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REVIEW

The anti-obesity effects of green tea in human intervention and basic molecular studies

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Many researchers have reported that obesity is a major risk factor for diabetes, cardiovascular diseases, several forms of cancer (such as breast, colon and prostate), pulmonary, osteoarticular and metabolic diseases in the past decades. Recently, the hypolipidemic and anti-obesity effects of green tea in animals and humans have slowly become a hot topic in nutritional and food science research. This review will up-date the information of the anti-obesity effects of green tea in human intervention and animal studies. During recent years, an increasing number of clinical trials have confirmed the beneficial effects of green tea on obesity. However, the optimal dose has not yet been established owing to the very different results from studies with a similar design, which may be caused by differences in the extent of obesity, dietary intake, physical activity intensity, the strength of subjects' compliance to test instruction, the genetic background of populations, body composition and dietary habits. Therefore, further investigations on a larger scale and with longer periods of observation and tighter controls are needed to define optimal doses in subjects with varying degrees of metabolic risk factors and to determine differences in beneficial effects among diverse populations. Moreover, data from laboratory studies have shown that green tea has important roles in fat metabolism by reducing food intake, interrupting lipid emulsification and absorption, suppressing adipogenesis and lipid synthesis and increasing energy expenditure via thermogenesis, fat oxidation and fecal lipid excretion. However, the exact molecular mechanisms remain elusive.

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INTRODUCTION

Obesity, defined as a body mass index (BMI) of $\geqslant 30\ kg/m^2$ in western countries,[1] is a nutritional and metabolic disorder, which has the clinical manifestations of fat cell hypertrophy and hyperplasia. In June 2013, the American Medical Association formally recognized 'Obesity' as a disease.[2] During the past few decades, many researchers have reported that obesity is a major risk factor for diabetes, cardiovascular diseases, several forms of cancer (such as breast, colon and prostate), pulmonary, osteoarticular and metabolic diseases.[3] Now, obesity has become epidemic in all industrialized countries.[4] Obesity and the comorbidities associated with it remain a global health problem.[5] Consumption of a high-fat diet is a major risk factor for the development of obesity. Epidemiological studies have shown that obesity is generally more prevalent in people who consume a Western-style diet, which, in addition to being deficient in several nutrients, is also high in fat (30–40% of kcal in diet).[6] Dietary, pharmacological and surgical strategies have been developed in the past decade to prevent the metabolic effects of a high-fat diet.[7] Although pharmacological and surgical interventions are often the more efficient means to preventing obesity, there are still several negative effects, high costs and potentially hazardous side effects associated with these two means of therapy, suggesting that nutritional administration may be the safest and the most cost-effective option for those who are moderately obese.[8] Nowadays, nutritional intervention is still the preferred method of treatment to prevent obesity.[9] A variety of natural products, including crude extracts and compounds isolated from plants, can induce body weight reduction and prevent diet-induced obesity. Therefore they have been widely used in treating obesity.[10,11]

Green tea, derived from the tea plant (*Camellia sinensis*), is the second most popular beverage in the world and contains high levels of polyphenols. During the past decade, the health-promoting effects of green tea and its polyphenols have been intensively investigated. A large body of research on green tea has focused on its effects related to the prevention of cancer, and encouraging knowledge regarding efficacy, safety and potential mechanisms of action has accumulated in this area.[12] In addition, the anti-inflammatory,[13] anti-arthritic,[14] anti-bacterial,[15] anti-angiogenic,[16] anti-oxidative,[17] anti-viral[18] and neuroprotective effects[19] of green tea and its isolated constituents have been also frequently examined.

Recently, the hypolipidemic and anti-obesity effects of green tea in animals and humans have slowly become a hot issue for molecular nutrition and food research. The past decade has shed considerable light on the role of green tea catechins controlling hyperlipidemia and fat mass gain in high-fat diet-induced obese rodent models. Surprisingly little is known, however, about the exact conclusion of anti-obesity effects of green tea in humans and the underlying molecular mechanism of body weight management, especially regarding the regulation pathway. These are the primary focuses of this review.

GREEN TEA POLYPHENOLS (GTPS)

According to the processing technology, green tea is an unfermented tea, which can retain most of the contents of fresh

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leaves, owing to its enzyme-inactivated procedure under high temperature during the manufacturing process. Green tea is a rich source of polyphenols, which account for approximately 18–36% of dry leaf content, including catechins (flavanols), flavonoids and flavonols, anthocyanins and leucoanthocyanidins, phenolic acid and depside. In addition, 70–80% of GTPs are catechins, which are mainly comprised of (−)-epicatechin, (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECG), (−)-epigallocatechin gallate (EGCG), (+)-catechin and (+)-gallocatechin (GC), plus a small amount of (−)-catechin gallate (CG) and (−)-gallocatechin gallate (GCG). Among the ingredients of the catechins in brewed green tea, EGC, ECG and EGCG are the predominant components, accounting for about 13.08, 15.44 and 60.89% of total catechins, respectively (Table 1).[20] Like other natural products, the array of polyphenolic compounds varies in concentration by the harvest season, age of the plant, climate, environmental conditions and processing conditions.[21]

Many of the putative health benefits of green tea are attributed to the high polyphenol content of this beverage.[22] Because of its high content in tea and the recent demonstration of its assumed health-promoting action, EGCG is regarded the most important of the tea catechins.[23] However, a study conducted on A/J mouse has underlined a greater effect of green tea on the inhibition of lung tumorigenesis than EGCG alone, suggesting that other catechins and caffeine may have an important role in the nutraceutical properties of green tea.[24] It is necessary to examine the synergism and antagonism actions among different monomeric catechin when investigating the health-elevating effects of GTPs.

WEIGHT MANAGEMENT EFFECT OF GREEN TEA IN CLINICAL TRIALS BY META-ANALYSIS

An early indication for the benefits of green tea for weight management is seen in Chinese traditions, where green tea is said to wash out fat. Thanks to the positive results from animal experiments and clinical trials, this ancient knowledge was gradually recognized and accepted by oriental and even western populations. Although trials testing the anti-obesity efficacy of green tea in humans are more difficult to carry out, the fat-cutting-off effects of green tea in several intervention studies have been examined in recent years. A summary of the clinical studies is provided in Table 2, which will be reviewed afterwords.

Intervention trials in western populations

In western populations, the anti-obesity efficacies of green tea have been given increasingly high importance recently. Chantre *et al*.[25] investigated the effects of green tea extract AR25 (Exolise) in moderately overweight subjects (average BMI of 28.9 kg/m^2) and observed a 3.5-kg decrease in body weight and a 4.14-cm reduction in waist circumference versus baseline. Unfortunately, as this trial was an open, uncontrolled study, the promising outcomes should be viewed with caution. Nevertheless, more tightly controlled studies also support the concept that green tea is effective in weight loss. A randomized controlled trial with a single-blind and permuted block randomization design was launched in subjects with obesity and metabolic syndrome (median BMI 36.3 kg/m^2), and the body weights and waist circumferences were significantly decreased following an 8-week supplementation with green tea beverage (928 mg catechins, whereof 440 mg was EGCG and 8.96 mg was caffeine) or encapsulated green tea extracts (870 mg catechins, whereof 460 mg was EGCG and 3.6 mg was caffeine).[26] However, the positive result has a limitation, as the subjects recruited in this study came solely from the University of Oklahoma campus to ensure compliance in the green tea beverage group; therefore it cannot be generalized to a larger population. Another single-center, placebo-controlled, double-blind study was started in sedentary and overweight or obese men (median BMI 31.6 kg/m^2), and a notable body weight reduction of 1.17 kg (versus placebo treatment) was reported following a short-term supplementation (6 weeks) with encapsulated green tea extracts (800 mg catechins, whereof 400 mg was EGCG and caffeine was < 10 mg).[27] Suliburska *et al*.[28] investigated the health benefits of green tea in obese subjects (median BMI 32.8 kg/m^2) on a lower dosage (379 mg catechins, whereof 208 mg was EGCG) with a longer intervention term, and a decreasing trend in body mass index and waist circumference was also found after 3 months of green tea extract supplementation. It is worth mentioning that the low-density cholesterol level of subjects in the green tea groups of the three trials described above were all lowered versus the corresponding control groups. Furthermore, although dietary intake and physical activity were not strictly followed, all participants in these studies were instructed to maintain their usual diet and lifestyle.

Other lipid-lowering strategies, such as exercise, were introduced into green tea anti-obesity trials. Hill *et al*.[29] evaluated the metabolic effects of EGCG supplementation (300 mg) when combined with regular aerobic exercise in overweight/obese postmenopausal women (38 females, median BMI 30.7 kg/m^2), but they received negative results. The author argued that the loss of body fat may require a higher intake of EGCG, other catechins or additional metabolic stimulants (for example, caffeine). Cardoso *et al*.[30] examined the effects of green tea consumption (320 mg polyphenols and 40 mg caffeine) plus resistance training on body composition in sedentary overweight or obese women (36 females, median BMI 30.6 kg/m^2). After 8 weeks of treatment, there were significant decreases in waist circumference (9.2 cm, $P < 0.05$) and body fat percentage (10.3%, $P < 0.05$) in the green tea plus resistance training group. One probable reason for the inconsistent results from the mentioned two studies is the presence or absence of caffeine in tea supplements. The participants of the first study were postmenopausal women, whose hormone level differed greatly from the normal person, which may have also contributed to the difference of these trials. Also, the most serious limitations of the two studies were the inclusion of only a single gender and the small populations. Therefore, the gender and population scale of the participants should be more tightly controlled. In another tightly controlled study, a larger number of subjects ($n = 132$ with 107 completers, median BMI 32.2 kg/m^2, female/male ratio of about 1:1) was enrolled in order to evaluate the influence of green tea catechin beverages on body composition and fat distribution in overweight and obese adults during exercise-induced weight loss.[31] After a 12-week supplementation of green tea, there was a trend (1.2 kg

Table 1. Catechin's composition of brewed green tea[a]

Flavan-3-ols	*Amount mg/100 g (100 ml)*	*Percentage of total flavan-3-ols*
(−)-Epicatechin	8.29 ±0.49	6.49
(−)-Epicatechin 3-gallate	19.73 ±2.76	15.44
(−)-Epigallocatechin	16.71 ±1.41	13.08
(−)-Epigallocatechin 3-gallate	77.81 ±6.97	60.89
(+)-Catechin	2.55 ± 1.53	2.00
(+)-Gallocatechin	1.54 ± 0.00	1.21
Theaflavin	0.05 ± 0.01	0.04
Theaflavin-3,3′-digallate	0.01 ± 0.01	0.01
Theaflavin-3′-gallate	0.01 ± 0.00	0.01
Theaflavin-3-gallate	0.01 ± 0.01	0.01
Thearubigins	1.08 ± 1.08	0.85
Total Flavan-3-ols[b]	127.79	

[a]USDA Database for the Flavonoid Content of selected foods. [b]Total flavan-3-ols content is estimated as the sum of individual flavan-3-ols in brewed green tea listed above.

