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Green tea and metabolic syndrome: A 10-year research update review

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ABSTRACT

Metabolic syndrome (MetS) has turned into a prevalent condition that has imposed a tremendous financial strain on public health care systems. It is believed that the MetS consists of four main factors (hypertension, dyslipidemia, hyperglycemia, and obesity) and may lead to cardiovascular events. *Camellia sinesis*, in the form of green tea (GT), is one of the most consuming beverages worldwide. Catechins are the dominant component of green tea leaves. Epigallocatechin gallate has the maximum potency. GT has been widely used as a supplement in various health conditions. As the oxidative stress pathway is one of the probable mechanisms of MetS etiologies and GT beneficial effects, GT may be a novel strategy to overcome the MetS. This review aims to reveal the probable pharmacological effects of GT on MetS. The last 10-year original articles on MetS parameters and GT have been gathered in this review. This manuscript has summarized the probable effects of green tea and its catechins on MetS and focused on each different aspect of MetS separately, which can be used as a basis for further investigations for introducing effective compounds as a way to interfere with MetS.
It seems that GT can reduce MetS parameters commonly via anti-inflammatory and anti-oxidative mechanisms. Further clinical trials are needed to confirm the use of GT and its constituents for the treatment of MetS.

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Introduction

Metabolic syndrome (MetS), which has also been named as "syndrome X", "Reaven syndrome" and "insulin resistance syndrome", was described by Reaven in 1988 for the very first time (1, 2). It is estimated that about 10% to 40% of the world population is suffering from the MetS. Excessive nutrient intake, sedentary lifestyle, and genetic factors are amongst predisposing causes to afflict people with MetS (3).

There is no complete agreement on the exact definition of MetS. According to the latest harmonized definition, MetS is a set of clinical signs including hypertension, dyslipidemia (comprises elevated triglycerides or reduced high-density lipoprotein (HDL) level), hyperglycemia, and central obesity. MetS diagnostic criteria is based on having 3 or more of the above components (1, 3). The implication to MetS would accelerate atherosclerosis which amplifies the risk of cardiovascular events. The etiology of MetS is not fully understood, but it is thought to be a proinflammatory and prothrombotic state (1). Treatment is based on prevention and lifestyle modification (3). In some of the previous studies, the effects of different herbals such as *Vitis vinifera* (4), *Crataegus pinnatifida* (5), *Rosmarinus officinalis* (6), *Allium sativum* (7), *Nigella sativa* (8), *Citrus paradisi* (9), *Capsicum annuum* (10), *Aloe vera* (11), *Berberis vulgaris* (12), *Persea americana* (13), *Silybum marianum* (14), *Garcinia mangostana* (15), *Crocus sativus* (16), *Cinnamomum verum* (17) and rutin (18) on MetS parameters had been reviewed.

The fresh leaves of *Camellia sinensis* are being consumed as white, green, oolong, and black tea based on the oxidation degree (19). Green tea (GT) is a universal herbal tea mostly used in Asia, some parts of North Africa, the United States, and Europe. This type of tea is known to have the most significant impact on human health (20, 21).

GT polyphenols or so-called catechins are known to be the main constituent in most of the beneficial effects of GT. Catechins include epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). The chemical structure of these compounds is shown in Figure 1. EGCG is the major component of GT polyphenols (21-23).

GT was included in "therapeutic compounds" of ancient times, and there are large sets of data on the medical properties of GT and its catechins. GT and its catechins have been studied in some diseases include obesity (24), diabetes(25), cardiovascular disease (26), dyslipidemia(27), cancer (28, 29), neurodegenerative disorders (30-32), antimicrobial (33) and antitoxin effects (34). Most of these beneficial properties are known to mediate through anti-oxidant properties (35).

Due to the increasing incidence of MetS in the last decades and because it is probably oxidative stress is one of the underlying mechanisms for expanding the disease

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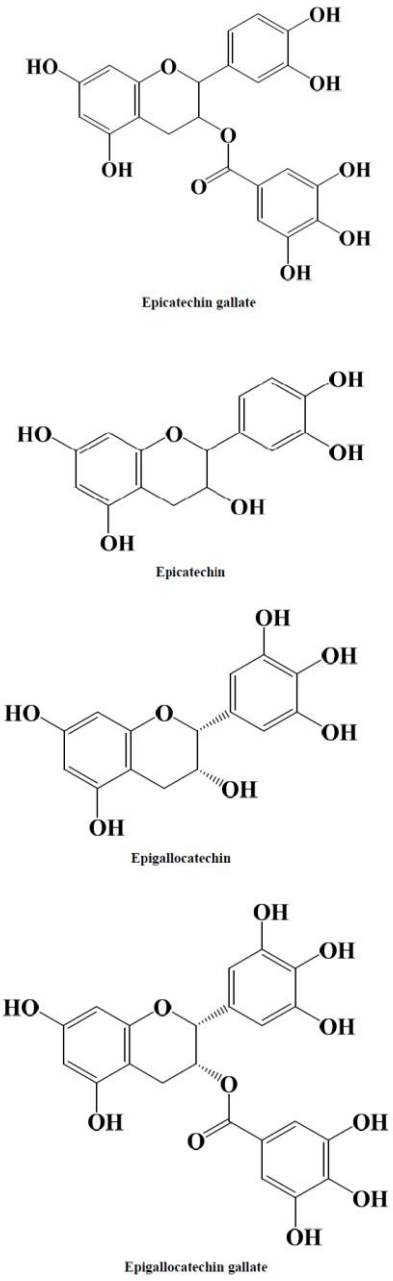

Figure 1. Chemical structures of green tea catechins

(1, 36), it is thought that adding herbal compounds with anti-oxidant properties such as GT and it's catechins to diet, may prevent or improve MetS. Moreover, the beneficial effects of GT on MetS factors have been widely investigated in the literature. Therefore, the data that have been reviewed here attempt to provide information about the effects of GT and its catechins on MetS components. The schematic description of the main GT's effects is shown in Figure 2.

