Chapter

Role of Tea Polyphenols in Metabolic Syndrome

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Abstract

Metabolic syndrome (MetS) increases the risk of type 2 diabetes and cardiovascular diseases (CVD). Tea (*Camellia sinensis*), one of the most consumed beverages in the world, is rich in polyphenols, mainly catechins. Tea polyphenols may ameliorate obesity by reducing body weight, increasing energy expenditure and fat oxidation, stimulating lipolysis, and improving thermogenesis. Tea polyphenols also reduce the risks of type 2 diabetes (T2D), hypertension, hyperlipidemia, and inflammation. Results of clinical trials on the effects of the consumption of tea beverage, tea extracts, or isolated tea polyphenols on biomarkers of metabolic syndrome will be reviewed in this study. The effects of tea polyphenols on antioxidant status and low-grade chronic inflammation and the molecular mechanisms involved will also be discussed.

Keywords: *Camellia sinensis*, catechins, inflammation, insulin resistance, dyslipidemia, hypertension, obesity

1. Introduction

Metabolic syndrome (MetS) is a cluster of interrelated prejudicial conditions that leads to type 2 diabetes (T2D) and cardiovascular disease (CVD). These conditions include elevated fasting plasma glucose level (hyperglycemia), abdominal/visceral obesity, dyslipidemia, and hypertension [1, 2]. The International Diabetes Federation (IDF) estimates that around 20–25% of the global adult population suffer from MetS and are more likely to die from a heart attack or stroke compared with people without MetS [1].

Since there is no specific treatment for MetS, individual characteristics must be taken into consideration. There is a need for long-term studies to determine whether existing and new therapeutic agents benefit patients with MetS, reducing the effects of MetS and preventing the appearance of associated diseases and to evaluate the potential of novel candidates as effective treatment options [3]. Several clinical studies demonstrate that lifestyle modification, especially dietary changes, is an effective strategy to reduce several factors responsible for the development of MetS. Introducing foods rich in dietary phytochemicals, such as polyphenols, into the diet of an individual is an effective lifestyle modification for the prevention of several diseases, including MetS [4, 5].

Polyphenols (phenolic compounds), one of the most relevant families of phytochemicals with health benefits, are biomolecules found in natural products. Several preclinical studies report that some polyphenols exert protective effects in

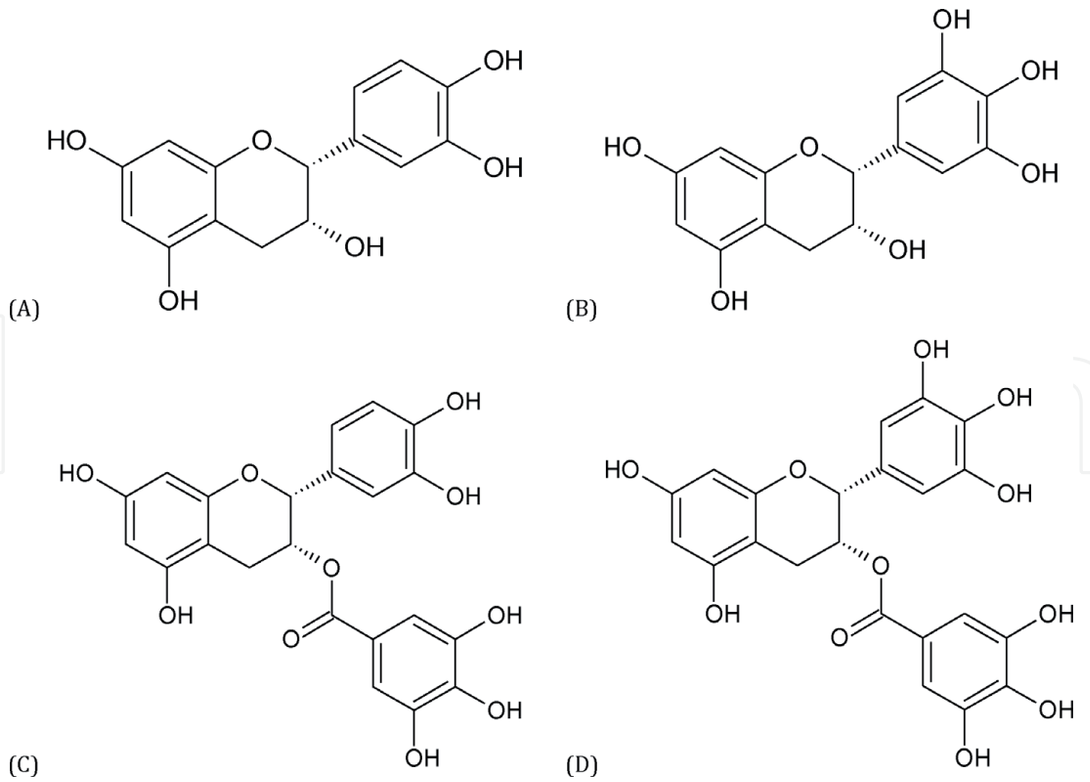

Figure 1.
Chemical structure of green tea catechins: epicatechin (A), epigallocatechin (B), epicatechin-3-gallate (C), epigallocatechin-3-gallate (D).