Table 2. Lipid-lowering effects of green tea in humans evaluated by interventional clinical studies

No.	Type of study	Participants	Test sites	Test components	Duration	Primary outcomes			Year (citations)
						Weight (kg)	Waist circumference (cm)	BMI	
1	Multicenter open study	7 M, 63 F BMI: 28.9 (25–32) kg/m^2 Age: 44.7 (18–69) years	France	Green tea extract AR25 (daily total of 375 mg green tea extract, whereof 270 mg was EGCG and 30 mg was caffeine)	12 weeks	− 3.5	− 4.14	—	2002 (25)
2	Randomized parallel, placebo controlled	26 M, 78 F BMI: 29.7 ± 2.6 kg/m^2 Age: 18–60 years	Netherlands	Control (placebo) Green tea (573 mg catechins, whereof 323 mg was EGCG, and 104 mg was caffeine)	13 weeks	0.6	0.3	0.2	2004 (34)
3	Double-blind, controlled	35 M, BMI: 25.0 ± 0.4 kg/m^2 Age: 24–46 years	Japan	Control (oolong tea containing 22 mg catechins, whereof 3 mg was EGCG and 78 mg was caffeine) Green tea extracts (690 mg catechins, whereof 136 mg was EGCG and 75 mg was caffeine)	12 weeks	− 1.1*	− 1.8#	− 0.4*	2005 (43)
4	Randomized parallel, placebo controlled	23 M, 53 F BMI: 27.5 ± 2.7 kg/m^2 Age: 18–60 years	France	Low habitual caffeine control (< 300 mg caffeine) (placebo) High habitual caffeine control (> 300 mg caffeine) (placebo) Low habitual caffeine GTE (< 300 mg caffeine) (375 mg catechins, whereof 270 mg was EGCG and 150 mg was caffeine) High habitual caffeine GTE (> 300 mg caffeine) (375 mg catechins, whereof 270 mg was EGCG and 150 mg was caffeine)	13 weeks	Low habitual caffeine − 2.8 High habitual caffeine 0.3	— —	− 0.9 0.2	2005 (35)
5	Randomized parallel, placebo controlled	34 F obese BMI: 30.9 ± 2.4 kg/m^2 Age: 34.8 ± 4.2 years	Hongkong	Control (placebo) Capsulated green tea powder (661 mg catechins, whereof 540 mg was EGCG and 152 mg was caffeine)	3 months	− 2.8	− 3.53%	− 1.0	2006 (41)
6	Double-blind, placebo-controlled, parallel design	46 F BMI: 27.7 ± 1.8 kg/m^2 Age: 41.7 ± 8.6 years	Netherlands	Control+low-energy diet (2790 mg maltodextrin) Green tea extract+low-energy diet (1206.9 mg catechins, whereof 595.8 mg was EGCG and 236.7 mg was caffeine)	12 weeks	0	− 0.9	0	2006 (32)
7	Double-blind, parallel, placebo controlled	18 M,62 F BMI: 31.2 ± 2.5 kg/m^2 Age: 47.6 ± 11.0 years	Denmark	Placebo treatment (50/50 cellulose and maltodextrin) Capsulated bioactive supplements(1500mg green tea extract, whereof 375mg was catechins and 150 mg was caffeine; 1218 mg was L-tyrosine; 152 mg was anhydrous caffeine; and 450 mg was Cayenne, whereof 1.2 mg was capsaicin; 3890 mg was calcium carbonate)	8 weeks	− 0.2	0	− 0.1	2007 (36)
8	Double-blind, placebo controlled	38 F BMI: 30.7 ± 0.6 kg/m^2 Age: 45–70 years	Switzerland	Teavigo capsules (containing 300 mg of EGCG)	12 weeks	0.53	1.67	0.19	2007 (29)
9	Double-blind parallel multicenter trial	100 F, 140 M, BMI: 26.8 ± 2.0 kg/m^2 Age: 41.7 ± 9.9 years	Japan	Control beverage (75 mg caffeine, 96.3 mg catechins, whereof 16.7 mg was EGCG) Green tea beverage (582.8 mg was catechins, whereof 100.3 mg was EGCG and 72.3 mg was caffeine)	12 weeks	− 1.6*	− 2.5*	− 0.6*	2007 (45)
10	Double-blind, placebo controlled	42 F, 18 M, BMI: 27.4 ± 3.3 kg/m^2 Age: 48.53 ± 5.5 years	Thailand	Control (cellulose) Green tea extract (140.8 mg catechins, whereof 100.7 mg was EGCG and 86.6 mg was caffeine)	12weeks	− 0.7*	− 0.1	− 1.09	2008 (48)
11	Randomized, double-blind, placebo controlled	78 obese F, BMI: 30.8 ± 4.1 kg/m^2 Age: 43.4 ± 11.8 years	Taiwan	Control (cellulose) Green tea extract (491 mg catechins, whereof 302 mg was EGCG and 27 mg was caffeine)	12 weeks	− 0.12	− 0.4	− 0.1	2008 (44)
12	Double-blind, randomized, controlled	28 M, 12 F, BMI: 27.2 ± 0.8 kg/m^2 Age: 6–16 years	Japan	Control beverage (75.4 mg catechins, whereof 11.5 mg was EGCG and 77.7 mg was caffeine) Green tea beverage (575.9 mg catechins, whereof 102 mg was EGCG and79.4 mg was caffeine)	24 weeks	− 1.2	− 1.6	− 0.4	2008 (49)
13	Multicenter clinical trial, controlled	56 M, 44 F, BMI:- Age: 25–60 years	Italy	Control (hypocaloric diet) Green tea extract (GreenSelect Phytosome, Indena, 300 mg, caffeine free) plus hypocaloric diet	90 days	− 9$	—	− 7%$	2009 (33)

Table 2. (Continued)

No.	Type of study	Participants	Test sites	Test components	Duration	Primary outcomes			Year (citations)
						Weight (kg)	Waist circumference (cm)	BMI	
14	Randomized, double-blind, controlled	67 M, 61 F, BMI: 32.2 ± 0.5 kg/m^2 Age: 48 ± 1.3 years	USA	Control beverage (containing 39 mg caffeine) Catechin beverage (624.7 mg catechins, whereof 214.4 mg was EGCG and 39 mg was caffeine)	12 weeks	−1.2	—	—	2009 (31)
15	Randomized, a single-blind controlled	8 M, 27 F, BMI: 36.3 ± 2.2 kg/m^2 Age: 42.3 ± 2.9 years	USA	Control (four cups water) Green tea (four cups, 928 mg catechins, whereof 440 mg was EGCG and 8.96 mg was caffeine) Green tea extracts (two capsules, 870 mg catechins, whereof 460 mg was EGCG and 3.6 mg was caffeine)	8 weeks		Green tea		2010 (26)
						−2.5#	1.02	−0.9#	
							Green tea extracts		
						−1.9*	−4.06	−0.7*	
16	Double-blind, placebo controlled	49 M, 133 F, BMI: 27.0 ± 2.2 kg/m^2 Age: 37.1 ± 9.3 years	China	Control drink (30 mg catechins, 30 mg caffeine) GT1 drink (458 mg catechins, 104 mg caffeine) GT2 drink (468 mg catechins, 126 mg caffeine) GT3 drink (886 mg catechins, 198 mg caffeine)	90 days		GT3 drink		2010 (46)
						−1.3*	−1.7*	—	
17	Single-center, placebo-controlled, double blind	70 M BMI: 31.6 ± 2.6 kg/m^2 Age: 49.4 ± 5.6 years	UK	Placebo treatment (two capsules, 1898 mg lactose) Decaffeinated green tea extracts (two capsules, 800 mg catechins, whereof 400 mg was EGCG and caffeine was < 10 mg)	6 weeks	−1.17*	—	—	2011 (27)
18	Randomized, double-blind, placebo controlled	24 M, 44 F BMI: 29.8 ± 1.6 kg/m^2 Age: 51.3 ± 9.1	Taiwan	Placebo treatment (three capsules, 1500 mg cellulose) Green tea extracts (three capsules, 1345 mg catechins, whereof 856.8 mg was EGCG and caffeine was < 1.05 mg)	16 weeks	−1.1	−2.2	−0.1	2011 (42)
19	Randomized, placebo controlled	20 M, 97 F BMI: 35.7 ± 5.2 kg/m^2 Age: 39.9 ± 11.7 years	Australia	Placebo treatment (12 capsules) Chinese herbal formula extracts (*Camellia sinens* (green tea) 40%, *Cassia obtusifolia* 40%, *Sophora Japonica* 20%, 12 capsules, 834 mg catechins, whereof 314 mg was EGCG and 184.5 mg was caffeine)	12 weeks	−2.0#	−0.8	−0.8*	2012 (37)
20	Randomized, double-blind, placebo controlled	23 M, 23 F BMI: 32.8 ± 2.5 kg/m^2 Age: 50.4 ± 8.3	Poland	Placebo treatment (one capsule, cellulose) Green tea extracts (one capsule, 379 mg catechins, whereof 208 mg was EGCG)	3 months	—	−0.67	−0.27	2012 (28)
21	Double-blind, controlled	20 M, 97 F BMI: 27 ± 0.8 kg/m^2 Age: 26.6 ± 1.8 years	Taiwan	Control beverage (162 mg catechins and 11.7 g inulin powder) Green tea extract beverage (534 mg catechins and 11.7g inulin powder)	6 weeks	−2.1*	−2.4	−0.7*	2012 (50)
22	Double-blind, randomized, controlled	39 M, 65 F BMI: 30.6 ± 3.2 kg/m^2 Age: 45.1 ± 9.6	China	Control beverage (86.2 mg catechins, whereof 14.8 mg was EGCG and 40.4 mg was caffeine) Green tea extract beverage (609.3 mg catechins, whereof 125.5 mg was EGCG and 68.6 mg was caffeine)	12weeks	−0.6	—	−0.2	2012 (47)
23	Double-blind, placebo controlled	36 F BMI: 30.6 ± 3.2 kg/m^2 Age: 25–40 years	Brazil	Group 1: green tea treatment (20 g soluble powder, of powdered green tea, whereof 320 mg was polyphenols and 40mg was caffeine) Group 2: placebo treatment (20 g same soluble powder, with the exception of powdered green tea, no polyphenols and caffeine) Group 3: green tea treatment plus resistance training Group 4: placebo treatment plus resistance training	8 weeks		Group 1		2013 (30)
						−5.4	−5.8	−2.4	
							Group 3		
						1.0	−9.2*	0.9	
24	Randomized, placebo controlled	13 M, 9 F BMI: 28.3 ± 0.5 kg/m^2 Age: 71.1 ± 1.2 years	Israel	Placebo treatment Green tea plus vitamin E treatment (3 cups Chinese green tea plus 400 IU V_E)	12 weeks	−1.7	−6.7*	—	2013 (51)

Abbreviations: BMI, body mass index; EGCG, (−)-epigallocatechin gallate; F, female; M, male. Note: Primary outcomes are the net effects of the green tea group versus the corresponding control group, *$P < 0.05$, #$P < 0.01$, $^{\$}P < 0.001$, represents significantly different from control.

decrease, $P = 0.079$) toward a greater loss of body weight in the catechin group (624.7 mg catechins, whereof 214.4 mg was EGCG and39 mg was caffeine) compared with the control group (39 mg caffeine, no catechins) and significant decreases in total abdominal fat area and serum triglycerides in the catechin group (versus control). It should be mentioned that a higher catechin dosage and a longer intervention duration were adopted in this study compared with the two studies described above, and an identical dose of caffeine was used in both the catechin and control groups. The findings of this tightly controlled study indicate that the catechin dose and intervention duration may have a more vital role in green tea-induced body fat loss when combined with exercises of certain intensities.