Materials and Methods

The databases PubMed, Scopus, and Web of Science were used for hunting the related articles for the last decade (2009-2019). Due to the popularity of GT's beneficial effects, there were extensive articles on this

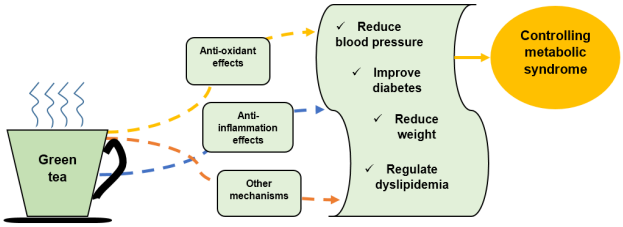

Figure 2. Schematic description of protective mechanisms of green tea on metabolic syndrome

topic; therefore, the authors have decided to include the newest experiments from 2009 onwards in this manuscript.

The keywords "Green tea", "*Camellia sinensis*" and "*Thea sinensis*" were used for GT and the keywords epicatechin, epicatechin-3-gallate, "epicatechin gallate", epigallocatechin, epigallocatechol, epigallocatechin-3-gallate, and "epigallo-catechin gallate" were used for the catechins.

The keywords for MetS include hypertension, "blood pressure", hypotensive, anti-hypertensive, diabetes, hyperglycemia, insulin, hypoglycemic, anti-hyperglycemic, anti-diabetic, "blood glucose", dyslipidemia, hyperlipidemia, "high cholesterol", "high triglyceride", hypercholesterolemia, hypertriglyceridemia, atherogenic, atherosclerosis, obesity, overweight, appetite, anti-obesity and "weight loss".

After finding 500 articles, the studies which used the combination of GT and other compounds or used modified-GT or the catechins of other herbs were excluded in this review article. The remaining original articles in animal or clinical models were selected exclusively.

Effects on metabolic syndrome

Animal studies

Animal models of MetS were induced through different mechanisms as drug-induced (37) and regimen-induced (38). Blood glucose (BG), triglycerides (TG) level, High density lipoprotein (HDL), low-density lipoprotein (LDL), blood pressure (BP), body weight (BW), and food intake were measured in the majority of studies as the most common indicators of MetS.

All of the animal experiments were done on rats except for one that used male mice as the MetS model. In mice, treatment with EGCG as a part of a high fat/Western-style diet (0.32%) for 17 weeks significantly attenuated body weight gain, BG, insulin resistance, and plasma cholesterol level in C57BL/6J mice (38).

Green tea extract (GTE) 200, 300 mg/kg, orally treated for 9 weeks decreased BP and improved the metabolic profile, adjusted adiponectin level, and adiponectin receptor gene expression and increased PPARα and PPARγ gene expression in MetS rat model (39-41). In another study, GT powder (10%) and GT ethanoic extract (5%) showed beneficial effects against hypercholesterolemia and hyperglycemia after 8 weeks (42). Razavi *et al.* found that GT aqueous extract at doses 25, 50, and 100 mg/kg/day (IP) for 11 days could modulate olanzapine-induced MetS parameters in rats (37).

Clinical studies

FBS, BP, lipid profile, and BW were amongst factors that were measured as MetS indicators (43-46). Water was used for the control group in some of the studies (43-45, 47).

In a series of randomized controlled trials with GT beverage (4 cups per day) and GTE (2 capsules per day) for 8 weeks in 35 obese subjects with MetS, plasma anti-oxidant capacity and whole blood glutathione were significantly increased. Likewise, plasma serum amyloid alpha (which is an independent risk factor for cardiovascular disease), BW, and BMI were significantly reduced, and lipid peroxidation was lowered (43, 44, 47).

An epidemiological study based on a self-administered questionnaire in the Korean population (n=15568, aged 19-65 years) revealed that regular consumption of GT beverage was inversely associated with MetS (48).

In a randomized control trial of 70 women with a confirmed diagnosis of MetS, anthropometric indices, BP, BG, and lipid profile significantly improved after drinking 200 ml of GT 3-times per day for eight weeks (45).

In an interventional study, Senger *et al.* concluded that consumption of three cups of GT (as 1 g sachets) for 60 days, induced weight loss, reduced BMI and waist circumference in 45 elderly with MetS, although not changing their lipidic and glycemic profile (46).

Effects on dyslipidemia

Animal studies

Different models have been developed to assess the beneficial effects of GT. Serving an atherogenic diet that contains high fat, cholesterol, and sugar was used in a series of work (27, 49-51). Intraperitoneal (IP) injection of EGCG (100 mg/kg/day) from day 31 of a 45-day atherogenic regimen in rats significantly alleviated inflammation markers such as C-reactive protein (CRP), which was increased due to the atherogenic diet (51). In a similar study with rats feeding an atherogenic diet followed by 7-15 days of GT catechin (100 mg/kg IP), the hepatic anti-oxidant profile improved (50).

Adding dextran sodium sulfate (DSS) to the drinking water of rats feeding an atherogenic diet, leading to dyslipidemia, increasing inflammation, and hepatic toxicity markers, which was diminished by GTE supplementation (0.2% in the diet) for 4 weeks (27).

Treatment of rats with sodium fluoride (25 mg/kg) for 4 weeks is another model which been used in the study of Miltonprabu and Thangapandiyan. Pre-administration of EGCG (40 mg/kg) protected the intoxicated rats against dyslipidemia and cardiotoxicity (52).

