed that intake of hot (brewed) tea, but not iced tea, was inversely associated with obesity and biomarkers of MetS and CVDs [45]. These results are

exciting and need confirmation from additional studies. On the other hand, two recent cross-sectional studies in Japan did not find a preventive effect of green tea consumption against MetS [46,47], which further support the idea that more studies on this topic are needed.

### 3.3 Lowering risk of diabetes in humans

The lowering of body weight and alleviation of MetS by tea should lead to the reduction of type 2 diabetes. Such an association was found in some, but not all, human studies (reviewed in [1–4]). For example, a prospective cross-sectional study with US women aged 45 years and older showed that consumption of more than four cups of tea per day was associated with a 30% lower risk of developing type 2 diabetes, whereas the intake of total flavonoids or flavonoid-rich foods was not associated with reduced risk [48]. A retrospective cohort study of 17 413 Japanese adults aged 40–65 years indicated that daily consumption of more than six cups of green tea (but not Oolong or black tea) lowered the risk of diabetes by 33% [49]. The effects of caffeine in these epidemiological studies are unclear. A meta-analysis based on seven studies (286 701 total participants) showed that individuals who drank three to four or more cups of tea per day had lower risks of type 2 diabetes than those consuming no tea [50]. A more recent RCT in patients with obesity-related hypertension showed that consumption of GTE (379 mg daily) for 3 months reduced fasting serum glucose and insulin levels [51]. Several clinical intervention studies have yielded inconclusive results concerning the effects of tea on insulin resistance and blood glucose control, but there are reported changes in certain biomarkers such as an increase in satiety, a reduction of hemoglobin A1c, and a decrease in diastolic blood pressure [52–55].

### 3.4 Lowering of blood cholesterol, blood pressure, and incidence of CVDs in humans

The alleviation of MetS by tea logically leads to the reduction of the risks for CVDs (reviewed in [56–58]). The lowering of plasma cholesterol levels and blood pressure as well as improvement of insulin sensitivity and endothelial function by green tea have been reported by many investigators [58]. In a review of 11 RCTs, both green and black teas decreased LDL cholesterol and blood pressure [59]. The strongest evidence for the reduction of CVD risk by the consumption of green tea is provided by large cohort studies in Japan. In the Ohsaki National Health Insurance Cohort Study ( $n = 40\,530$ ), deaths due to CVDs were decreased dose dependently by tea consumption at quantities of 1 to >5 cups of tea per day [60]. In another study with 76 979 Japanese adults, the consumption of green tea was also associated with decreased CVD mortality, but daily consumption of >6 cups of tea was needed to manifest the effect [61]. In a recent

study in Japan, consumption of three to four cups of tea was associated with a decreased incidence of stroke [62]. A case-control study in China also showed a correlation between the consumption of green (or Oolong) tea and a decreased risk of ischemic stroke [63]. A meta-analysis of 14 prospective studies, covering 513 804 participants with a median follow-up of 11.5 years, found an inverse association between tea consumption and risk of stroke, and the protective effect of green tea appeared to be stronger than that of black tea [64].

Many, but not all, studies in the United States and Europe demonstrated an inverse association between black tea consumption and CVD risk (reviewed in [56]). For example, in the Determinants of Myocardial Infarction Onset Study, black tea consumption (> 2 cups daily) was associated with reduced CVD mortality and lower prevalence of ventricular arrhythmia for myocardial infarction during a follow-up of 3.8 years [65]. In a Dutch cohort study involving 37 514 healthy men and women followed for 13 years, consumption of black tea (three to six cups daily) was associated with a decreased risk for CVD mortality [66]. In this study, however, tea consumption was also associated with a healthy lifestyle. The quantity and types of tea consumed are also key factors in affecting the results of these studies. For example, in the Women's Health Study [67], the level of tea consumption was rather low (only a small percentage of women drank more than four cups of black tea per day), and only a trend in the prevention of CVD was observed. In a previous meta-analysis, green and black tea drinkers were shown to have lower incidences of myocardial infarction and ischemic stroke [68]. A subsequent meta-analysis, including six case-control and 12 cohort studies (five measured green tea and 13 measured black tea as the exposure), found a reduced risk of coronary artery disease by 28% via green tea consumption (10% decrease in risk with an increment in consumption of one cup per day). However, there was no significant protective effect from black tea [69].