Besides exercise, an energy-restricted diet is another effective approach to reduce excess body fat. Diepvens *et al*.[32] investigated the effects of green tea extract along with a low-energy diet on weight loss. No effects of 1206 mg catechins and 236 mg caffeine on body weight and body fat were found in overweight females (BMI 27.7) who had been on a low calorie diet with supplementation for 12 weeks. This unexpected finding might have been caused by the high caffeine background intake (about 300 mg per day) of the participants; another cause for this outcome may be the poor absorption of natural polyphenols in oral administration. Di Pierro *et al*.[33] examined the anti-obesity effects of a commercial oral formulation (called Monoselect Camellia), containing high-bioavailable green tea extract phytosomes, plus a hypocaloric diet on overweight subjects (20–40% over the ideal weight). After the 90-day supplementation of 300 mg Monoselect Camellia (caffeine-free) plus a low energy diet, notable reductions of 9 kg body weight ($P < 0.001$) and 7% BMI ($P < 0.001$) were observed versus the control group. Several studies approached the topic of weight management effects of green tea from slightly different angles. The influences of green tea catechins on body weight regain after energy-restricted diet-induced weight loss programs were examined in these trials.[34–36] Neither the expected significant body weight loss nor a difference in body weight regain in response to green tea catechins could be demonstrated. Possibly, the effects of the catechins are not additional to the weight-reducing effect of the low calorie diet, as the latter already represents a strong stimulus to lose body weight and body fat. In addition, researchers also carried out some studies examining the anti-obesity effects of green tea combined with other bioactive ingredients and received positive results in most of these investigations. Notable fat mass loss was found in the study of Belza *et al*.,[36] in which green tea extract was combined with L-tyrosine, anhydrous caffeine and capsaicin to form a bioactive supplement. The following study is a typical example of this kind of green tea-based bioactive supplement. Lenon *et al*.[37] used several Chinese herbals forming a fat loss formula (green tea 40%, *Cassia obtusifolia* 40%, *Sophora Japonica* 20%; 834 mg catechins, whereof 314 mg was EGCG and 184.5 mg was caffeine). Significant decreases in body weight (2.0 kg, $P < 0.01$) and BMI (0.8, $P < 0.05$) were found in participants (BMI 35.7) in this study after a 12-week supplementation of this fat loss formula.

Intervention trials in the oriental population

Compared with the western countries, the percentage of obese people in Asian countries is lower. However, with the rapid development of the eastern obese population, this situation is currently changing.[38] Most obese individuals in Asia fall into the category of central obesity (also called visceral fat-type obesity), who often deposit excessive visceral fat.[39] The insulin resistance in central obese patients is usually more serious, harder to correct and more closely connected with cardiovascular disease.[40] As a dominant beverage, green tea is traditionally used as a medication based on experience, and the physiological activities of components of tea have been extensively described in Asian countries, mainly in Japan and China. Although there have been some neutral or negative results, clinical intervention trials trying to examine the anti-obesity efficacy of green tea in eastern populations have also obtained exciting findings in recent years.

In obese female patients (median BMI 30.5 kg/m^2) with polycystic ovary syndrome, a body weight reduction of −2.8 kg versus the control group was reported following a 12-week supplementation with encapsulated green tea.[41] Unfortunately, this promising finding lacks statistical significance for the between-group difference. Hsu *et al*.[42] also examined the effect of a decaffeinated green tea extract on obese individuals (median BMI 29.8 kg/m^2) with type 2 diabetes. Although body weight, BMI and waist circumstance of subjects in the green tea groups show a decreasing trend, no statistical difference has been found between the groups to date. These negative results may be a result of different responses of the patients to the green tea catechins, due to the high degree of obesity, as well as various metabolic changes due to disease when compared with studies of overweight but otherwise healthy subjects.

Nagao *et al*.[43] demonstrated that significant reductions in body weight and body fat of overweight (median BMI 25.0 kg/m^2) but healthy subjects could be seen after a 12-week supplementation with green tea catechin-enriched oolong tea (690 mg catechins, 75 mg caffeine) when compared with the control group (oolong tea containing 22 mg catechins, 78 mg caffeine). Being a small-scale ($n = 35$) and gender-biased (male) trial, this encouraging result needed further verification. In another gender-biased study, the researchers obtained neutral results with green tea treatment. Specifically, 78 obese women (median BMI 30.8 kg/m^2) were employed in this study to examine the effect of green tea extract (491 mg catechins, 27 mg caffeine) on obese females.[44] The results showed no statistical difference in reduction in body weight, BMI and waist circumstance between the green tea and placebo groups after 12 weeks of treatment. One or both of the following influences could have contributed to the contrary outcomes of these researches: green tea dose and the extent of obesity in participants.

Several tightly controlled trials carried out in China and Japan obtained encouraging results. Nagao *et al*.[45] showed significant reductions in body weight, waist circumstance and BMI in subjects (median BMI 26.8 kg/m^2) who had been maintaining their usual lifestyle while taking green tea catechins. This study is of special value, because the obese style of participants was the representative eastern visceral fat-type obesity, and it also correlated anti-obesity effects of green tea catechins with improvements in cardiovascular risk factors in a relatively large ($n = 240$) population. In another large scale trial, 182 moderately overweight Chinese subjects (median BMI 27.0 kg/m^2) were employed to investigate the effects of a high-catechin green tea on body composition.[46] In this study, the daily consumption of a control beverage with low doses of green tea catechins (30 mg) and caffeine (30 mg) was compared with three higher dose levels of green tea extract beverages, and the significant reductions of body weight, BMI and fat mass were all observed in the highest dose treatment (886 mg catechins, 198 mg caffeine). In view of the fact that the subjects in the two above studies were moderately obese, Zhang *et al*.[47] further examined the effects of catechin-enriched green tea on visceral fat-type obese Chinese adults (median BMI 30.6 kg/m^2). In the green tea group, a notable reduction in visceral fat was reported when compared with the control group; however, no significant changes in body weight, BMI or body fat were observed between the two groups. This neutral result indicates that it is not easy for the current green tea interventional dosage and duration to cause positive findings in body weight and fat loss in eastern central obese people, which is in contrast to the results obtained from western systematic obese individuals. For example, Basu *et al*.[26] demonstrated that significant reductions in body weight and BMI were observed in obese Americans (median BMI

36.3 kg/m^2) after an 8-week supplementation with green tea beverage (928 mg catechins and 8.96 mg caffeine). In this study, the author argued that effects of green tea may be more pronounced in subjects with clinically significant obesity (BMI 35 kg/m^2) than in overweight adults. Another study from Thailand reported a moderate but statistically significant reduction in body weight of 0.7 kg after supplementation of small amounts of catechins (140.8 mg catechins and 27 mg caffeine) over a 12 week period.[48] It is important to mention that the study population consisted of sedentary overweight (BMI 27–28 kg/m^2) subjects whose diet was provided by a hospital-based nutrition unit. Thus, in this type of study, diet as one of the main confounders should be controlled more tightly.

Matsuyama *et al*.[49] conducted a novel research to evaluate the effects of a catechin-rich beverage on body fat and cardiovascular disease risk factors in obese children (age 6–16 years, median BMI 27.2 kg/m^2). After 24 weeks of supplementation of green tea beverage (575.9 mg catechins and 79.4 mg caffeine), there were no significant differences in body weight, BMI or body fat mass between the catechin and control groups. When, however, the analysis was stratified using the median of the week-0 values, notable reductions in waist circumference and low-density lipoprotein cholesterol levels were observed in the catechin group compared with the control group at week 24. There have also been several studies that have investigated the fat loss effects of green tea combined with other bioactive supplements. Yang *et al*.[50] investigated the effect of catechin-rich green tea in combination with inulin on body weight and fat mass in obese and overweight adults, while Narotzki *et al*.[51] examined the effects of green tea plus vitamin E in addition to exercise on body composition and metabolic and antioxidant parameters in healthy elderly individuals. Both studies obtained positive outcomes.

Summary

In general, the green tea catechins/extracts interventional dosage of the above-mentioned studies ranged from 140.8 to 1500 mg/day, and the duration was 6 to 24 weeks. Most of the trials selected the dosage of 600–900 mg/day (equivalent to 3–4 cups of brewed green tea) and the duration of 12 weeks. Although supplementation with green tea led to significant decreases in body weight and body fat when compared with baseline, these reductions in several trials were somewhat diminished when compared with the control groups. The very different results obtained from studies with similar design were probably caused by variances in the control of the main confounders, such as obesity extent, dietary intake, physical activity intensity and the strength of subjects' compliance to test instruction.

The anti-obesity effect of both western and oriental population is summarized in Table 2. There were 5 (out of a total 11) trials getting significant weight loss outcome (ranging from 1.0 to 2.0 kg) in eastern populations. However, the notable weight loss (ranging from 1 to 9 kg) was only observed in 3 (out of a total 13) trials in people of western countries. That is to say, more obvious and consistent data were obtained from studies in oriental populations. The great differences of eastern and western populations in genetic background, body composition and dietary habits might have contributed to the distinct or contrary results from some analogous trials. Therefore, the anti-obesity result of green tea in eastern populations needs further research when it has been substantiated and generalized to people in western countries and *vice versa*. Also, the positive results in westerners were more likely to occur when the consumption of green tea was combined with other weight loss strategies, such as a low energy diet and aerobic exercise, while the intervention of green tea in eastern people was often along with their usual lifestyle. Therefore, the weight management effects of green tea in combination with changes in lifestyle should be tested more carefully in western populations in the future. Another distinction between the eastern and western populations of the mentioned trials was that the control group in a study of easterners usually consumes tea with a low dose of catechins and a certain amount of caffeine, while the control group in western populations often consumed placebo. The design of the control group in this way in easterners should take the oriental tea drinking custom into account. Furthermore, this type of strategy could examine the effect of green tea catechins in a direct manner.

As a metabolic stimulant, the role of caffeine in a green tea-induced weight management program should be carefully examined. Consumption of green tea extracts has been shown to increase fat oxidation and energy expenditure, particularly if combined with a metabolic stimulant such as caffeine.[52,53] In these studies, Bérubé-Parent *et al*.[52] and Boschmann *et al*.[53] successively confirmed that 300 mg/day of pure EGCG with 200 mg/day of caffeine resulted in a greater increase in fat oxidation than the same or a higher dose of EGCG (600 mg/day) or 200 mg/day of caffeine alone, thereby demonstrating a synergistic effect of 300 mg/day of EGCG and 200 mg/day of caffeine. Also, in the majority of reports showing that caffeine increases fat oxidation and thermogenesis, >100 mg caffeine was used. Therefore it could be deduced that the observed effects on body weight and body fat in the above-mentioned studies with a small dose of caffeine (<100 mg) were likely to be caused by the green tea catechins.

UNDERLYING ANTI-OBESITY MECHANISMS OF GREEN TEA BASED ON CELL LINES AND ANIMAL STUDIES

As characterized above, obesity is a nutritional and metabolic disorder, which has the clinical manifestations of fat cell hyperplasia and hypertrophy. Fat cell hyperplasia is caused by proliferation and the differentiation of preadipocytes, disorders of which could lead to excessive lipid deposition in adipose tissue, and directly influence the body composition and the morbidity of adiposity and related diseases.[54] With regard to fat cell hypertrophy, this often develops when energy intake exceeds energy expenditure. Additionally, fat cell proliferation is mainly controlled by genes, while nutritional factors also have a certain role. The expansion of adipocytes is tightly related to the level of energy in the diet.