many diseases, including CVD and MetS, both triggered by oxidative stress [6, 7]. These compounds present antioxidant and anti-inflammatory properties and may be able to delay or prevent MetS by decreasing blood pressure, blood glucose levels, and body weight, as well as by improving lipid metabolism [7, 8]. One of the main sources of polyphenols is tea prepared from the processed leaves of *Camellia sinensis*, an herbal plant belonging to the Theaceae family. The chemical composition of tea is characterized by the presence of polyphenols (especially catechins), phenolic acids, amino acids, proteins, and fats. The catechins most commonly found in tea include epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) (**Figure 1**). These compounds constitute up to 30% of the dry leaf weight. A typical green tea beverage, with 2.5 g of tea leaves and 250 mL of hot water, contains 240–320 mg catechins and 60–65% EGCG [7, 9, 10]. Although the bioavailability of tea polyphenols is not clearly known, it depends on the molecular size and the number of phenolic groups. A review demonstrated that the consumption of 2 or 3 cups of tea daily resulted in 0.2–0.3 μM peak plasma levels of tea catechins [9, 11]. Notably, the health-promoting properties of green tea are due to the presence of the catechins mentioned earlier, mainly because of their antioxidant (scavenging of reactive oxygen species, inhibition of the formation of free radicals, and lipid peroxidation) and anti-inflammatory effects [10].

2. Tea, obesity, and inflammation

Obesity is a major health concern in the developed and developing world. Obesity leads to an inflammatory condition that is directly involved in the etiology of CVD, T2D, and certain types of cancer. Furthermore, the accumulation of adipose tissue in the abdominal region is a significant risk factor for the development of MetS and associated morbidities. It should be noted that inflammation is

a common feature implicated in the pathophysiology of many obesity-associated disorders. The inflammatory response in obese and MetS individuals manifests systemically and is characterized by a chronic low-intensity reaction, unlike classical inflammation [12–16].

The anti-inflammatory and anti-obesity effects of *Camellia sinensis* have been associated with its catechin content, and EGCG is the most abundant and pharmacologically active catechin. Green tea, which is more effective than black tea, has been shown to significantly alleviate MetS symptoms, such as abdominal adiposity indicated by waist circumference in obese subjects. The anti-obesity mechanisms of tea polyphenols are associated with two major mechanisms: (i) decreasing the absorption of lipids and proteins in the intestine by tea constituents, thus reducing calorie intake, and (ii) activating adenosine monophosphate-activated protein kinase (AMPK) by tea polyphenols that are bioavailable in the liver, skeletal muscle, and adipose tissues. The relative importance of these two mechanisms depends on the types of tea and diet consumed by individuals. It should be noted that AMPK activation can reduce gluconeogenesis and fatty acid synthesis, leading to bodyweight reduction and MetS alleviation [17, 18].

Clinical trials [19–21] verified that green tea reduced body weight and other biomarkers linked to MetS (**Table 1**).

Cellular, animal, and human experiments demonstrated that green tea and its major component, EGCG, have anti-inflammatory effects. Moreover, EGCG

Participants	Study type	Intervention	Outcomes	Ref.
35 subjects with obesity and MetS	Randomized, controlled prospective trial	Green tea (4 cups/day), green tea extract (2 capsules and 4 cups of water/day), or placebo for 8 weeks	Both interventions ↓ body weight and BMI. Green tea beverage also ↓ lipid peroxidation	[19]
70 moderately overweight subjects	Intervention	Green tea extract (4 capsules/day—375 mg of catechins) for 12 weeks	↓ Body weight	[20]
23 overweight subjects	Double-blind study	Green tea beverage containing 588 mg or 126 mg catechins for 12 weeks	↓ Body fat parameters	[21]
56 obese, hypertensive subjects	Double-blind, placebo-controlled trial	1 capsule (379 mg green tea extract) or placebo for 3 months	↓ TNF-α and CRP serum levels ↑ antioxidant status and HDL-C ↓ TC, LDL-C, and TG	[22]
1.704 overweight or obese subjects	Meta-analysis	Green tea/green tea extract (126–800 mg catechins) for 12–24 weeks	↓ LDL-C and TC	[23]
1356 subjects	Meta-analysis	EGCG (107 to 857 mg/day—2 to 8 cups of green tea per day) for 4 to 14 weeks	↓ LDL-C	[24]

BMI, body mass index; CRP, C-reactive protein; EGCG, epigallocatechin gallate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor-alpha; ↑, Increase; ↓, reduction.