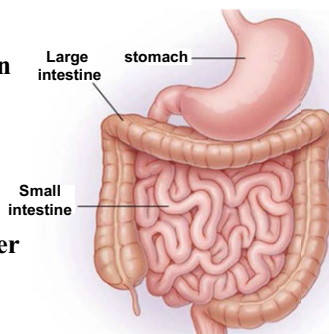
## 4 Molecular mechanisms of action of tea constituents in body weight reduction and MetS mitigation

In the above-reviewed publications, many possible mechanisms have been suggested. They can be summarized into two major types of actions as shown in Fig. 2. One is the action of tea constituents in the gastrointestinal tract in decreasing digestion and absorption of macronutrients, or by altering the gut microbiota. The second type of action is produced by tea constituents after systemic absorption in the inhibition of anabolism and stimulation of catabolism in liver, muscle, adipose, and other tissues. The combined effects would reduce body weight, alleviate MetS, and reduce the risk of diabetes and CVDs. These mechanisms of action of tea constituents are discussed below.

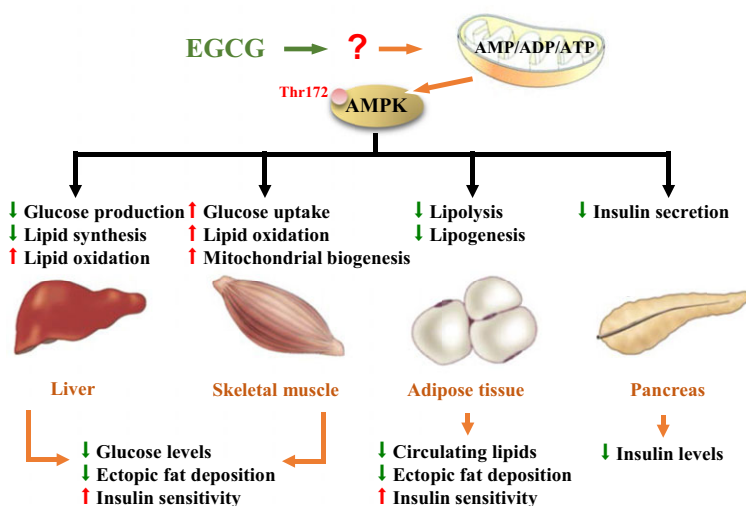


## A Actions of Tea Polyphenols in the Gastrointestinal Tract

- Reduce digestion and absorption of lipids, proteins, and carbohydrates
- Affect gut microbiota
- Possibly affect the gut-brain-liver axis



## B The AMPK Hypothesis of Action in Internal Organs



**Figure 2.** Proposed mechanisms for the actions of tea constituents in lowering body weight and alleviating MetS. (A) Actions of tea polyphenols in the gastrointestinal tract. (B) A hypothesis on the central role of AMPK in metabolic regulation by EGCG. EGCG is proposed to activate AMPK through affecting the ratios of AMP/ADP/ATP. The activated (phosphorylated) AMPK regulates metabolism in different organs toward the direction of reducing ( $\downarrow$ ) gluconeogenesis, fatty acid synthesis, insulin secretion, and ectopic fat deposition in muscle and liver. These are accompanied by increased ( $\uparrow$ ) insulin sensitivity and the oxidation of glucose and fatty acids. The lower part of the figure was modified from ref. 84.

### 4.1 Actions in the gastrointestinal tract

#### 4.1.1 Reduction of macronutrient digestion and absorption

Ingestion of green tea polyphenols has been shown to increase fecal lipid and total nitrogen contents, suggesting that polyphenols can decrease digestion and absorption of lipids and proteins [1, 2, 26, 27, 70]. For example, in mice fed a high-fat diet, EGCG dose dependently decreased food digestibility and increased the fecal mass; with a  $^{13}\text{C}$ -triglyceride-enriched diet, EGCG supplementation increased  $^{13}\text{C}$  levels in the feces [70].