Rains *et al*.[55] reviewed the underlying mechanisms whereby green tea catechins influence body weight and body composition. Much of the work in humans has focused on the effects of green tea catechins on thermogenesis and substrate oxidation, both of which are mediated by sympathetic nervous system activity. Other potential mechanisms, including modifications in appetite control, downregulation of enzymes involved in hepatic lipid metabolism and decreased nutrient absorption, were also examined in this literature. However, with regard to the extraordinary nature of the human trials, these conclusions are mostly plausible, theoretically speculated or indirectly determined. As strong support for the arguments presented above, many direct mechanic evidences for the anti-obesity of green tea from cell lines and animal models have been frequently reported by researchers in recent years, which will be intuitively presented in Figure 1 and reviewed below.

Inhibiting adipogenesis and inducing apoptosis of adipocytes

Adipocytes are derived from mesenchymal stem cells. Once preadipocytes are triggered to mature, they begin to change shape and undergo a round of cell division known as clonal expansion, followed by initiation of the genetic program that allows them to synthesize and store triglycerides. Two critical events occur during the early stages of differentiation, namely, mitotic clonal expansion and an irreversible commitment to

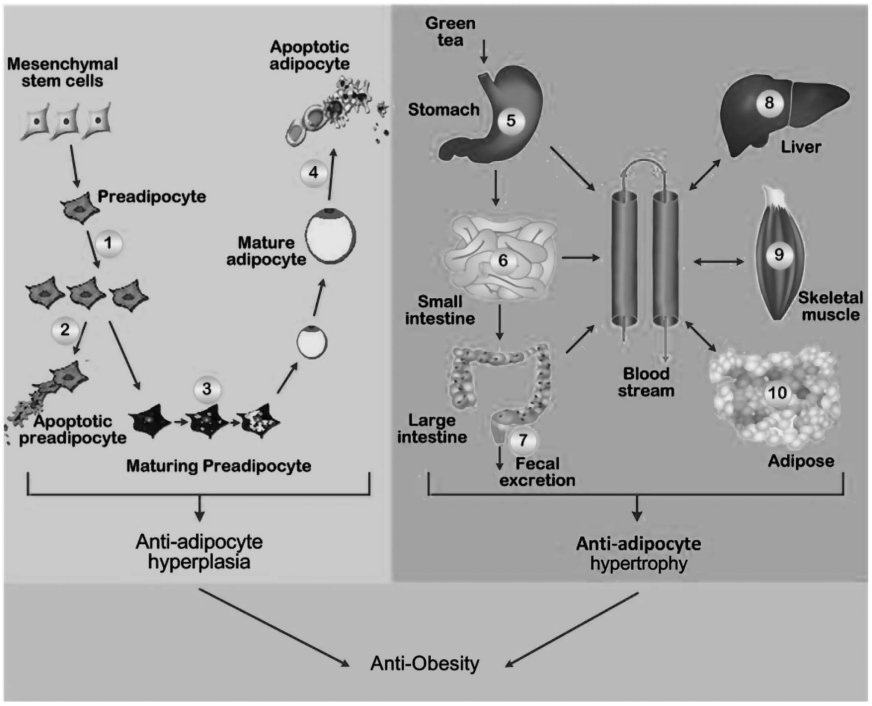

Figure 1. The underlying anti-obesity mechanisms of green tea. After intake, green tea catechins interfere with processes of energy absorption and metabolism in animals, including (1) to inhibit proliferation of preadipocyte, (2, 4) to induce the apoptosis of the preadipocyte and mature adipocyte, (3) to inhibit the differentiation of preadipocyte and the adipogenesis of maturing adipocyte, (5, 6) to inhibit the activity of gastrointestinal digestive enzymes, the luminal emulsification, hydrolysis and micellar solubilization of lipids and to interfere with the uptake and intracellular processing of lipids and assembly and secretion of chylomicrons in enterocytes, (7) to increase the fecal energy excretion, (8) to downregulate the hepatic gene expression of lipogenic enzymes and related transcription factors and to upregulate the hepatic mRNA level of fat β-oxidation genes, (9) to motivate the fatty acid oxidation and glucose uptake in skeletal muscle and (10) to stimulate the gene expression of lipolysis and fatty acid oxidation-related genes in adipose tissue and to suppress the glucose intake and the gene expression of fat synthesis-related genes in this organ. A full color version of this figure is available at the *European Journal of Cinical Nutrition* journal online.

differentiation. Members of the CCAAT/enhancer binding protein (C/EBPs) family and peroxisome proliferator-activated receptor gamma (PPARγ) are key regulators of the adipogenesis process. Exposure of preadipocytes to the adipogenic cocktail induces C/EBPs, which in turn activate PPARγ.[56] During the terminal phase of differentiation, adipocytes in culture markedly increase *de novo* lipogenesis. Mature adipocytes can store lipid when energy intake exceeds output and can mobilize and oxidize lipid when energy output exceeds input. Furthermore, mature adipocytes can also undergo apoptotic cell death under certain conditions.[11]

3T3-L1 is a murine cell line that is widely used to examine the effect of GTPs on adipogenesis. Hung *et al*.[57] reported that high concentrations of EGCG (50–400 μM) inhibited the differentiation of 3T3-L1 preadipocytes and induced apoptosis of adipocytes. These studies also indicated that the inhibition of proliferation in preadipocytes by EGCG may be due to its ability to induce cell cycle arrest at the G0/G1 phase and that such a blockage was probably mediated via the extracellular signal–regulated kinase (ERK)/mitogen-activated protein kinase (MAPK)- and the cyclin-dependent kinase 2 (Cdk2)-dependent pathways. Chen *et al*.[58] found that high concentrations (50–200 μM) of EGCG inhibited the proliferation of porcine preadipocytes and suppressed mRNA expression of PPARγ2 and C/EBPα from the early to the middle stages of preadipocyte–adipocyte development. However, the results obtained with high EGCG concentrations may not reflect the physiological response of the body to EGCG administration, as under a regular-based consumption in humans, the highest plasma concentration is around 1μM EGCG. Although it is slowly removed from the body, high plasma concentrations of EGCG cannot be achieved when it is regularly consumed.[59]

Furuyashiki *et al*.[60] investigated the effects of various monomeric catechins in 3T3-L1 cells during different stages of differentiation on a low dosage. The results showed that 30 μM CG and EGC could suppress the differentiation of preadipocytes into mature adipocytes and downregulate the expression of PPARγ2, C/EBPα and glucose transporter 4 (GLUT4).[60] Chan *et al*.[61] used physiologically attainable (0.1, 0.2, 0.5 and 1 μM) and pharmacological concentrations (5 and 10 μM) of EGCG to elucidate the biological response of preadipocytes. EGCG decreased the cell proliferation rate when applied to cell cultures either at the growth phase, during the induction of differentiation, or during its maturation with 0.1 μM EGCG or higher concentrations; the highest and most significant decrease in cell proliferation was obtained with 10 μM EGCG. This study also showed that EGCG induces an inhibitory effect on cell cycle progression at the G2/M phase when applied to cell cultures during every phase of the 3T3-L1 cell lifecycle. These data suggest that catechin may block proliferative events through the modulation of signaling pathways, which involve the activation of p53 and WAF1/p21,[62] c-Jun N-terminal kinase and MAPK,[63] or the inhibition of Cdks and AKT.[64] However, these results are not consistent with the results from Hung *et al*.[57] and need to be further investigated. Moreover, the suppressive effects of cell differentiation by EGCG and the accompanied decreases in mRNA and protein levels of C/EBPα and PPARγ were also found after the exposure of 3T3-L1 cells to different EGCG concentrations in this investigation.[61] Sakurai *et al*.[65] showed that EGCG at doses of 5–10 μM reduced fat accumulation and induced the expression of genes related to insulin sensitivity (including FABP4, Cd36, lipoprotein lipase (LPL), Pck1, Acox1, Lypla3 and Uncoupling protein-2 (UCP2)) and adipocyte differentiation (PPARγ1, PPARγ2, C/EBPs and PPARγC1a)

and reported that these increases were only seen in the early, and not late, stages of differentiation. The authors argued that EGCG has two differential effects: first, to enhance the expression of genes related to adipocyte differentiation and fat accumulation, and second, to enhance the expression of genes related to heat production and β-oxidation for adipocytes during the early stage.

Unlike the studies above, Morikawa *et al*.[66] examined the effect of EGCG on the proliferation and differentiation of preadipocytes using a human preadipocyte cell line, AML-I, which was derived from a lineage of human bone marrow stromal cells. In this experiment, the cell proliferation suppression and apoptosis induction were only found in the presence of high concentrations of EGCG (⩾100 μM), and the EGCG-induced apoptosis was considered owing to the accumulation of Bad and the reduction of pAkt and nuclear factor-kB. Abnormally, exposure of AML-I to EGCG (100 μM) increased the amounts of cytoplasmic lipid droplets as well as the expression of fatty acid synthase and PPARγ proteins.

Reducing nutrient absorption

Green tea catechins, particularly the principal green tea catechin EGCG, are not readily absorbed. Only a small percentage of orally ingested catechins was found in the blood of rats[67] and humans.[68,69] Because of the rather poor absorption and greater availability of green tea catechins in the intestinal lumen, it is likely that the lipid-lowering effect of green tea and catechins is mediated largely via their influence on the intestinal processes involved in the digestion and absorption of energy compounds.[70] Recently, the decreased absorption of energy nutrients in the digestive tract by green tea has been frequently investigated in animals, cell lines and *in vitro*. A couple of papers have reported that green tea catechins, especially with a galloyl moiety, could significantly inhibit the gastrointestinal absorption of dietary nutrition and increase fecal energy excretion.[71–74] In order to elucidate the underlying mechanism of this suppressive energy intake effected by green tea, various examinations from different angles have been proposed in recent years.

Several *in vitro* studies have indicated that the postprandial glucose-suppression effect of green tea may be initiated by its inhibitory effects against gastrointestinal digestive enzymes, which are particularly related to starch digestion, such as α-amylase and α-glucosidase.[75–79] Furthermore, Lo Piparo *et al*.[80] also studied the structural requirements of flavonoids for inhibiting human α-amylase by a computational ligand-docking method. The results showed that the inhibitory activity of flavonols and flavones depends on: (i) hydrogen bonds between the hydroxyl groups of the polyphenol ligands and the catalytic residues of the binding site and (ii) the formation of a conjugated π-system that stabilizes the interaction with the active site. After digestion, nutritional ingredients will enter the body through the intestinal epithelial cells. In mammals, intestinal glucose uptake is mainly performed by its specific transporters, such as sodium-dependent glucose transporter 1 (SGLT 1), and GLUT2 and GLUT5, which are expressed in the intestinal epithelial cells. By using human intestinal epithelial Caco-2 cells, marked inhibition of intestinal glucose uptake by green tea extracts was observed.[81] Also, the inhibition of SGLT 1, GLUT2 and GLUT5 was found in green tea catechin-treated Caco-2 cells or brush border membrane vesicles.[81,82]

Interestingly, the effect of tea polyphenols on the postprandial glycemic response to cooked starches differs with amylose contents. An *in vivo* test using a mouse model showed a moderate reduction of the postprandial glycemic response to co-cooked normal (containing 27.8% amylose) or waxy corn starch with 10% tea polyphenols (dry weight of starch), while an augmented glycemic response with a delayed blood glucose peak was observed when high amylose corn starch (containing 79.4% amylose) was used as the starch component.[83] The authors argued that an interaction between tea polyphenols and amylose might exist, which facilitates the association of amylose molecules to form a special non-ordered structure that could produce a high and sustained postprandial glycemic response. Thus a combination of tea polyphenols and specific starches could be used to manipulate postprandial glycemic response for glycemic control and optimal health.