Apo lipoprotein-E knockout mice, which is a well-established model for human atherosclerosis, have been used along with a high-fat diet (HFD) (53-55). The intragastric administration of EGCG (40 mg/kg/d for 18 weeks) significantly suppressed atherosclerotic plaque formation and lipid accumulation in the liver and also modulated dyslipidemia (53). In a similar study, GT polyphenols (3.2 or 6.4 g/l in drinking water for 15 weeks) significantly suppressed the atherogenesis rate through lipid metabolism improvement and increasing the expression of hepatic PPARα and autophagy markers in the mice vessel walls (55). Cai *et al.* used *Porphyromonas gingivalis* as an auxiliary factor for accelerating atheroma formation in the proximal aorta. EGCG supplementation (via drinking water for 15 weeks) suppressed atherosclerosis lesions through anti-inflammatory and anti-oxidative effects (54).

Furthermore, EC (0.1% w/w in diet) alleviated atherosclerosis development and restrained progression from mild to severe lesions with no effect on dyslipidemia in apoE*3-Leiden mice fed an atherogenic diet probably through anti-inflammatory pathways (49).

LDL receptor knockout murine model fed a hypercholesterolemic diet has been used by Minatti *et al.* GTE at low doses (50, 100 mg/kg/day by gavage) reversed endothelial dysfunction which has led to reduction of atherosclerosis progression along with lowering plasma TG and Monocyte chemoattractant protein-1 (MCP-1) level (56).

Other studies about the effects of GT on dyslipidemia parameters are shown in Table 1.

Clinical studies

TG, HDL, LDL, and total cholesterol levels were the most prevalent indicators of dyslipidemia which were measured in the available clinical studies about GT.

The first study was a randomized, multicenter placebo-controlled, double-blind study of 30 patients with hypertriglyceridemia, aged 18-55 years old, who were given a total daily dose of 100 mg EC in the form of 25 mg capsules for 4 weeks. It is concluded that EC could have an integrated positive metabolic response which may be beneficial in cardiovascular disease risk (57).

Another study was done with 250 mg capsules of GTE and placebo for 8 weeks in 33 patients, aged 21-71 years old, with a low-fat diet (25-35% of total calories and 200 mg of cholesterol per day) as a prospective, double-blind crossover study. LDL-cholesterol levels and total cholesterol were significantly reduced, which demonstrates the profitable effects of GT (26).

One double-blind, placebo-controlled trial in 56 obese, hypertensive subjects caused a remarkable attenuation in LDL, total cholesterol, and TG and increased HDL after giving 1 GTE capsule daily for 3 months (25). EC (1 mg/kg 30 min before tests) lowered TG concentrations by boosting lipid oxidation in 20 normal weight and overweight subjects in a pilot crossover, open-labeled study (58). GTE reduced LDL but showed no effect on total cholesterol, TG, and HDL after a 6-week GTE consumption in obese and overweight women (59). In 120 overweight women, daily GT capsules for 12 weeks remarkably lowered total cholesterol and LDL levels in a double-blind study (60). In another clinical trial, consuming the GT formula for 12 weeks in overweight or obese subjects caused significant effects on total cholesterol and LDL levels [79]. Moreover, a remarkable improvement in TG and HDL levels was reported after GTE consumption (500 mg TDS) for 16 weeks in 92 type-2 diabetes (T2D) and dyslipidemia subjects in a double-blinded, randomized and placebo-controlled clinical trial (61)

Effects on Obesity

Animal studies

Obesity-related effects that are commonly reported in the studies include reduction of BW (38, 62-73), decline

Table 1. Effects of green tea and it's components on dyslipidemia in animal studies

Treatment features	Model	Effects	Reference
Catechins and EGCG in functional drinks – 56 days	Rats fed high cholesterol and high sucrose diet	Cholesterol and LDL reduction	(73)
Catechins and EGCG in functional drinks	Rats fed high cholesterol and high sucrose diet	Improving serum anti-oxidant potential	(136)
GT ethanolic extract and powder – 8 weeks	Rats	Beneficial effects against hypercholesterolemia	(42)
GT 1% (w/v) in drinking water- last week of the 5-week study course	Rats fed a high cholesterol diet	COX-2 downregulation, oxidative DNA damage reduction, no significant effect on cholesterol level	(137)
GTE 50 mg/kg/day orally	HfrD fed rats	Decreasing myocardial fibrosis, increasing hepatic catalase activity	(138)
GT given as protective regimen (PG) and curative regimen (CG)	Rats fed a Hypercholesterolemic diet	Significant improvement of dyslipidemia, lower SOD activity in CG, stronger liver protection in PG, a significant decrease in Atherogenic Index	(139)
GTP in drinking water	Diet-induced obese rats	Reduced liver TG level	(62)
GTC	Diet-induced obese rat	Decreased liver TG levels	(68)
GTE 1 or 2 g/kg in a diet for 6 weeks	HFrD fed rats	Decreased TG levels	(103)
GT 500 mg/kg/day, 5days/week for 12 weeks	Diet-induced obese rat	Reduced liver and plasma lipid content, increased fatty acid oxidation	(70)
GTE	Diet-induced obese rat	Anti-lipidemia properties	(83)
GT 0.2 or 1 g/kg/day for 4 weeks	Spontaneously hypertensive rats	No effect on plasma total cholesterol	(126)
GT + GTC 30 or 100 mg	T2D rats	Decreased serum cholesterol, TG, LDL, vLDL	(140)
GTE 0.75% or 1.0% in diet	HFD fed rats born of obese dams	Decreased liver TG in offspring	(141)
GTP 200 mg/kg/day in drinking water for 6 weeks	HFrD fed rats	Attenuation of cholesterol, TG, and LDL	(104)
EGCG	Rabbits	Decreasing lipid deposition	(142)
EGCG oral and IP consecutive treatment for 14 days	Mice	Increasing serum lipids, hepatotoxicity (reversible)	(143)
EGCG	Diet-induced obese mice	Improved serum lipid profiles	(65)
GT added to the diet	Diet-induced obese mice	Reduced TG	(81)
EGCG as in situ hydrogel SC implant for 1 month	Diet-induced obese mice	Decreased total cholesterol, TG and LDL, increased HDL	(63)
EGCG 10, 20 and 40 mg/kg/day IP for 4 weeks	non-alcoholic fatty liver disease (NAFLD) mice	Modulate hyperlipidemia	(110)
EGCG supplementation for 12 weeks	senescence-accelerated mice (SAM) prone 8 (SAMP8)	Prevention of hepatic liver accumulation, modulate lipid homeostasis in skeletal muscles and liver	(98)
GTP 50,100 mg/kg for 20 days	Chicken	Reduced serum TG, cholesterol, and LDL levels suppressed fatty acid synthesis	(74)