After ingestion, lipids are emulsified, hydrolyzed, and absorbed in the small intestine. Lipid transporters on the apical surface of the intestine facilitate the transfer of fatty acid and cholesterol into the enterocytes. The absorbed lipids are packaged into chylomicrons and secreted into the lymphatic system. Many *in vitro* studies have demonstrated that tea polyphenols can interfere with emulsification and inhibit pancreatic lipase and phospholipases (reviewed in [2]). Such actions have been used to explain results from animal studies.

For example, the lowering of intestinal absorption of cholesterol in rats was attributed to decreased micellar solubility of cholesterol by black tea polyphenols [71]. EGCG was shown to inhibit pancreatic lipase and reduce body weight gain in mice fed a high-fat diet [72]. The possible inhibition of lipid transporters has also been suggested [73].

The mechanisms for the inhibition of digestion and absorption of proteins by tea catechins have not been studied extensively. Tight binding to ingested proteins and digestive proteinases by catechins through H-bonding and hydrophobic interactions would lead to decreased digestion.

The inhibitory activities of catechins against digestive enzymes,  $\alpha$ -amylase and glucosidases, as well as glucose transporters have been demonstrated in many studies *in vitro* (reviewed in [2]). Gallated tea catechins such as EGCG (10 mg/kg, *i.v.*), but not nongallated tea catechins, have shown inhibitory effects on glucose absorption in intestinal cells due to the competitive inhibition of Na-glucose cotransporter 1 [74]. When EGCG was coadministered with common corn starch to mice, the decrease of digestion and absorption of glucose was proposed to be due to the inhibition of  $\alpha$ -amylase by EGCG [75].

In summary, decreased digestion and absorption of nutrients could play a significant role in lowering body weight and alleviating MetS by green tea polyphenols. We propose that such a mechanism of action is even more important for the action of black tea polyphenols (theaflavins and thearubigins), which have very low or no bioavailability.

#### 4.1.2 Possible effects on intestinal microbiota

The possibility that tea may affect gut microbiome has been studied in mice. For example, green tea powder and *Lactobacillus plantarum* feeding affected gut microbiota, lipid metabolism, and inflammation in high-fat fed C57BL/6 mice [76]. Green tea reduced the body fat content and hepatic triglyceride and cholesterol accumulation, and the reduction was correlated with the amount of *Akkermansia* and/or the total amount of bacteria in the small intestine [76]. The abundance of *Akkermansia muciniphila* has been shown previously to be increased in prebiotic-treated *ob/ob* mice, which had lower fat mass compared to the control *ob/ob* mice [77]. Changing gut microbiota, e.g. by the administration of *Saccharomyces boulardii*, has also been shown to reduce hepatic steatosis, low-grade inflammation, and fat mass in obese and type 2 diabetic *db/db* mice [78]. In humans, green tea consumption has been reported to increase the proportion of the *Bifidobacterium* species in fecal samples [79]. Increase of intestinal *Bifidobacteria* by a prebiotic (oligofructose) has been shown to decrease biomarkers for diabetes in mice [80]. These results suggest the possibility that tea may alleviate MetS by enriching the probiotic population in the intestine. However, more studies with green and black tea preparations are needed to assess this possibility.

#### 4.1.3 Possible actions on the gut–brain–liver axis

Recently, evidence for a gut–brain–liver axis mechanism has been provided for the acute glucose lowering effect by intraduodenal infused metformin in diabetes rat models [81]. According to this mechanism, metformin activates AMP-activated protein kinase (AMPK) in duodenal mucosa, and subsequently lowers hepatic glucose production (without involving hepatic AMPK) through a neuronal-mediated gut–brain–liver pathway. As will be discussed in the Section 4.2.1, hepatic AMPK is proposed as a major mediator of EGCG in chronic glucose-lowering effects. The possibility that the EGCG activates the gut AMPK–brain–liver pathway, intestinal endocrine systems, or intestinal receptors has not been assessed and warrants investigation.