As for fat digestion and absorption, the available information suggests that green tea and its catechins could interfere with or inhibit the luminal emulsification, hydrolysis and micellar solubilization of lipids. In several *in vitro* studies, Juhel *et al*.,[84] He *et al*.[75] and Gondoin *et al*.[85] successively showed that green tea and catechins significantly inhibited gastric and pancreatic lipase activities. Similarly, two other studies demonstrated that catechins with a galloyl moiety reduced body weight gain and suppressed postprandial hypertriacylglycerolemia by slowing down triacylglycerol absorption through the inhibition of pancreatic lipase in dietary fat-fed obese rodents.[86,87] Wu *et al*.[88] characterized the interaction of EGCG and porcine lipase by fluorescence spectroscopy, circular dichroism, isothermal titration calorimetry and molecular docking. The results suggested that the interaction process was spontaneous, with hydrogen bonds and electrostatic force perhaps primarily responsible for the interaction, with a 1:1 interaction of lipase and EGCG. Furthermore, the weakness of lipid emulsification likely slows the rate of hydrolysis of fat, as pancreatic lipase activity decreases with increasing emulsion droplet size and decreasing surface area.[89] Using a model emulsion system containing olive oil, phosphatidylcholine and bile salt, Shishikura *et al*.[90] revealed that green tea catechins at the levels achievable by typical daily intake markedly altered the physicochemical properties of a lipid emulsion by increasing its particle size and reducing the surface area. In addition, Wang *et al*.[74] found that green tea catechins also inhibit pancreatic phospholipase A2, as determined by an *in vitro* assay. The previous studies indicated that the potent inhibitory effect of EGCG on pancreatic PLA2 activity might be largely responsible for the decreased absorption of lipids, because luminal phosphatidylcholine hydrolysis was critical for facilitating intestinal lipid digestion and absorption.[91] Two similar studies from Wang *et al*.[72,74] also demonstrated that the inhibition of luminal phosphatidylcholine hydrolysis by EGCG might be responsible for the rather marked inhibition of the lymphatic absorption of cholesterol and α-tocopherol of extreme hydrophobicity and the moderate or small effect of EGCG on less hydrophobic compounds, such as retinol and fatty acids.

After fat digestion, the next critical step followed is the absorption of lipids through the intestinal tract, which comprises the uptake and intracellular processing of lipids and the assembly and secretion of chylomicrons. The absorption of dietary fats and cholesterol is largely dependent on the intestinal expression of several active transporters. The lipid transporters, which are highly expressed on the apical surface of the intestine, facilitate the fatty acid and cholesterol transfer/homeostasis in enterocytes.[92] Koo *et al*.[73] speculated that green tea catechins might influence the uptake of cholesterol and other lipids by the enterocyte through interaction with transporters, particularly those exposed to the intestinal lumen. Subsequently, the intracellular processing and packaging of lipids, including the reacylation or resynthesis of lipids, might also be disturbed by green tea. At present, no direct evidence has been reported. However, Qin *et al*.[92] demonstrated that cinnamon polyphenols inhibited genes associated with increased cholesterol, triacylglycerols and apolipoprotein-B48 levels, including the adenosine triphosphate-binding cassette subfamily proteins G5 (*Abcg5*), Niemann-Pick c1-like 1 (*Npc1l1*), Cd36, microsomal triacylglycerol transfer protein (*Mttp*), and sterol regulatory element-binding protein- 1c (*Srebp1c*), and facilitated Abca1 expression. Casaschi *et al*.[93] indicated that the flavonoid

quercetin inhibits the activity of diacylglycerol acyltransferase and the lipidation of apoB-containing lipoproteins by microsomal triglyceride transfer protein in Caco-2 cells. Thus it is possible that green tea catechins may influence critical steps involved in the assembly and secretion of chylomicrons from the enterocyte into the lymphatics.

Interfering with lipid metabolism

The expansion of adipose tissue mainly depends on the transportation and deposition of fat *in vivo*. There are two principle sources of internal lipids in animals, one of which is the *de novo* synthesis in liver and adipose tissues, and the other is the absorption in the gastrointestinal tract. Moreover, the catabolic oxidation of fat is mostly carried out in the liver and skeletal muscle. When fat input exceeds its catabolic oxidation, obesity would probably arise. Therefore most studies aiming to reveal the underlying mechanism of the anti-obesity efficacy of green tea have investigated its influence on lipid anabolism and catabolism in the liver, muscles and adipose tissues of animals.

The liver is an extremely vital metabolic organ *in vivo*, and lipogenesis in humans mainly occurs in this organ.[94] Previous studies on the metabolism of catechins have also demonstrated that high levels of catechins were detected in the liver after ingestion,[95] suggesting that this organ is susceptible to the effects of dietary tea catechins. A study using ovariectomized rats that were fed fructose showed that green tea significantly downregulated the hepatic expression of sterol regulatory element-binding protein-1c (SREBP-1c) and its target genes, such as fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD1) and the genes that regulate hepatic cholesterol synthesis (3-hydroxy-3-methyl-glutaryl-CoA reductase, HMGR) and efflux (ATP binding cassette superfamily of transporter proteins 1, Abca1).[96] SREBP-1c and Abca1 are liver X receptor (LXR) target genes. Another study using human mononuclear cells indicated that GTPs decreased the expression of LXRα and PPARγ in a dose-dependent manner, both of which upregulate the expression of lipogenic genes, including SREBP-1c.[97] Recently, a series of investigations using high-fat diet-induced obese mice, rats, chickens or zebrafish revealed that green tea and its catechins could downregulate the expression of fat synthesis genes (malic enzyme (ME), glucose-6-phosphate dehydrogenase, SCD1) and upregulate the mRNA level of fat β-oxidation genes (carnitine palmitoyltransferase-1 (CPT-1), acyl-CoA oxidase (ACO), acyl-CoA dehydrogenase (MCAD), PPARα).[71,98–104] In order to examine the anti-obesity effects of other ingredients in green tea extracts besides EGCG, Yasui *et al*.[105] also showed that an EGCG-free fraction derived from green tea could reduce the hepatic gene expression of lipogenic enzymes and the related transcription factor (FAS, HMGR, acetyl-CoA carboxylase (ACC), SREBP-1c). Lu *et al*.[106] identified 12 GTP-targeted genes in the high-fat diet-induced obese rat model using PCR array, including three orexigenic genes (Agrp, Ghrl and Nr3c1), seven anorectic genes (Apoa4, Cntf, Ghr, IL-1b, Ins1, Lepr, and Sort) and two genes that are related to energy expenditure (Adcyap1r1 and Adrb1).

Many questions remain, however, regarding why the lipid metabolism genes were modulated by green tea in such a coordinated way. There may be a metabolic regulator involved in producing these effects. AMP-activated protein kinase (AMPK) activation results in the phosphorylation and inhibition of ACC and the loss of inhibition of CPT-1 by decreasing the concentration of malonyl-CoA, leading to increased fatty acid oxidation. In regulating adipogenesis, AMPK activation inhibits adipocyte differentiation and suppresses the expression of lipogenic molecules, such as FAS, ACC and PPARγ;[107] therefore, based on the central role of AMPK in the regulation of energy metabolism, it may be a promising molecular target for the suppression of obesity and the treatment of metabolic syndrome. Murase *et al*.[108] examined the effects of green tea catechins on the AMPK signaling pathway in cultured cells (Hepa 1–6, L6 and 3T3-L1) and in mice. They demonstrated that catechins with a gallocatechin moiety or a galloyl residue activate LKB1/AMPK in cultured cells, and the oral administration of EGCG in mice stimulates energy expenditure concomitant with the upregulation of AMPKα phosphorylation and AMPKα activity in the liver. Banerjee *et al*.[109] also showed that green tea extract administered by gavage at 50 and 100 mg/kg caused a 2- to 3-fold increase in hepatic AMPK phosphorylation of female C57BL/6J mice at 3 and 6 h after dosing and a 1.5- to 2-fold increase in LKB1 phosphorylation at these same time points.

Adipose tissue and muscle are important organs related to lipid metabolism and energy consumption. Regulation of lipid metabolism by green tea in these two tissues is of great interest. White adipose tissue is the major site for energy storage, and a certain amount of fatty acids was also synthesized *in vivo* in adipocytes using absorbed glucose. Skeletal muscle is a mitochondria-rich tissue and requires sufficient energy derived from carbohydrates and fat to maintain its movement function. Therefore the modulation of energy uptake into peripheral tissues and lipogenesis in white adipose tissue is one of the most effective strategies to reduce the risk of obesity. Many investigations have shown that green tea could have a part in this process. Recent studies have suggested that green tea or its catechins could suppress the mRNA levels of lipogenesis, adipogenesis and fatty acid uptake genes, such as FAS, ACC, SCD1, SREBP-1c, C/EBPα, PPARγ,PPAR-γ coactivator-1 α (PGC-1α), preadipocyte factor-1 (Pref-1) and LPL, and stimulate the expression of fatty acid mobilization genes, CPT-1, hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), in white adipose tissue or *in vitro* adipocytes.[71,100,102,110–115] In addition, HSL and ATGL, the rate-limiting enzymes of intracellular triglyceride hydrolysis, are major determinants of fatty acid mobilization in adipose tissue, which can be activated by perilipin (a lipid droplet scaffold) and abhydrolase domain 5 (ABHD5).[116–118] Cunha *et al*.[119] revealed that green tea administered concomitantly with a high-fat diet increased the protein level of HSL, ABHD5 and perilipin in mesenteric adipose tissue of mice fed a high-fat diet, and this was associated with reduced body weight and adipose tissue gain. Brown adipose tissue is another type of adipose tissue, the main function of which is to transfer energy from food into heat. When the tissue is active, high amounts of lipids and glucose are combusted in the tissue. UCP1 is a characteristic protein developed in brown adipose tissue.[120] Nomura *et al*.[121] showed that the suppressive effect of green tea catechins on body fat accumulation is associated with the upregulated expression of UCP1 in brown adipose tissue.

Several investigations also indicated that green tea could modulate the energy uptake system in adipose tissue and skeletal muscle and motivate mitochondrial fatty acid oxidation in skeletal muscle. Murase *et al*.[122] showed that 0.2–0.5% (wt/wt) green tea extract in the diet could increase the β-oxidation activity and the level of fatty acid translocase/CD36 mRNA in the muscle of BALB/c mice. Another study indicated that drinking green tea for 3 weeks significantly reduced glucose uptake accompanied by a decrease in translocation of GLUT4 in adipose tissue, while it significantly stimulated glucose uptake with GLUT4 translocation in the skeletal muscle of male Wistar rats.[115] Sae-Tan *et al*.[123] revealed that 0.32% dietary EGCG supplement for 16 weeks increased the expression of genes related to fat oxidation in the skeletal muscle of high-fat-fed C57BL/6J mice, such as nuclear respiratory factor (Nrf)1, medium chain acyl-CoA dehydrogenase (MCAD), UCP3 and PPARα. An *in vitro* study also demonstrated that EGCG inhibited cellular glucose uptake and enhanced the expression and secretion of retinol binding protein 4 (RBP4) in 3T3-L1 adipocytes at a biologically achievable concentration ($\leqslant$10 μM).[124] As RBP4 secreted from adipocytes can inhibit muscular glucose

uptake and enhance hepatic glucose output, the systemic effect of EGCG associated with its effect on RBP4 secretion should be further determined.