GT: green tea; EGCG: Epigallocatechin gallate; GTE: green tea extract, GTP: green tea polyphenols; GTC: green tea catechin; HFD: high-fat diet; HfrD: high fructose diet; T2D: type-2 diabetes; IP: intraperitoneal; SC: subcutaneous; SOD: superoxide dismutase

in fat mass (67, 71, 72, 74, 75) or body organs weight (68, 69), and modifying gut microbiomes (67, 76).

The mentioned effects are thought to occur via different mechanisms, as shown in Figure 3. Molecular mechanisms consist of modulating PPAR (68, 74, 77), 5' AMP-activated protein kinase (AMPK) (70), or insulin-like growth factor-binding protein 1 (IGFBP-1) (78). The effects on obesity-related gene expression (62) are also considered to be another molecular mechanism. Moreover, the systemic effects of GT consist of anti-oxidant (69) and anti-inflammatory effects (38, 62, 64, 65, 67, 71, 79) and hormonal mechanisms through decreasing leptin level (72, 80, 81) and estrogen-dependent effects (62) have been considered in several articles. The enzymatic mechanisms such as inhibiting alpha-amylase activity (82), metabolic mechanisms such as reducing lipogenesis (67, 70) and stimulating lipolysis (64, 71, 74), and gastrointestinal mechanisms through decreasing lipid absorption (38, 72) and digestion (66) are amongst other probable effects of GT.

Most of the studies used mice fed with the HFD diet as an obesity model. Except for several studies that used rats (68, 70, 73, 83) and a work by Huang that used chickens as a model (74).

The preventive role of GT in obesity was assessed in several studies. It is thought that supplementation with

Figure 3. Different mechanisms for anti-obesity effects of green tea

GT polyphenols for 3 weeks, may prevent obesity in mice fed with HFD due to the prebiotic-similar activities (76). IGFBP-1, a novel molecule in obesity prevention, was elevated in white adipose tissue by adding GT to drinking water for 14 weeks (78). Other study protocols have been reviewed in Table 2.

Clinical studies

In a single-blind, placebo-controlled, parallel clinical trial on a population of the north of Iran, GT (a cup of GT half an hour after breakfast and lunch for 12 weeks) was introduced as an efficient option in obesity owing to the remarkable effects on BW, BMI, waist and hip circumferences (84). A 12 weeks' treatment with high dose GTE (containing 857 mg EGCG) in women with central obesity, made a remarkable weight loss in a randomized, double-blind study (85). Another 12 weeks clinical trial by consuming the GT formula in overweight or obese subjects showed greater weight loss and body fat mass reduction than the control group (86). Using 500 mg GT tablets for 8 weeks in overweight men caused a significant attenuation in BW, BMI, and waist-hip ratio in a semi-experimental study (87)

Several studies were done to understand the

Table 2. Effects of green tea and it's components on obesity in animal studies

Treatment features	Model	Effects	Reference
FGT extract	Diet-induced obese mice	Reduced BW and fat mass with no effect on food intake, downregulation of lipogenic and inflammatory genes, modulation of gut microbiomes	(67)
EC in diet	Diet-induced obese mice	Downregulation of inflammation-related genes	(79)
EGCG in the diet for 17 weeks	Diet-induced obese mice	Reduced BW and inflammatory cytokines, increased fecal lipids	(38)
EGCG	Diet-induced obese mice	Reduced BW and fat infiltration in liver tissue, anti-inflammatory effects	(65)
EGCG- 10 mg/kg/day through gavage for 2 weeks	Diet-induced obese mice	Reduced fat mass, normalizing inflammatory and oxidative markers	(75)
GT added to the diet	Diet-induced obese mice	Reduction of adipose tissue, modulation of leptin level	(81)
EGCG for 17 weeks	Diet-induced obese mice	Reduced BW, liver and kidney weight	(69)
GTE 400 mg/kg through gavage for 8 weeks	Diet-induced obese mice	Reduced BW and adipose tissue and inflammatory cytokines, increased lipolysis	(71)
EGCG as in situ hydrogel SC implant for 1 month	Diet-induced obese mice	Modulation of weight gain	(63)
GT 2% in the diet	Diet-induced obese mice	Reduced BW, fat mass, liver weight, induced lipolysis, anti-inflammatory effects	(64)
EGCG oral administration for 30 days	Diet-induced obese mice	Inhibition of alpha-amylase activity reduced lipid accumulation	(82)
GTE in the diet for 8 weeks	Diet-induced obese mice	Reduced BW and fat mass, Modulation of PPAR-delta	(77)
EGCG 50 mg/kg/day for 10 weeks	Mice fed HFD	Decreased BW increment	(101)
GT 500 mg/kg for 12 weeks	HFD fed mice	Reduced BW, increased energy expenditure	(102)
GTE in diet in 3 regimens: GTE 1g/kg of diet for 3 days, GTE 1g/kg of diet for 28 days, GTE 0.1g/kg of diet for 28 days	Glutamate induced obese mice	No effect on average BW, decreased food intake in third regimen, reduced leptin level in the first regimen	(144)
GTE	Monosodium glutamate treated mice model	Decreased leptin levels	(80)
EGCG in drinking water for 3 days	Dextran sulfate sodium-treated mice model	Reduced BW, decreased protein and lipid digestion, anti-inflammatory effects	(66)
Green tea polyphenon E 0.1% in the diet for 7 weeks	db/db mice (leptin deficiency model)	Decreased mesenteric fat	(145)
GTE 2% in the diet for 8 weeks	RGS10 knockout mice fed a HFD	Suppressed HFD-induced obesity	(100)
EGCG 10, 20 and 40 mg/kg/day IP for 4 weeks	non-alcoholic fatty liver disease (NAFLD) mice	Reduced BW	(110)
GTC	Diet-induced obese rat	Modulation of BW and liver weight, modification of PPAR	(68)
GT 500 mg/kg/day, 5days/week for 12 weeks	Diet-induced obese rat	Reduced-fat synthesis, BW and fat depots, AMPK activation, modulation of metabolism-related genes	(70)
Green tea polyphenols in drinking water	Diet-induced obese rat	Reduced BW, Regulation of orexigenic, anorectic, and energy expenditure-related genes, modulation of anti-inflammation and anti-oxidant effects, estrogen-related actions	(62)
Green tea as functional drinks for 56 days	Diet-induced obese rat	Reduced BW	(73)
GTE	Diet-induced obese rat	Anti-obesity properties	(83)
GTE	Rat	Decreased BW, fat mass, and leptin levels, increased fecal lipids, and total daily energy consumption	(72)
GTE (2 or 4g/kg in diet)	NaCl-induced hypertensive rats	No effect on body mass	(128)
GTP 50,100 mg/kg for 20 days	Chicken	Reduced-fat masses, downregulation of lipid anabolism genes, and upregulation of lipid catabolism genes	(74)