### 4.2 Actions of tea constituents after systemic absorption

The antiobesity and antidiabetes effects of tea polyphenols have been studied in different experimental animal models and systems in vitro (reviewed in [1–4, 82]). However,

the relevance of some in vitro studies is uncertain because the concentrations of catechins used (20–100  $\mu$ M or higher) were much higher than their blood or tissue levels observed after tea ingestion. This is especially a concern with black tea polyphenols that have very low or no bioavailability [23]. Therefore, we will weigh studies in animal models heavily and try to distinguish between direct effects of tea constituents and indirect effects due to the reduction of body weight. In addition to decreasing the absorption of nutrients as discussed in Section 4.1.1, tea constituents can increase energy expenditure. In an experiment with indirect calorimetry, a single dosage of EGCG (200 mg/kg body weight, i.g.) to mice was shown to significantly increase oxygen consumption and fat oxidation in mice during the first 3 h following administration [83].

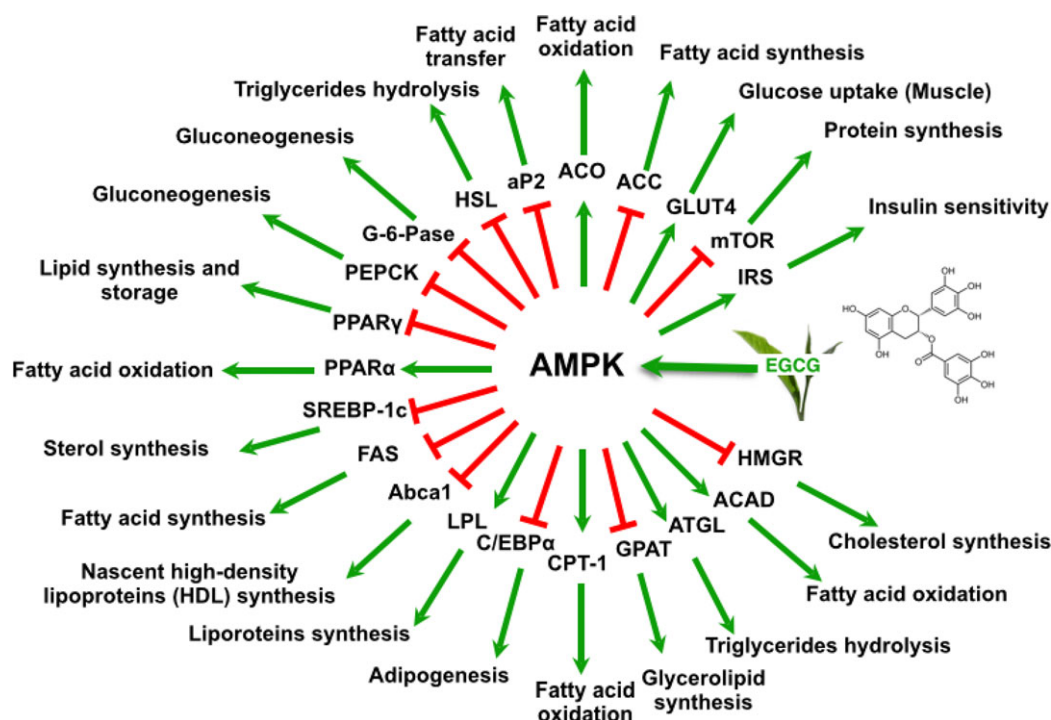
#### 4.2.1 In general energy metabolism

The observations in many studies that ingestion of tea catechins suppressed gluconeogenesis and lipogenesis and enhanced lipolysis in a coordinated manner [reviewed in [1–4]] suggest that these actions of tea catechins are mediated by energy-sensing molecules, such as AMPK. In response to falling energy status, AMPK is activated to inhibit energy-consuming processes and promote catabolism to produce ATP [84–86]. In addition to maintaining cellular energy homeostasis, AMPK also responds to different hormone signals to maintain whole body energy balance [86]. We propose that the activation of AMPK is the main mechanism for EGCG and other catechins to influence energy metabolism and to alleviate MetS, and this proposal will be referred to as the “AMPK hypothesis.”