In addition, a number of studies recently aimed to investigate the regulation pathway in green tea modulation of lipid metabolism and energy consumption in adipose tissue and skeletal muscle. An investigation demonstrated that the inhibitory action of EGCG on insulin-stimulated glucose uptake in adipocytes could be mediated through the 67kD laminin receptor (67LR) and AMPK pathways.[125] Hasumura *et al*.[103] also indicated that green tea extract exposure significantly decreased the visceral fat expression of suppressor of cytokine signaling 3 in diet-induced obese zebrafish, which inhibits leptin signaling. In addition, green tea was reported to affect the sympathetic nervous system. Tea catechins can inhibit the enzyme catechol O-methyltransferase, which contributes to the degradation of the neurotransmitter norepinephrine. When this neurotransmitter is not degraded, fat oxidation and thermogenesis increase. More encouragingly, Lee *et al*.[126] clearly showed that EGCG activates the Wnt/β-catenin pathway in 3T3-L1 adipocytes, resulting in the upregulation of β-catenin, which downregulates the expression of major genes involved in the adipogenesis pathway, including PPARγ, C/EBPα, fatty acid binding protein (FABP)4 and FAS.

Summary

As shown in Figure 1, after intake, green tea catechins interfere with processes of energy absorption and metabolism in animals. Specifically, green tea could inhibit the proliferation, differentiation, adipogenesis of preadipocyte and maturing adipocyte and induce the apoptosis of these cells. It could also inhibit the activity of gastrointestinal digestive enzymes, the luminal emulsification, hydrolysis and micellar solubilization of lipids and interfere with the uptake and intracellular processing of lipids and assembly, and secretion of chylomicrons in enterocytes, consequently, increase the fecal energy excretion. As for the lipid metabolism *in vivo*, green tea could downregulate the hepatic gene expression of lipogenic enzymes and related transcription factors, upregulate the hepatic mRNA level of fat β-oxidation genes, motivate the fatty acid oxidation and glucose uptake in skeletal muscle, stimulate the gene expression of lipolysis and fatty acid oxidation related genes in adipose tissue and suppress the glucose intake and the gene expression of fat synthesis related genes in this organ.

The anti-obesity effect of green tea is the result of the systematic regulation of the adipogenesis and apoptosis of adipocytes, digestion and absorption of nutrition and energy metabolism and translocation among different tissues. Although a large amount of research has been carried out to illustrate the anti-obesity underlying mechanism of green tea from different points or angles, there are still many unclear issues that require further investigation. The biological response of preadipocytes to green tea catechins at physiologically attainable ($<1\,\mu M$) and pharmacological concentrations (5–10 μM) needs more in-depth research. In enterocytes, the uptake and intracellular processing of lipids and the assembly and secretion of chylomicrons after fat digestion might also be disturbed by green tea. However, no direct evidence has been obtained at present. Green tea or its catechins were reported to modulate gene and protein expression levels or the activities of key enzymes and transcription factors related to energy metabolism and translocation in the liver, adipose tissue and skeletal muscles. However, there is little known about the pathways by which green tea exerts its regulatory effectiveness in different tissues. Although several studies have indicated that the AMPK pathway in the liver and the Wnt/β-catenin pathway in adipose tissue might act as the main regulators, further research is needed to confirm this mechanism or to identify a new mechanism.

Additionally, green tea has been speculated to inhibit appetite. Conversely, most of the investigations in animal models have shown that green tea or its catechins have no effect on food intake through oral administration, except for one study which indicated that EGCG administered by intraperitoneal injection induces appetite inhibition.[127]

CONCLUDING REMARKS

Human and animal studies have provided a large body of evidence to support the oriental traditional custom stemming from the fact that green tea and its catechins may be beneficial for the prevention or treatment of obesity. In clinical trials, however, further investigations on a larger scale and with a longer period of observation as well as tighter controls are critical to define optimal doses in subjects with varying degrees of metabolic risk factors and to determine differences in beneficial effects among diverse populations. Moreover, the combination of green tea intervention with lifestyle changes such as increased physical activity and energy-restricted diets, especially in western populations, would receive more encouraging outcomes.

In animals or cell lines, green tea was illustrated to have a role in fat loss by reducing food intake, interrupting lipid emulsification and absorption, suppressing adipogenesis and lipid synthesis and increasing energy expenditure via thermogenesis, fat oxidation and fecal lipid excretion. In further studies, the following question needs to be answered: does every regulatory point listed above exert equally in the regulation of lipid metabolism by green tea? There may be one key factor, which the others are regulated by, or merely change following the alteration of this key element. Taking the very poor bioavailability of flavonoids and flavanol compounds into account, the regulation of green tea in the gastrointestinal tract might have this key role, as green tea could easily attain a high concentration in this site. However, further investigations are needed to confirm this hypothesis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The authors alone are responsible for the content and writing of the paper.

REFERENCES

1 Grove KA, Lambert JD. Laboratory, epidemiological, and human intervention studies show that tea (Camellia sinensis) may be useful in the prevention of obesity. *J Nutr* 2010; **140**: 446–453.
2 Apovian CM, Mechanick JI. Obesity IS a disease! *Curr Opin Endocrinol Diabetes Obes* 2013; **20**: 367–368.
3 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *New Engl J Med* 2003; **348**: 1625–1638.
4 Gonzalez-Castejon M, Rodriguez-Casado A. Dietary phytochemicals and their potential effects on obesity: a review. *Pharmacol Res* 2011; **64**: 438–455.
5 Popkin BM. Recent dynamics suggest selected countries catching up to US obesity. *Am J Clin Nutr* 2010; **91**: 284S–288S.
6 Schulz LO, Bennett PH, Ravussin E, Kidd JR, Kidd KK, Esparza J *et al.* Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the US. *Diabetes Care* 2006; **29**: 1866–1871.