BW: body weight; FGT: fermented green tea; EC: epicatechin; EGCG: epigallocatechin gallate; GT: green tea; GTE: green tea extract; GTC: green tea catechin; GTP: green tea polyphenols; SC: subcutaneous; HFD: high-fat diet; PPAR: Peroxisome Proliferator-Activated Receptor; AMPK: 5' AMP-activated protein kinase; RGS10: Regulator of G-protein Signaling 10

catechins' effects. In a pilot crossover, the open-labeled study of 20 normal weight and overweight subjects were given 1 mg/kg of EC 30 min before the tests, the fat oxidation increased following a meal which was more vigorous in overweight subjects (58). Moreover, a low dose of ECGC (300 mg orally for 3 days) intensified fat oxidation in obese men after a meal. However, it did not show any effects on energy consumption in a randomized, placebo-controlled, double-blind crossover trial (88). In another study, 14 healthy volunteers given 300 ml GT with breakfast reported remarkably higher satiety and lower desire to eat rather than the control group in a randomized controlled trial (89). An 8-week-period study with GT in 58 T2D patients with BMI ≥ 25 showed a significant reduction in weight and BMI in a double-blind randomized clinical trial (90). Another randomized clinical trial also reported considerable mitigation in BW, BMI, and waist circumference in T2D patients drinking 4 cups of GT daily (91).

One of the studies was done on a special population i.e., overweight polycystic ovary syndrome (PCOS) women. In this double-blind, placebo-controlled, randomized clinical trial on overweight PCOS women, GT tablets (twice daily) reduced BW significantly 12 weeks after the intervention (92).

On the other hand, some of the scientific papers revealed little to no effect of GT on obesity. For instance, EGCG (300 mg/d in the diet for 12 weeks) had no effects on energy-restricted diet-induced adiposity deprivation and weight-loss-induced alterations in cardiometabolic risk factors in obese Caucasian women in a randomized, double-blind, placebo-controlled study (93). A 6 weeks' intervention with GTE effectively elevated leptin levels, although not affect other overweight-related biochemical markers in obese and overweight women (59). In another randomized trial, GT supplementation (3 cups/day for 10 weeks) did not demonstrate any effects on apelin and orexin-A in obese women (94). Finally, In a controlled, randomized clinical trial in overweight or obese subjects, GT (5 g/day for 8 weeks) had no remarkable effects on leptin and paraoxonase (PON-1), which is an indicator of inflammation (95).

Effects on diabetes

Animal studies

GT has valuable effects on BG and insulin levels and improves insulin resistance. The underlying mechanisms for these effects were discussed in several studies that are being introduced briefly.

As a result of diabetes-induced regimens, the activation of insulin signaling cascade members (such as insulin receptor, insulin receptor substrate-1 (IRS1), Protein kinase B (Akt), and Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2) diminished and negative modulators (such as Protein Kinase C (PKC), IkappaB kinase beta (IKK), c-Jun N-terminal kinase (JNK), and protein tyrosine phosphatase 1B (PTP1B) augmented. Supplementation with EC could prevent these alterations (96). Moreover, the downregulation of the inhibitory molecules PKC, IKK, JNK, and PTP1B by EC led to the attenuation of obesity-related insulin resistance (97). Supplementation with EGCG (for 12 weeks) diminished BG and insulin levels through restoring Akt activity and Glucose transporter type 4 (GLUT4) expression and enhancing AMPKα activation in skeletal muscle (98). Other experiments which discussed the beneficial effects of GT on these molecules are shown in table 3 (99).

Some studies showed that inflammation is involved in insulin resistance (79, 100-104). In one study, the regulator of G-protein Signaling 10 (RGS10) deficiency, which could intensify HFD-induced insulin resistance and inflammation, was restrained by GTE (100). Otton *et al.* concluded that MicroRNA (miR)-335 links inflammation to impaired metabolism in adipose tissue, which was decreased by GT treatment (500 mg/kg for 12 weeks) in HFD-fed mice (102).