AMPK is activated by phosphorylation of Thr172 in the activation loop within the kinase domain of the  $\alpha$ -subunit. AMP binding to the regulatory domain of the  $\gamma$ -subunit causes allosteric activation, which promotes the phosphorylation by the upstream kinase, such as liver kinase B1, and protects AMPK from dephosphorylation [86]. It was also demonstrated that ADP binding to one of the two exchangeable AXP (AMP/ADP/ATP) binding sites on the  $\gamma$ -subunit regulatory domain protects the enzyme from dephosphorylation, and the binding affinity of ADP is much higher than that of Mg-ATP. This observation explains how AMPK is regulated under physiological conditions where the concentration of Mg-ATP is higher than that of ADP and much higher than that of AMP [87]. It appears that AMPK activation is regulated by both ADP/ATP and AMP/ATP ratios. The formation of AMP is catalyzed by adenylate kinase in the following reversible reaction, when the cells are in need of ATP.



The possible mediation of the action of EGCG by AMPK in the liver, skeletal muscle, adipose tissue, and pancreas is shown in Fig. 2. The activation of AMPK by EGCG and different types of teas has been demonstrated in vivo and in vitro



**Figure 3.** EGCG induces changes in proteins and genes that are mediated by AMPK. mTOR, homolog of target of rapamycin; ACC, acetyl-CoA carboxylase; ACO, acyl-CoA oxidase; aP2, adipocyte protein 2; HSL, hormone sensitive lipase; PEPCK, phosphoenolpyruvate carboxykinase; SREBP-1c, sterol regulatory element binding protein-1c; Abca1, ATP-binding cassette superfamily of transporter proteins 1; LPL, lipoprotein lipase; C/EBP $\alpha$ , CCAAT enhancer binding protein  $\alpha$ ; GPAT, glycerol phosphate acyltransferase; ATGL, adipose triglyceride lipase; ACAD, acyl-CoA dehydrogenase.

[8,83,88–93]. It has been shown that at 1, 3, and 6 h after i.g. administration of GTE (100 mg/kg body weight) to mice, the phosphorylation of AMPK and its upstream kinase, LKB1, increased in the liver (by 2–3 and 1.5–2 fold, respectively) [88]. However, BTE was ineffective. Nevertheless, there are also reports indicating that AMPK was activated in adipose tissues and skeletal muscle by black tea, as well as by Oolong and Pu-erh teas [8, 93]. The detailed mechanism by which EGCG activates AMPK is still unclear, although the involvement of ROS has been suggested based on studies in vitro [90]. The situation in vivo could be different due to the lack of auto-oxidation of EGCG as discussed in Section 2.2. It has been suggested that EGCG blocks mitochondrial electron transport to produce ROS [12]. ROS may further decrease ATP levels, because glutathione and NADPH are required for the detoxification of ROS in the mitochondria and mitochondrial proton gradient is required to drive the transhydrogenase to reduce NADP<sup>+</sup> (by NADH) to form NADPH [94]. EGCG has also been reported to inhibit mitochondrial oxidative phosphorylation to decrease ATP levels [95]. Another possibility is that EGCG may serve as an uncoupler of oxidative phosphorylation. All these actions would result in an increase of ADP/ATP ratio to activate AMPK, but these possibilities remain to be investigated.

Activated AMPK has been shown to decrease the expressions or activities of phosphoenolpyruvate carboxykinase

and glucose-6-phosphatase (G-6-Pase, for gluconeogenesis), acetyl-CoA carboxylase, and fatty acid synthase (FAS, for fatty acid synthesis), 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR, for cholesterol synthesis), glycerol phosphate acyltransferase (for glycerolipid synthesis), and homolog of target of rapamycin (for protein synthesis) [84–86]. It also activates glucose transporter type 4 (GLUT4), carnitine palmitoyltransferase 1 (CPT-1), and acyl-CoA dehydrogenase to increase the catabolism of glucose and fatty acids. All these actions have also been demonstrated by EGCG as summarized in Fig. 3 and discussed in the following sections. We propose that most of the reported effects of EGCG or green tea on metabolism can be explained by the AMPK hypothesis (Figs. 2 and 3). The bioavailability of EGCG and its action on AMPK in different organs determine most of the biological effects. In addition, the direct inhibitory action of EGCG on enzymes with low inhibitory constants may play a role.