7 Sae-tan S, Grove KA, Lambert JD. Weight control and prevention of metabolic syndrome by green tea. *Pharmacol Res* 2011; **64**: 146–154.
8 Poulose BK, Griffin MR, Moore DE, Zhu Y, Smalley W, Richards WO *et al.* Risk factors for post-operative mortality in bariatric surgery. *J Surg Res* 2005; **127**: 1–7.
9 Daskalopoulou S, Mikhailidis D, Elisaf M. Prevention and treatment of the metabolic syndrome. *Angiology* 2004; **55**: 589–612.
10 Han L-K, Kimura Y, Okuda H. Anti-obesity effects of natural products. *Stud Nat Prod Chem* 2005; **30**: 79–110.
11 Rayalam S, Della-Fera MA, Baile CA Phytochemicals and regulation of the adipocyte life cycle. *J Nutr Biochem* 2008; **19**: 717–726.
12 Yang CS, Hong J. Prevention of chronic diseases by tea: Possible mechanisms and human relevance. *Annu Rev Nutr* 2013; **33**: 161–181.
13 Donà M, Dell'Aica I, Calabrese F, Benelli R, Morini M, Albini A *et al.* Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis. *J Immunol* 2003; **170**: 4335–4341.
14 Ahmed S, Wang N, Lalonde M, Goldberg VM, Haqqi TM. Green tea polyphenol epigallocatechin-3-gallate (EGCG) differentially inhibits interleukin-1β-induced expression of matrix metalloproteinase-1 and-13 in human chondrocytes. *J Pharmacol Exp Ther* 2004; **308**: 767–773.
15 Roccaro AS, Blanco AR, Giuliano F, Rusciano D, Enea V. Epigallocatechin-gallate enhances the activity of tetracycline in staphylococci by inhibiting its efflux from bacterial cells. *Antimicrob Agents Ch* 2004; **48**: 1968–1973.
16 Oak M-H, El Bedoui J, Schini-Kerth VB. Antiangiogenic properties of natural polyphenols from red wine and green tea. *J Nutr Biochem* 2005; **16**: 1–8.
17 Zhang Y-M, Rock CO. Evaluation of epigallocatechin gallate and related plant polyphenols as inhibitors of the FabG and FabI reductases of bacterial type II fatty-acid synthase. *J Biol Chem* 2004; **279**: 30994–31001.
18 Weber JM, Ruzindana-Umunyana A, Imbeault L, Sircar S. Inhibition of adenovirus infection and adenain by green tea catechins. *Antivir Res* 2003; **58**: 167–173.
19 Weinreb O, Mandel S, Amit T, Youdim MB. Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. *J Nutr Biochem* 2004; **15**: 506–516.
20 USDA Database for the Flavonoid Content of Selected Foods Nutrient Data Laboratory. Food Composition Laboratory. Beltsville Human Nutrition Research Center. Nutrient Data Laboratory. United States Department of Agriculture. Available at http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/Flav/Flav02-1.pdf. Accessed 20 November 2009.
21 Lin YS, Tsai YJ, Tsay JS, Lin JK. Factors affecting the levels of tea polyphenols and caffeine in tea leaves. *J Agric Food Chem* 2003; **51**: 1864–1873.
22 Balentine DA, Wiseman SA, Bouwens LC. The chemistry of tea flavonoids. *Crit Rev Food Sci* 1997; **37**: 693–704.
23 Yang CS, Landau JM. Effects of tea consumption on nutrition and health. *J Nutr* 2000; **130**: 2409–2412.
24 Chung FL, Schwartz J, Herzog CR, Yang YM. Tea and cancer prevention: studies in animals and humans. *J Nutr* 2003; **133**: 3268S–3274S.
25 Chantre P, Lairon D. Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. *Phytomedicine* 2002; **9**: 3–8.
26 Basu A, Sanchez K, Leyva MJ, Wu M, Betts NM, Aston CE *et al.* Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. *J Am Coll Nutr* 2010; **29**: 31–40.
27 Brown AL, Lane J, Holyoak C, Nicol B, Mayes AE, Dadd T. Health effects of green tea catechins in overweight and obese men: a randomised controlled cross-over trial. *Br J Nutr* 2011; **106**: 1880–1889.
28 Suliburska J, Bogdanski P, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Effects of green tea supplementation on elements, total antioxidants, lipids, and glucose values in the serum of obese patients. *Biol Trace Elem Res* 2012; **149**: 315–322.
29 Hill AM, Coates AM, Buckley JD, Ross R, Thielecke F, Howe PR. Can EGCG reduce abdominal fat in obese subjects? *J Am Coll Nutr* 2007; **26**: 396S–402S.
30 Cardoso GA, Salgado JM, Cesar Mde C, Donado-Pestana CM. The effects of green tea consumption and resistance training on body composition and resting metabolic rate in overweight or obese women. *J Med Food* 2013; **16**: 120–127.
31 Maki KC, Reeves MS, Farmer M, Yasunaga K, Matsuo N, Katsuragi Y *et al.* Green tea catechin consumption enhances exercise-induced abdominal fat loss in overweight and obese adults. *J Nutr* 2009; **139**: 264–270.
32 Diepvens K, Kovacs EM, Vogels N, Westerterp-Plantenga MS. Metabolic effects of green tea and of phases of weight loss. *Physiol Behav* 2006; **87**: 185–191.
33 Di Pierro F, Menghi AB, Barreca A, Lucarelli M, Calandrelli A. Greenselect Phytosome as an adjunct to a low-calorie diet for treatment of obesity: a clinical trial. *Altern Med Rev* 2009; **14**: 154–160.
34 Kovacs EM, Lejeune MP, Nijs I, Westerterp-Plantenga MS. Effects of green tea on weight maintenance after body-weight loss. *Br J Nutr* 2004; **91**: 431–437.
35 Westerterp-Plantenga MS, Lejeune MP, Kovacs EM. Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. *Obes Res* 2005; **13**: 1195–1204.
36 Belza A, Frandsen E, Kondrup J. Body fat loss achieved by stimulation of thermogenesis by a combination of bioactive food ingredients: a placebo-controlled, double-blind 8-week intervention in obese subjects. *Int J Obesity* 2007; **31**: 121–130.
37 Lenon GB, Li KX, Chang YH, Yang AW, Da Costa C, Li CG *et al.* Efficacy and safety of a Chinese herbal medicine formula (RCM-104) in the management of simple obesity: a randomized, placebo-controlled clinical trial. *Evid Based Compl Alternat Med* 2012; **2012**: 1–11.
38 Kelly T, Yang W, Chen C, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obesity* 2008; **32**: 1431–1437.
39 Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH *et al.* Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006; **368**: 1681–1688.
40 Indulekha K, Anjana RM, Surendar J, Mohan V. Association of visceral and subcutaneous fat with glucose intolerance, insulin resistance, adipocytokines and inflammatory markers in Asian Indians (CURES-113). *Clin Biochem* 2011; **44**: 281–287.
41 Chan CC, Koo MW, Ng EH, Tang OS, Yeung WS, Ho PC. Effects of Chinese green tea on weight, and hormonal and biochemical profiles in obese patients with polycystic ovary syndrome--a randomized placebo-controlled trial. *J Soc Gynecol Invest* 2006; **13**: 63–68.
42 Hsu C, Liao Y, Lin S, Tsai T, Huang C, Chou P. Does supplementation with green tea extract improve insulin resistance in obese type 2 diabetics? A randomized, double-blind, and placebocontrolled clinical trial. *Altern Med Rev* 2011; **16**: 157–163.
43 Nagao T, Komine Y, Soga S, Meguro S, Hase T, Tanaka Y *et al.* Ingestion of a tea rich in catechins leads to a reduction in body fat and malondialdehyde-modified LDL in men. *Am J Clin Nutr* 2005; **81**: 122–129.
44 Hsu CH, Tsai TH, Kao YH, Hwang KC, Tseng TY, Chou P. Effect of green tea extract on obese women: a randomized, double-blind, placebo-controlled clinical trial. *Clin Nutr* 2008; **27**: 363–370.
45 Nagao T, Hase T, Tokimitsu I. A green tea extract high in catechins reduces body fat and cardiovascular risks in humans. *Obesity* 2007; **15**: 1473–1483.
46 Wang H, Wen Y, Du Y, Yan X, Guo H, Rycroft JA *et al.* Effects of catechin enriched green tea on body composition. *Obesity* 2010; **18**: 773–779.
47 Zhang Y, Yu Y, Li X, Meguro S, Hayashi S, Katashima M *et al.* Effects of catechin-enriched green tea beverage on visceral fat loss in adults with a high proportion of visceral fat: a double-blind, placebo-controlled, randomized trial. *J Funct Foods* 2012; **4**: 315–322.
48 Auvichayapat P, Prapochanung M, Tunkamnerdthai O, Sripanidkulchai BO, Auvichayapat N, Thinkhamrop B *et al.* Effectiveness of green tea on weight reduction in obese Thais: a randomized, controlled trial. *Physiol Behav* 2008; **93**: 486–491.
49 Matsuyama T, Tanaka Y, Kamimaki I, Nagao T, Tokimitsu I. Catechin safely improved higher levels of fatness, blood pressure, and cholesterol in children. *Obesity* 2008; **16**: 1338–1348.
50 Yang HY, Yang SC, Chao JC, Chen JR. Beneficial effects of catechin-rich green tea and inulin on the body composition of overweight adults. *Br J Nutr* 2012; **107**: 749–754.
51 Narotzki B, Reznick AZ, Navot-Mintzer D, Dagan B, Levy Y. Green tea and vitamin E enhance exercise-induced benefits in body composition, glucose homeostasis, and antioxidant status in elderly men and women. *J Am Coll Nutr* 2013; **32**: 31–40.
52 Bérubé-Parent S, Pelletier C, Doré J, Tremblay A. Effects of encapsulated green tea and Guarana extracts containing a mixture of epigallocatechin-3-gallate and caffeine on 24 h energy expenditure and fat oxidation in men. *Br J Nutr* 2005; **94**: 432.
53 Boschmann M, Thielecke F, Franke G, Adams F, Birkenfeld A, Luft F *et al.* Evaluation of EGCG on thermogenesis and fat oxidation. *Am J Clin Nutr* 2007; **25**: 441–449.
54 Fève B. Adipogenesis: cellular and molecular aspects. *Best Pract Res Clin Endocrinol Metab* 2005; **19**: 483–499.
55 Rains TM, Agarwal S, Maki KC. Antiobesity effects of green tea catechins: a mechanistic review. *J Nutr Biochem* 2011; **22**: 1–7.
56 Gregoire FM. Adipocyte differentiation: from fibroblast to endocrine cell. *Exp Biol Med* 2001; **226**: 997–1002.
57 Hung PF, Wu BT, Chen HC, Chen YH, Chen CL, Wu MH *et al.* Antimitogenic effect of green tea (-)-epigallocatechin gallate on 3T3-L1 preadipocytes depends on the ERK and Cdk2 pathways. *Am J Physiol Cell Physiol* 2005; **288**: C1094–C1108.
58 Yang CS, Chen L, Lee M-J, Balentine D, Kuo MC, Schantz SP. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 351–354.