Oxidative stress is another possible mechanism for GT's effects. In one study, dietary EGCG reduced advanced glycation end products (AGE) level, inhibited the AGE receptor, and enhanced reduced glutathione/oxidized glutathione ratio (GSH/GSSG ratio) (69). There are other studies in this regard that are mentioned in table 3 (103, 105-107). In another experiment, GT treatment restored oxidative and inflammation parameters in the retina, and it was suggested for the treatment of diabetic retinopathy (108).

One study introduced the immune system in the favorable effects of GT. EC regulated immune function (by increasing interleukin-10 level), reduced pancreatic insulitis, and also improved pancreatic islet mass, which led to type-1 diabetes prevention(109).

EGCG boosted insulin clearance by hepatic Insulin-degrading enzyme (IDE), which led to improving insulin resistance in a dose-dependent manner (110). Furthermore, EGCG (10 μM) given to diabetic pregnant mice resulted in a lower rate of neural tube defect incidence. Therefore, it is thought that GT can attenuate hyperglycemia-induced teratogenic effects (111). The studies about the correlation between GT and diabetes are shown in Table 3.

Clinical studies

The results of the clinical studies in this area are contradictory. Some studies reported valuable effects from GT on diabetes parameters.

In a double-blind, placebo-controlled trial in 56 obese, hypertensive subjects, daily supplementation with 1 capsule of GTE (379 mg) for 3 months led to a significant reduction in fasting serum glucose, insulin level, and insulin resistance. Also, mitigation in serum (Tumor Necrosis Factor-α) TNF- α and CRP level and an increase in total anti-oxidant status was observed (25). Another study revealed that GTE (500 mg TDS for 16 weeks) remarkably improved insulin resistance and augmented glucagon-like peptide 1 in 92 T2D and dyslipidemia subjects in a double-blinded, randomized, and placebo-controlled clinical trial (61). One cross-sectional observational study on 75 healthy volunteers and 75 T2D patients concluded that GT could lower BG in diabetic subjects (112).

In a comparative study between usual and high doses of GT in healthy adolescents, higher doses of GT reduced postprandial blood glucose (PBG) level. Hence, higher doses were recommended for better control of PBG (113). In another cross-sectional study in 35 male

Table 3. Effects of green tea and it's components on diabetes in animal studies

Treatment features	Model	Effects	Reference
EGCG 10 mg/kg/day in drinking water GTE 10 mg/kg/day in drinking water	Mice administered 30% glucose	No significant effect on FBG, IPGTT, gAUC, insulin resistance, and HOMA-B, increasing insulin level	(146)
GTE in diet in 3 regimens: GTE 1g/kg of diet for 3 days, GTE 1g/kg of diet for 28 days, GTE 0.1g/kg of diet for 28 days	Glutamate induced obese mice	No effect on anti-oxidation systems, a significant reduction in insulin level	(144)
Green tea polyphenon E 0.1% in the diet for 7 weeks	db/db mice (leptin deficiency model)	Decreased FBG, increased insulin level	(145)
EC 20 mg/kg in the diet for 15 weeks	HFD-induced insulin resistance in mice	Improved insulin sensitivity	(97)
EC 2-20 mg/kg	HFD-induced insulin resistance in mice	Attenuation of insulin resistance	(107)
GTE 2% in the diet for 8 weeks	RGS10 knockout mice fed a HFD	Regulation of impaired glucose tolerance test and insulin resistance	(100)
EC 0.5% in drinking water	Non-obese diabetic mice	Increased plasma insulin level, decreased HbA1C concentrations	(109)
EGCG 0.05% in drinking water	Non-obese diabetic mice	Increased plasma insulin level, decreased HbA1C concentrations	(147)
EGCG 10, 20 and 40 mg/kg/day IP for 4 weeks	non-alcoholic fatty liver disease (NAFLD) mice	Mitigation of hyperglycemia, hyperinsulinemia, and insulin resistance in a dose-dependent manner	(110)
EGCG 50 mg/kg/day for 10 weeks	Mice fed HFD	Improved insulin sensitivity and glucose tolerance	(101)
EGCG supplementation for 12 weeks	senescence-accelerated mice (SAM) prone 8 (SAMP8)	Improved insulin sensitivity by attenuating BG and insulin level	(98)
GT 500 mg/kg for 12 weeks	HFD fed mice	Improved insulin sensitivity	(102)
EGCG 25 or 75 mg/kg i.p 3times/week for 17 weeks	HFD fed C57BL/6 mice	Remarkably reduced plasma glucose and insulin level	(69)
EC 200 mg/kg in diet	HFD fed C57BL/6 mice	Protection from insulin resistance	(79)
EGCG 1 or 10 μM in drinking water at embryonic day 5.5	Diabetic pregnant mice	EGCG 10 μM remarkably reduced neural tube defect incidence	(111)
FGT extract	Diet-induced obese mice	Decreased glucose intolerance	(67)
GT added to the diet	Diet-induced obese mice	Reduced BG and insulin levels	(81)
EGCG oral administration for 30 days	Diet-induced obese mice	Decreased serum glucose	(82)
GTE	Monosodium glutamate treated mice model	Decreased insulin levels	(80)
GTE 1 or 2 g/kg in the diet for 6 weeks	HFrD fed rats	Decreased glucose an insulin level, improved insulin resistance	(103)
Functional drinks containing catechins and EGCG	High cholesterol and high sucrose diet-fed rats	Mitigation of serum glucose and insulin levels	(73)
EGCG 3.2 g/kg in the diet for 16 weeks	HFD fed rats	Decreased fasting plasma insulin and homeostasis model assessment-insulin resistance index, increased glucose infusion rate	(148)
EC 20 mg/kg in the diet for 8 weeks	HFrD fed rats	Attenuation of insulin resistance	(96)
GT ad libitum for up to 90 days	T1D rats	Mitigation of periodontal breakdown and prevention of vascular disturbances	(149)
EGCG 50 mg/kg/day orally for 2 months	IDDM rats	Increased cardiac function synergistically with stem cell treatment	(150)
EGCG	Streptozotocin and HFD induced diabetic rats	Significant reduction in the expression and activity of P-glycoprotein	(151)
GT + GTC 30 or 100 mg	T2D rats	Decreased serum glucose level (more severe in GT+100 mg GTC)	(140)
GT in drinking water for 21 days	Streptozotocin-induced diabetic rats	Reduced hyperglycemia	(152)
GTE 200 mg/kg orally for 16 weeks	Streptozotocin-induced diabetic rats	Reduced BG and Hba1c level	(108)
GTE 0.75% or 1.0% in diet	HFD fed rats born of obese dams	Reduced insulin resistance in offspring	(141)
EGCG IV infusion with intralipid-heparin for 48 hrs	Over-night fasted rats	Remarkably prohibited free fatty acid-induced peripheral insulin resistance	(153)
EGCG 2g/l as a beverage for 10 weeks	Streptozotocin-induced diabetic rats	Prevention of diabetes-induced loss of cavernous smooth muscle with no effect on vascular growth factor expression	(154)
GTP 200 mg/kg/day in drinking water for 6 weeks	HFrD fed rats	Mitigation of blood glucose and plasma insulin, improved insulin signaling	(104)
EGCG 25 mg/kg/day for 8 weeks	Streptozotocin-induced diabetic rats	Reduced glucose level	(105)
EGCG 1 or 10 mu mol/l	Day-9 rat conceptuses cultures	Attenuation of vasculopathy and malformations induced by hyperglycemia	(99)
Green tea ethanolic extract and powder – 8 weeks	Hyperglycemic rats	Reduced serum glucose level	(42)
GTP in drinking water	Diet-induced obese rat	Reduced BG, insulin resistance	(62)
GT 500 mg/kg/day, 5days/week for 12 weeks	Diet-induced obese rat	Restpred insulin sensitivity	(70)
GTC 150 or 300 mg/kg/day in the diet for 4 weeks GTC 20 mg/kg/day in diet for 45 days	HFD fed KK-ay and C57BL/6 mice HFD fed rats	Attenuated glucose level and enhanced glucose tolerance	(106)