#### 4.2.2 In the liver, skeletal muscle, and adipose tissues

The liver is a vital organ for metabolic processing of different nutrients and is the major organ for lipogenesis and gluconeogenesis. Muscle is the major site of ATP production and energy consumption; the uptake and oxidation of glucose and



fatty acids are key molecular events. White adipose tissue is the major site of fatty acid storage, and some fatty acids can be synthesized from glucose. Most of the reported molecular changes caused by EGCG as described below may be mediated by the activation of AMPK as illustrated in Fig. 3.

The downregulation of the two key enzymes in gluconeogenesis, phosphoenolpyruvate carboxykinase, and G-6-Pase, and associated decrease of glucose production in the liver by EGCG has been shown to be mediated by AMPK activation [90]. The activated form, p-AMPK, is also known to phosphorylate and inactivate acetyl-CoA carboxylase, the rate-limiting enzyme of fatty acid synthesis. The resulting lowered levels of malonyl-CoA can activate CPT-1, which facilitates long-chain fatty acyl CoA transport into mitochondria for  $\beta$ -oxidation [84].

In ovariectomized rats that were fed fructose, green tea treatment significantly downregulated the hepatic expression of sterol regulatory element-binding protein-1c and its target genes coding for FAS and stearoyl-CoA desaturase 1 as well as the expression of HMGCR and efflux proteins (ATP-binding cassette superfamily of transporter proteins 1, Abca1) [96]. A series of investigations in high-fat diet-induced obese mice, rats, or chickens have shown that green tea and catechins downregulate the expression of genes coding for fat synthesis (malic enzyme, G-6-P also dehydrogenase, and stearoyl-CoA desaturase 1), and upregulate the mRNA levels of enzymes for fatty acid  $\beta$ -oxidation (CPT-1, acyl-CoA oxidase, acyl-CoA dehydrogenase, and PPAR $\alpha$ ) in the liver (reviewed in [2, 3]).

In studies with rats on a high-fructose diet, green tea administration for 6 wk increased GLUT4 and increased insulin receptor substrate (IRS) mRNA levels in the liver and muscle [97]. In insulin-resistant rats, green tea polyphenol treatment also increased the cardiac mRNA levels of IRS1, IRS2, GLUT1, GLUT4, and glycogen synthase 1 and decreased proinflammatory cytokines [32]. In insulin-resistant dogs, tea extract treatment upregulated PPAR $\alpha$  and lipoprotein lipase in the skeletal muscle and induced GLUT4 translocation into the plasma membrane in muscle cells [33]. The enhanced GLUT4 translocation and activation of AMPK (together with activation of PI3K/AKT) in skeletal muscle have been observed in mice treated with Oolong, black, or Pu-erh tea (2% extracts as drinking fluid) for 7 days [93]. The active constituents of these teas are probably EGCG (and other catechins) and caffeine. The induction of AMPK in skeletal muscle by caffeine has been reported [98].

Treatment with extracts of Oolong, black, or Pu-erh tea (in drinking fluid, similar to the experiment described above) was shown to activate AMPK in white adipose tissues [8]. Dietary supplementation of EGCG (0.2 or 0.5% in high-fat diet) to mice for 8 wk significantly decreased the mRNA levels of adipogenic genes, such as those for PPAR $\gamma$ , CCAAT enhancer binding protein  $\alpha$ , sterol regulatory element-binding protein-1c, lipoprotein lipase, and FAS in the epididymal white adipose tissues. This was accompanied by the increase of mRNA levels of lipolytic and catabolic genes such as hormone sensitive lipase, adipose triglyceride lipase, and CPT-1