59 Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr* 2004; **79**: 727–747.
60 Furuyashiki T, Nagayasu H, Aoki Y, Bessho H, Hashimoto T, Kanazawa K *et al.* Tea catechin suppresses adipocyte differentiation accompanied by down-regulation of PPARγ2 and C/EBPα in 3T3-L1 cells. *Biosci Biotech Biochem* 2004; **68**: 2353–2359.
61 Chan CY, Wei L, Castro-Muñozledo F, Koo WL. (−)-Epigallocatechin-3-gallate blocks 3T3-L1 adipose conversion by inhibition of cell proliferation and suppression of adipose phenotype expression. *Life Sci* 2011; **89**: 779–785.
62 Gupta S, Ahmad N, Nieminen A-L, Mukhtar H. Growth inhibition, cell-cycle dysregulation, and induction of apoptosis by green tea constituent (-)-epigallocatechin-3-gallate in androgen-sensitive and androgen-insensitive human prostate carcinoma cells. *Toxicol Appl Pharm* 2000; **164**: 82–90.
63 Chen C, Shen G, Hebbar V, Hu R, Owuor ED, Kong A-NT. Epigallocatechin-3-gallate-induced stress signals in HT-29 human colon adenocarcinoma cells. *Carcinogenesis* 2003; **24**: 1369–1378.
64 Nihal M, Ahmad N, Mukhtar H, Wood GS. Anti-proliferative and proapoptotic effects of (-)-epigallocatechin-3-gallate on human melanoma: Possible implications for the chemoprevention of melanoma. *Int J Cancer* 2005; **114**: 513–521.
65 Sakurai N, Mochizuki K, Kameji H, Shimada M, Goda T. (-)-Epigallocatechin gallate enhances the expression of genes related to insulin sensitivity and adipocyte differentiation in 3T3-L1 adipocytes at an early stage of differentiation. *Nutrition* 2009; **25**: 1047–1056.
66 Morikawa K, Ikeda C, Nonaka M, Pei S, Mochizuki M, Mori A *et al.* Epigallocatechin gallate-induced apoptosis does not affect adipocyte conversion of pre-adipocytes. *Cell Biol Int* 2007; **31**: 1379–1387.
67 Chen L, Lee MJ, Li H, Yang CS. Absorption, distribution, and elimination of tea polyphenols in rats. *Drug Metab Dispos* 1997; **25**: 1045–1050.
68 Warden BA, Smith LS, Beecher GR, Balentine DA, Clevidence BA. Catechins are bioavailable in men and women drinking black tea throughout the day. *J Nutr* 2001; **131**: 1731–1737.
69 Lee MJ, Maliakal P, Chen L, Meng X, Bondoc FY, Prabhu S *et al.* Pharmacokinetics of tea catechins after ingestion of green tea and (−)-epigallocatechin-3-gallate by humans formation of different metabolites and individual variability. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1025–1032.
70 Löest HB, Noh SK, Koo SI. Green tea extract inhibits the lymphatic absorption of cholesterol and α-tocopherol in ovariectomized rats. *J Nutr* 2002; **132**: 1282–1288.
71 Klaus S, Pultz S, Thone-Reineke C, Wolfram S. Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation. *Int J Obesity* 2005; **29**: 615–623.
72 Wang S, Noh SK, Koo SI. Epigallocatechin gallate and caffeine differentially inhibit the intestinal absorption of cholesterol and fat in ovariectomized rats. *J Nutr* 2006; **136**: 2791–2796.
73 Koo SI, Noh SK. Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect. *J Nutr Biochem* 2007; **18**: 179–183.
74 Wang S, Noh SK, Koo SI. Green tea catechins inhibit pancreatic phospholipase A (2) and intestinal absorption of lipids in ovariectomized rats. *J Nutr Biochem* 2006; **17**: 492–498.
75 He Q, Lv Y, Yao K. Effects of tea polyphenols on the activities of α-amylase, pepsin, trypsin and lipase. *Food Chem* 2007; **101**: 1178–1182.
76 Naz S, Siddiqi R, Dew TP, Williamson G. Epigallocatechin-3-gallate inhibits lactase but is alleviated by salivary proline-rich proteins. *J Agr Food Chem* 2011; **59**: 2734–2738.
77 Koh LW, Wong LL, Loo YY, Kasapis S, Huang D. Evaluation of different teas against starch digestibility by mammalian glycosidases. *J Agr Food Chem* 2010; **58**: 148–154.
78 Forester SC, Gu Y, Lambert JD. Inhibition of starch digestion by the green tea polyphenol, (-)-epigallocatechin-3-gallate. *Mol Nutr Food Res* 2012; **56**: 1647–1654.
79 Matsui T, Tanaka T, Tamura S, Toshima A, Tamaya K, Miyata Y *et al.* α-Glucosidase inhibitory profile of catechins and theaflavins. *J Agr Food Chem* 2007; **55**: 99–105.
80 Lo Piparo E, Scheib H, Frei N, Williamson G, Grigorov M, Chou CJ. Flavonoids for controlling starch digestion: structural requirements for inhibiting human α-amylase. *J Med Chem* 2008; **51**: 3555–3561.
81 Shimizu M, Kobayashi Y, Suzuki M, Satsu H, Miyamoto Y. Regulation of intestinal glucose transport by tea catechins. *Biofactors* 2000; **13**: 61–65.
82 Hossain SJ, Kato H, Aoshima H, Yokoyama T, Yamada M, Hara Y. Polyphenol-induced inhibition of the response of Na+/glucose cotransporter expressed in Xenopus oocytes. *J Agric Food Chem* 2002; **50**: 5215–5219.
83 Liu J, Wang M, Peng S, Zhang G. Effect of green tea catechins on the post-prandial glycemic response to starches differing in amylose content. *J Agric Food Chem* 2011; **59**: 4582–4588.
84 Juhel C, Armand M, Pafumi Y, Rosier C, Vandermander J, Lairon D. Green tea extract (AR25®) inhibits lipolysis of triglycerides in gastric and duodenal medium *in vitro*. *J Nutr Biochem* 2000; **11**: 45–51.
85 Gondoin A, Grussu D, Stewart D, McDougall GJ. White and green tea polyphenols inhibit pancreatic lipase *in vitro*. *Food Res Int* 2010; **43**: 1537–1544.
86 Ikeda I, Tsuda K, Suzuki Y, Kobayashi M, Unno T, Tomoyori H *et al.* Tea catechins with a galloyl moiety suppress postprandial hypertriacylglycerolemia by delaying lymphatic transport of dietary fat in rats. *J Nutr* 2005; **135**: 155–159.
87 Grove KA, Sae-tan S, Kennett MJ, Lambert JD. (-)-Epigallocatechin-3-gallate inhibits pancreatic lipase and reduces body weight gain in high fat-fed obese mice. *Obesity* 2012; **20**: 2311–2313.
88 Wu X, He W, Li Y, Zhang H, Liu Z, Wang W *et al.* Characterization of binding interactions of (−)-epigallocatechin-3-gallate from green tea and lipase. *J Agric Food Chem* 2013; **61**: 8829–8835.
89 Armand M, Pasquier B, André M, Borel P, Senft M, Peyrot J *et al.* Digestion and absorption of 2 fat emulsions with different droplet sizes in the human digestive tract. *Am J Clin Nutr* 1999; **70**: 1096–1106.
90 Shishikura Y, Khokhar S, Murray BS. Effects of tea polyphenols on emulsification of olive oil in a small intestine model system. *J Agric Food Chem* 2006; **54**: 1906–1913.
91 Koo SI, Noh SK. Phosphatidylcholine inhibits and lysophosphatidylcholine enhances the lymphatic absorption of α-tocopherol in adult rats. *J Nutr* 2001; **131**: 717–722.
92 Qin B, Dawson HD, Schoene NW, Polansky MM, Anderson RA. Cinnamon polyphenols regulate multiple metabolic pathways involved in insulin signaling and intestinal lipoprotein metabolism of small intestinal enterocytes. *Nutrition* 2012; **28**: 1172–1179.
93 Casaschi A, Wang Q, Dang Ko, Richards A, Theriault A. Intestinal apolipoprotein B secretion is inhibited by the flavonoid quercetin: potential role of microsomal triglyceride transfer protein and diacylglycerol acyltransferase. *Lipids* 2002; **37**: 647–652.
94 Patel MS, Owen OE, Goldman LI, Hanson RW. Fatty acid synthesis by human adipose tissue. *Metabolism* 1975; **24**: 161–173.
95 Suganuma M, Okabe S, Oniyama M, Tada Y, Ito H, Fujiki H. Wide distribution of [3H](-)-epigallocatechin gallate, a cancer preventive tea polyphenol, in mouse tissue. *Carcinogenesis* 1998; **19**: 1771–1776.
96 Shrestha S, Ehlers SJ, Lee JY, Fernandez ML, Koo SI. Dietary green tea extract lowers plasma and hepatic triglycerides and decreases the expression of sterol regulatory element-binding protein-1c mRNA and its responsive genes in fructose-fed, ovariectomized rats. *J Nutr* 2009; **139**: 640–645.
97 Kaul D, Sikand K, Shukla A. Effect of green tea polyphenols on the genes with atherosclerotic potential. *Phytother Res* 2004; **18**: 177–179.
98 Kim HJ, Jeon SM, Lee MK, Jung UJ, Shin SK, Choi MS. Antilipogenic effect of green tea extract in C57BL/6J-Lep ob/ob mice. *Phytother Res* 2009; **23**: 467–471.
99 Murase T, Nagasawa A, Suzuki J, Hase T, Tokimitsu I. Beneficial effects of tea catechins on diet-induced obesity: stimulation of lipid catabolism in the liver. *Int J Obesity* 2002; **26**: 1459–1464.
100 Osada K, Funayama M, Fuchi S, Sami M, Ohta Y, Kanda T *et al.* Effects of dietary procyanidins and tea polyphenols on adipose tissue mass and fatty acid metabolism in rats on a high fat diet. *J Oleo Sci* 2006; **55**: 79–89.
101 Li RW, Douglas TD, Maiyoh GK, Adeli K, Theriault AG. Green tea leaf extract improves lipid and glucose homeostasis in a fructose-fed insulin-resistant hamster model. *J Ethnopharmacol* 2006; **104**: 24–31.
102 Chen N, Bezzina R, Hinch E, Lewandowski PA, Cameron-Smith D, Mathai ML *et al.* Green tea, black tea, and epigallocatechin modify body composition, improve glucose tolerance, and differentially alter metabolic gene expression in rats fed a high-fat diet. *Nutr Res* 2009; **29**: 784–793.
103 Hasumura T, Shimada Y, Kuroyanagi J, Nishimura Y, Meguro S, Takema Y *et al.* Green tea extract suppresses adiposity and affects the expression of lipid metabolism genes in diet-induced obese zebrafish. *Nutr Metab* 2012; **9**: 1–7.
104 Huang J, Zhang Y, Zhou Y, Zhang Z, Xie Z, Zhang J *et al.* Green tea polyphenols alleviate obesity in broiler chickens through the regulation of lipid-metabolism-related genes and transcription factor expression. *J Agric Food Chem* 2013; **61**: 8565–8572.
105 Yasui K, Paeng N, Miyoshi N, Suzuki T, Taguchi K, Ishigami Y *et al.* Effects of a catechin-free fraction derived from green tea on gene expression of enzymes related to lipid metabolism in the mouse liver. *Biomed Res* 2012; **33**: 9–13.
106 Lu C, Zhu W, Shen CL, Gao W. Green tea polyphenols reduce body weight in rats by modulating obesity-related genes. *PLoS One* 2012; **7**: e38332.
107 Habinowski SA, Witters LA. The effects of AICAR on adipocyte differentiation of 3T3-L1 cells. *Biochem Biophis Res Commun* 2001; **286**: 852–856.
108 Murase T, Misawa K, Haramizu S, Hase T. Catechin-induced activation of the LKB1/AMP-activated protein kinase pathway. *Biochem Pharmacol* 2009; **78**: 78–84.

109 Banerjee S, Ghoshal S, Porter TD. Phosphorylation of hepatic AMP-activated protein kinase and liver kinase B1 is increased after a single oral dose of green tea extract to mice. *Nutr Res* 2012; **32**: 985–990.
110 Lee MS, Kim CT, Kim Y. Green tea (-)-epigallocatechin-3-gallate reduces body weight with regulation of multiple genes expression in adipose tissue of diet-induced obese mice. *Ann Nutr Metab* 2009; **54**: 151–157.
111 Serisier S, Leray V, Poudroux W, Magot T, Ouguerram K, Nguyen P. Effects of green tea on insulin sensitivity, lipid profile and expression of PPARα and PPARγ and their target genes in obese dogs. *Br J Nutr* 2008; **99**: 1208–1216.
112 Park HJ, DiNatale DA, Chung MY, Park YK, Lee JY, Koo SI *et al*. Green tea extract attenuates hepatic steatosis by decreasing adipose lipogenesis and enhancing hepatic antioxidant defenses in ob/ob mice. *J Nutr Biochem* 2011; **22**: 393–400.
113 Lee MS, Kim CT, Kim IH, Kim Y. Inhibitory effects of green tea catechin on the lipid accumulation in 3T3-L1 adipocytes. *Phytother Res* 2009; **23**: 1088–1091.
114 Wolfram S, Raederstorff D, Wang Y, Teixeira SR, Elste V, Weber P. TEAVIGO (epigallocatechin gallate) supplementation prevents obesity in rodents by reducing adipose tissue mass. *Ann Nutr Metab* 2005; **49**: 54–63.
115 Ashida H, Furuyashiki T, Nagayasu H, Bessho H, Sakakibara H, Hashimoto T *et al*. Anti-obesity actions of green tea: possible involvements in modulation of the glucose uptake system and suppression of the adipogenesis-related transcription factors. *Biofactors* 2004; **22**: 135–140.
116 Granneman JG, Moore H-PH, Krishnamoorthy R, Rathod M. Perilipin controls lipolysis by regulating the interactions of AB-hydrolase containing 5 (Abhd5) and adipose triglyceride lipase (Atgl). *J Biol Chem* 2009; **284**: 34538–34544.
117 Caviglia JM, Betters JL, Dapito D-H, Lord CC, Sullivan S, Chua S *et al*. Adipose-selective overexpression of ABHD5/CGI-58 does not increase lipolysis or protect against diet-induced obesity. *J Lipid Res* 2011; **52**: 2032–2042.
118 Gandotra S, Lim K, Girousse A, Saudek V, O'Rahilly S, Savage DB. Human frame shift mutations affecting the carboxyl terminus of perilipin increase lipolysis by failing to sequester the adipose triglyceride lipase (ATGL) coactivator AB-hydrolase-containing 5 (ABHD5). *J Biol Chem* 2011; **286**: 34998–35006.
119 Cunha CA, Lira FS, Rosa Neto JC, Pimentel GD, Souza GI, da Silva CM *et al*. Green tea extract supplementation induces the lipolytic pathway, attenuates obesity, and reduces low-grade inflammation in mice fed a high-fat diet. *Mediat Inflamm* 2013; **2013**: 1–8.
120 Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiol Rev* 2004; **84**: 277–359.
121 Nomura S, Ichinose T, Jinde M, Kawashima Y, Tachiyashiki K, Imaizumi K. Tea catechins enhance the mRNA expression of uncoupling protein 1 in rat brown adipose tissue. *J Nutr Biochem* 2008; **19**: 840–847.
122 Murase T, Haramizu S, Shimotoyodome A, Nagasawa A, Tokimitsu I. Green tea extract improves endurance capacity and increases muscle lipid oxidation in mice. *Am J Physiol Regul Integr Comp Physiol* 2005; **288**: R708–R715.
123 Sae-tan S, Grove KA, Kennett MJ, Lambert JD. (−)-Epigallocatechin-3-gallate increases the expression of genes related to fat oxidation in the skeletal muscle of high fat-fed mice. *Food Funct* 2011; **2**: 111–116.
124 Sung HY, Hong CG, Suh YS, Cho HC, Park JH, Bae JH *et al*. Role of (−)-epigallocatechin-3-gallate in cell viability, lipogenesis, and retinol-binding protein 4 expression in adipocytes. *Naunyn Schmiedebergs Arch Pharmacol* 2010; **382**: 303–310.
125 Hsieh CF, Tsuei YW, Liu CW, Kao CC, Shih LJ, Ho LT *et al*. Green tea epigallocatechin gallate inhibits insulin stimulation of adipocyte glucose uptake via the 67-kilodalton laminin receptor and AMP-activated protein kinase pathways. *Planta Med* 2010; **76**: 1694–1698.
126 Lee H, Bae S, Yoon Y. The anti-adipogenic effects of (-) epigallocatechin gallate are dependent on the WNT/β-catenin pathway. *J Nutr Biochem* 2013; **24**: 1232–1240.
127 Kao YH, Hiipakka RA, Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. *Endocrinology* 2000; **141**: 980–987.