FGT: fermented green tea; EC: epicatechin; EGCG: epigallocatechin gallate; GT: green tea; GTE: green tea extract; GTP: green tea polyphenols; GTC: green tea catechin; HFD: high-fat diet; RGS10: Regulator of G-protein Signaling 10; HFrD: high fructose diet; T1D: type-1 diabetes; T2D: type-2 diabetes; IDDM: Insulin-dependent diabetes mellitus; BG: blood glucose; FBG: fasting blood glucose; HOMA: homeostatic model assessment; IPGTT: intraperitoneal glucose tolerance test; gAUC: glucose area under the curve; Hba1c: glycosylated hemoglobin A1c

volunteers in Japan, the lowering effects of 3% GT on fasting blood glucose (FBG) and fructosamine tended to be higher than 1% concentration. However, the frequency of drinking did not affect these parameters (114).

EGCG used as dietary supplementation in the third semester of 472 pregnant women with Gestational diabetes mellitus successfully improved maternal diabetic parameters and mitigated the number of neonatal incidents in a double-blind randomized controlled trial (115).

In a pilot crossover, open-labeled study, 1 mg/kg EC was given to 20 normal weight and overweight subjects 30 min before the tests. EC remarkably reduced postprandial plasma glucose (PPG), which was more prominent in overweight subjects (58).

In a double-blind, crossover design short term GTE consumption (1050 mg/day for 7 days) in 11 sedentary subjects, overweight men did not affect PBG at rest, but reduced PPG after exercise, which is thought to be through alterations of glucose uptake in skeletal muscle (116). One randomized, double-blind placebo-controlled trial of GTE (300 or 600 or 900 mg/day) in 51 T2D patients indicated that stimulation of Soluble receptor for advanced glycation end products (sRAGE) production, which led to the receptor for advanced glycation end-products (RAGE) ligand inhibition is one of the underlying mechanism for EGCG effects in diabetes (117). One more mechanistic study targeted increased adiponectin level as the main mechanism for the T2D controlling effect of an 8-week-period of GT consumption which led to improving glycosylated hemoglobin A1c (HbA1C) levels in 58 T2D patients with BMI≥25 in a double-blind randomized clinical trial (90). In a two-group, double-blind, placebo-controlled, randomized clinical trial GT tablets (twice daily) reduced fasting insulin in 60 overweight PCOS women after 12 weeks (92). Daily GT capsules for 12 weeks reduced fasting glucose in 120 overweight women in a double-blind study (60).

On the other hand, some experiments showed no to less effect from GT consumption. In a randomized controlled trial on 40-65 years old overweight or obese male subjects, no observable effect on glucose tolerance, insulin sensitivity, or insulin secretion was reported from EGCG capsules (400 mg BD for 8 weeks)(118). In another randomized controlled trial, 14 healthy volunteers were given 300 ml of GT or water together with the same breakfast. Postprandial glucose levels 120 min after ingestion GT containing meal were higher. Moreover, there were not any significant differences in serum insulin levels and glucose/insulin area under the curve (AUC) (89).

In a survey of Shanghai health study, data on type and amount of tea drinking habits were collected and the incident of T2D was assessed through follow-up surveys. This survey revealed that the risk of T2D was higher in the current GT drinkers (119). In one randomized human cohort of GT (3 cups daily for 14 weeks followed by a 2-week washout period) in pre-diabetic subjects, it is concluded that the timescale was not enough to exhibit GT effects on fasting plasma glucose and HbA1c (120).