(Fig. 3) [99]. Oral gavage of GTE (400 mg/kg) for 8 wk significantly reduced body weight and adipose tissue gain and this was associated with increased hormone sensitive lipase, 1-acylglycerol-3-phosphate O-acyltransferase, and perilipin in mesenteric adipose tissues [100]. Green tea (catechins) has also been proposed to prevent obesity or reduce fat deposits in mice or rats on a high-fat diet by increasing the insulin-like growth factor binding protein-1 in adipose tissues [101], or by activating the extracellular signal regulated kinase 1 (ERK1)/2-PPAR $\gamma$ -adiponectin pathway [102]. It has also been suggested that EGCG improves insulin signaling in adipose tissues of rats maintained on a high-fat diet by attenuating inflammation, decreasing macrophage content, and inhibiting toll-like receptor 4 activity [103].

Green tea or catechins have been shown, in white adipose tissue or in adipocytes in vitro, to suppress the mRNA levels of lipogenesis, adipogenesis, and fatty acid uptake genes (reviewed in [2]). The possible antimitogenic and differentiation effects of EGCG on preadipocytes and the involvement of 67R have been discussed [104, 105] primarily based on cell line studies with rather high EGCG concentrations (50, 100  $\mu$ M, or higher). Whether such effects can be exerted by EGCG after tea ingestion by animals remains to be determined.

#### 4.2.3 In the cardiovascular system

As discussed above, reduction of body weight and alleviation of MetS by tea consumption would decrease the stress to the cardiovascular system. Beneficial effects of tea catechins in lowering plasma cholesterol levels, preventing hypertension and improving endothelial function contribute to the prevention of CVDs. The cholesterol-lowering effect is likely due to the decrease of cholesterol absorption or reabsorption by catechins as well as the decrease of cholesterol synthesis via the inhibition of HMGCR (mediated by the activation of AMPK). Enhanced nitric oxide signaling has been suggested as a common mechanism for catechins to decrease blood pressure and the severity of myocardial infarction [58]. Several studies showed that green tea or black tea polyphenols increased endothelial nitric oxide synthase activity in bovine aortic endothelial cells and rat aortic rings [106–108], possibly mediated by AMPK and other signal pathways. Tea catechins may suppress the expression of caveolin-1, a negative regulator of endothelial nitric oxide synthase [109]. Similarly, EGCG has also been shown to lower the expression of endothelin-1, possibly through the activation of AMPK, and this reduces vasoconstrictor tone and may directly increase bioavailability of nitric oxide to improve endothelial function [110]. AMPK has also been suggested to regulate the antioxidant status [111] and to mediate the anti-inflammatory activity of EGCG in endothelial cells [112]. EGCG has also been shown to induce the expression of heme oxygenase 1 in aortic endothelial cells [113], and this may increase anti-inflammatory activity to benefit the cardiovascular system. While moderate doses

of EGCG have yielded beneficial effects, a very high dose (1% in diet) has been shown to promote, rather than to attenuate, vascular inflammation in hyperglycemic mice [114].

#### 4.2.4 In neuroendocrine system

There have been a few studies on the effects of EGCG administration on endocrine systems (reviewed in [104]). The thorough study in rats by Kao et al. [115] is rather intriguing. The effective concentration of EGCG used, 85 mg/kg intraperitoneally, is rather high. The molecular basis for the significant suppression of appetite, body and organ (prostate, uterus, and ovary) weights, and levels of several hormones is not known. Since this dose is beyond human EGCG exposure from consumption of tea, the relevance of these interesting observations is unknown.

Epinephrine and norepinephrine, two hormones produced in adrenal medulla in animals under stress conditions, increase delivery of oxygen to muscle and ATP production. Both hormones are inactivated by a methylation reaction catalyzed by COMT. EGCG and other catechins may prolong the effectiveness of these hormones, because they have been shown to be inhibitors of COMT [116]. This is the mechanism suggested by Dulloo et al. to explain their observations that tea catechins increased energy expenditure and fat oxidation in humans [117]. Caffeine, an important constituent in tea, has been well documented to increase energy expenditure [118].