Effects on hypertension

Animal studies

There are 2 similar studies by Gomez *et al.* about the effects of EC on hypertension. The first study revealed that 4 weeks oral administration of EC (2 or 10 mg/kg) in (N(G)-Nitro-L-arginine methyl ester) (L-NAME)-induced hypertensive rats had no effect on hypertension development, a weak effect on endothelial dysfunction induced by L-NAME and prevented the cardiac hypertrophy. By blocking nitric oxide (NO) production, EC suppressed the proatherogenic and proinflammatory status of the vascular wall (121). The second study was done in 11-deoxycorticosterone (DOCA)-salt-induced hypertensive rats and improvements in systolic blood pressure (SBP), proteinuria, and vascular dysfunction by the high dose of EC were recorded probably via oxidative stress suppression and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity inhibition (122). One similar experiment about the effect of 28 days of low EC (1 mg/kg/day) in DOCAsalt-induced hypertensive rats showed the regulation of myocardial stiffness and left ventricular compliance, reduction of BP, and malondialdehyde (MDA) concentration with no effect on cardiac hypertrophy (123).

L-NAME hypertensive rats that were given GT ad libitum for 1 week showed a reduction in hypertension and improved arterial baroreceptor function through the mitigation of vascular and systemic oxidative stress (124). In a study of high fructose diet-fed rats which were supplemented with EC (20 mg/kg), BP increment was suppressed, oxidative stress was diminished and nitric oxide synthase (NOS) activity was boosted (125).

One comparative study between low dose (0.2g/kg/day) and high dose (1 g/kg) of GT for 4 weeks in spontaneously hypertensive rats reported suppression of SBP increment and dose-dependent protection of left ventricular myocardium and aortic vascular smooth muscle cells from oxidative damages (126).

A mechanistic study was designed to determine the involvement of miRNA in the anti-hypertensive effect of EGCG and it was found that miRNA-150-5p is responsible for this effect (127). Another study undertook several mechanisms such as anti-inflammatory and anti-oxidant pathways for GTE (2 or 4g/kg in diet) beneficial effects on NaCl-induced hypertensive rats (128).

An experiment by Wang *et al.* was done on the effects of EGCG on HTN-induced disorders. In addition to the anti-hypertensive effects, EGCG regulated impaired learning, memory, and locomotor activity, which is thought to be through anti-oxidative mechanisms (129).

In 2 studies by Yi *et al.* 4 weeks of bilateral PVN hypothalamic paraventricular nucleus (PVN) infusion of EGCG (20 μg/h) via osmotic minipumps in spontaneously hypertensive rats model and renovascular hypertensive rats model, resulted in anti-hypertensive effects which seemed to be through the suppression of inflammation and oxidative stress and led to regulation of neurotransmitters in PVN, helping to improve hypertension (130, 131).

Clinical studies

There are a limited number of clinical studies about the effects of GT on hypertension.

A cross-sectional observational study that was done on 75 healthy individuals and 75 T2D patients showed remarkable improvements in SBP and diastolic blood pressure (DBP) after 90 days of GT consumption (112). SBP of 20 obese pre-hypertensive women was significantly reduced after supplementation with 500 mg GTE capsules 3 times daily for 4 weeks. DBP and other parameters showed no change in this crossover, randomized, double-blind, placebo-controlled clinical trial (132). 56 obese, hypertensive subjects who were given 1 GTE capsules daily for 3 months, experienced a remarkable reduction in SBP and DBP in a double-blind, placebo-controlled trial (25). Another experiment about the effects of GTE capsules (containing 75 mg EGCG, BD for 3 weeks) showed no effect on SBP, DBP and heart rate (HR) but a satisfactory effect on mean arterial BP (MAP) and rate pressure product (RPP) response 1 hour after an acute resistance exercise in 24 sedentary middle-aged women (133). Supplementation with GT (3 cups daily for 14 weeks) in pre-diabetic subjects caused suppression of MAP increment of both sexes in one randomized human cohort (120).

On the other hand, some experiments noted opposite effects on BP. For instance, in one observational study 76 women, who were given a GT decoction, a moderate elevation in BP, and a great reduction in HR have been reported (134). Moreover, in another controversial study in 29 older adults, drinking GT before lunch enhanced SBP and DBP significantly with no effect on HR. GT was introduced as a BP pressor in postprandial hypotension in the elderly (135).

Conclusion

In the present study, different experiments about the effects and probable mechanisms of GT and its catechins on MetS parameters such as dyslipidemia, obesity, diabetes, and hypertension were reviewed. The majority of studies in animal and clinical studies agreed on the affirmative effects of GT. However, there were contradictory experiments in some topics that need further studies for clarification. Almost all of the experiments were suggestive of the beneficial effects of GT on MetS parameters.

Animal studies and the scant number of clinical experiments are in good agreement about the beneficial effects of GT on dyslipidemia and atherogenesis through anti-oxidative and anti-inflammatory properties. The anti-obesity effects of GT were assessed in most of the animal and clinical experiments. The prevalent mechanisms are as follows: suppressing inflammation, oxidative stress, and leptin levels, stimulating lipolysis, and regulating Peroxisome Proliferator-Activated Receptor (PPAR). The majority of animal studies agree on the valuable effects of GT on diabetes by affecting diabetes modulators, anti-inflammatory, and anti-oxidative properties. However, the clinical experiments were not in total agreement and needed more investigation. Almost all of the animal studies showed positive effects of GT on hypertension, mostly through oxidative stress and inflammation suppression. However, the clinical studies were limited and controversial. Hence there is a need for more studies to reach a final outcome.

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Authors' Contributions

EE Preparation of original draft; BMR Critical revision of the paper, supervision of the research; HH Study conception, design and supervision of the research. All authors have agreed to the contents and approved the final version for publication

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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