#### 4.2.5 Antioxidant effects

Tea polyphenols are generally recognized as strong antioxidants, and their antioxidant action has been suggested to contribute to the alleviation of MetS. The antioxidant activities of tea and tea polyphenols have been studied extensively in animals and humans. A recent meta-analysis of 31 intervention studies on this topic, however, indicated that there was limited evidence that regular consumption of green tea increased plasma antioxidant capacity and reduced oxidation of LDL cholesterol [119]. In recent studies in subjects with MetS or obesity [38, 120], however, green tea supplementation has been shown to increase the antioxidant capacity. It appears that the antioxidant effect of tea is more apparent in animals and humans under higher oxidative stress and when rather high doses of tea catechins are used. It remains to be determined whether the observed “antioxidant” activity is due to the direct antioxidant effects of tea polyphenols or due to its “indirect antioxidant” effect through activation of Nrf2-mediated antioxidant enzymes [14, 15].

## 5 Concluding remarks

As discussed in the earlier part of this article, tea consumption at the levels of three to four cups (600–900 mg tea cate-

chins) or more a day has shown to reduce body weight gain, alleviate MetS, and reduce the risk for diabetes and CVDs. These results are supported by laboratory studies in animal models. We proposed the hypothesis that most of these beneficial effects can be explained by the decreased absorption of macronutrients plus the systemic effects of tea catechins in metabolic regulation, which are mediated mostly by the activation of AMPK. We further hypothesize that the relative importance of these two types of action depends on the types and amounts of tea consumed as well as the dietary conditions. For example, with black tea, the decrease of macronutrient absorption, especially with a high-fat diet, may play a more important role than its systemic effects, because of the low bioavailability of theaflavins and thearubigins. Another possibility is that these large molecular weight black tea polyphenols are degraded to form smaller molecular weight metabolites, which can be absorbed and exhibit biological effects on internal organs. Experimental evidence for this proposal is still lacking.

Even though our “AMPK hypothesis” proposes that AMPK plays a major role in mediating the actions of EGCG on gluconeogenesis, fatty acid synthesis, and catabolism of fat and glucose, actions that are independent of AMPK could also be involved. Some of these actions are described in this article, and some have been discussed in reviews by Wang et al. [3] and by Kim et al. [92]. It is puzzling why EGCG, a single molecule, can have so many diverse activities, and it is likely that some of these reported activities are secondary events.

Recent studies have shown that administration of moderate doses of EGCG to mice can produce ROS, which activates the Nrf2-mediated induction of antioxidant and other cytoprotective enzymes [14, 15]. ROS has also been proposed to activate AMPK [90]. Considering the effective doses of tea catechins in animal studies and in human consumption in alleviating MetS, an interesting question is whether the beneficial effects are due to the prooxidant activity of EGCG. Further research is needed to determine whether EGCG and other catechins exert their health beneficial effects by their classical antioxidant activity in quenching ROS, by their prooxidant activities, by inhibiting digestive or other enzymes, or by their actions as inhibitors or uncouplers of oxidative phosphorylation to decrease cellular ATP levels and activate AMPK.

From a public health point of view, consumption of tea at a level of three to four cups a day is achievable in some individuals, but not in other individuals. Green tea, especially when consumed in large amounts on an empty stomach, is known to cause irritation in the gastrointestinal system. Black tea is considered to be milder (less irritating), but the beneficial health effects are weaker. Dark tea is also considered milder, and its composition and health effects need to be systematically studied. Caution should be applied in using dietary supplements that contain high concentrations of tea extracts, since liver toxicity has been reported (reviewed in [1]). In addition to tea catechins, many other dietary substances have been shown to activate AMPK, reduce body weight gain, or alleviate MetS. These include resveratrol, curcumin, capsaicin,

and garlic constituents (reviewed in [3, 85]). An interesting possibility, which remains to be explored, is that the effects of these dietary materials can work additively to reduce body weight gain and alleviate MetS.

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