Table 1.
Clinical trials showing the effects of tea or tea catechins on inflammation, obesity, and lipid profile.

inhibits the in vitro activation of the transcription factor NF-κB and attenuates the IκB-α degradation induced by tumor necrosis factor-alpha (TNF-α) activation. The anti-inflammatory mechanism of EGCG seems to be associated with a decrease in the activity of the IKK-β protein, involved in the phosphorylation of IκB-α. Because of this effect on the NF-κB signaling pathway, catechins can reduce the gene expression of COX-2. In addition, EGCG demonstrates anti-inflammatory activities in the MAPK pathway by inhibiting the phosphorylation of p38. Catechins also reduce the gene expression of c-Jun N-terminal kinase (JNK) protein and the transcription factor AP-1 [25, 26].

It should be noted that only a limited number of studies on humans provided strong evidence related to the anti-inflammatory activity of green tea. One example is a double-blind, placebo-controlled trial, in which 56 obese, hypertensive subjects received green tea extract or placebo for 3 months [22]. Green tea extract reduced diabetes and inflammation risk, increased total antioxidant status, and improved the lipid profile.

3. Tea and lipid profile

Hyperlipidemia, characterized by increased levels of total cholesterol (TC) and low-density lipoprotein (LDL-C), is a major risk factor for CVD. Several clinical trials demonstrated that the ingestion of polyphenols such as flavonoids and phenolic acids can improve the concentrations of TC, LDL-C, and high-density lipoprotein (HDL-C) [8].

Green tea beverage consumption and green tea extract supplementation can also improve lipid profile, reducing blood TC and LDL-C concentrations, especially when used for a long time. These changes are due to the presence of major tea polyphenols, namely, the catechins [27, 28]. A study conducted on rats fed with atherogenic diet demonstrated that the supplementation with green tea preparation consisting of 66.5% EGCG and other catechins could decrease plasma TC and LDL-C levels and increase plasma HDL-C levels [29]. Another study on rats and atherogenic diet indicated that EGCG can significantly reduce TC, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), triacylglycerols (TG), and cardiac risk ratio values while increasing the concentration of HDL-C [30].

Studies on humans also reported that EGCG can improve lipid profile. Its mechanisms may be associated with decreasing the absorption of lipids, inhibiting the lipogenesis pathway, and attenuating inflammation [23, 24, 31] (**Table 1**).

Other green tea catechins may have a beneficial effect on plasma TC and LDL-C levels in humans. Kim et al. [32] reviewed 20 trials and verified that the intake of green tea catechins, at doses of 145 to 3.000 mg per day, reduced TC by 5.5 mg/dL and LDL-C by 5.3 mg/dL, while there were no changes in plasma HDL-C levels.

More importantly, green tea can decrease plasma TC and LDL-C levels in overweight or obese people with no side effects, especially with long-term consumption [23].

Consumption of green tea extract catechin complex (843 mg of EGCG, 202 mg of ECG, 107 mg of EGC, and 107 mg of EC), for 12 months, significantly reduced (compared with the placebo group) plasma TC, LDL-C, and non-HDL-C levels in postmenopausal women. In hypercholesterolemic participants, green tea extract supplementation resulted in a reduction of 8.5% in TC and 12.4% in LDL-C concentrations. This study suggests that green tea extract, with high concentrations of catechins, may be recommended for lowering cholesterol, especially in those with high cholesterol concentrations [33].

4. Tea and blood pressure

Hypertension is a multifactorial clinical condition characterized by constant elevation of systolic blood pressure (SBP) levels ≥140 and/or diastolic blood pressure (DBP) ≥ 90 mmHg. It is often associated with metabolic disorders and functional and/or structural changes in target organs, aggravated by the presence of other risk factors, such as dyslipidemia, abdominal obesity, glucose intolerance, and T2D [34]. Hypertension is one of the leading risk factors for CVD, and it is a major cause of premature death worldwide; it affects about 1 billion people worldwide [34].

Tea flavonoids can reduce the risk of hypertension and consequently the risk of CVD [9, 35]. Catechins act as antioxidants and vasodilators and inhibit endothelial dysfunction and thrombogenesis [9, 36]. Catechins might reduce blood pressure by enhancing nitric oxide signaling [9]. The health benefits of tea for blood pressure were demonstrated in healthy subjects, diabetic subjects, and obese and/or hypertensive subjects [37]. Clinical trials showing the effect of tea on blood pressure are summarized in **Table 2**. It should be noted that several factors may influence the effect of tea consumption on blood pressure such as the duration and frequency of consumption, dosage, tea bioactive compounds, the evaluated population, and the degree of hypertension [37].

4.1 Molecular mechanisms of tea regulating blood pressure

Evidence indicates that vascular superoxide anion inactivates nitric oxide (NO) and plays a critical role in the development of hypertension. NO reacts with superoxide anion to form peroxynitrite. Peroxynitrite can cause protein tyrosine nitration, which modifies protein structure and function and affects cell homeostasis, oxidizes LDL-C, and leads to reduced activity of endothelial nitric oxide synthase (eNOS) [44, 45]. Angiotensin II generates vascular superoxide anion by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Superoxide anion contributes to increased blood pressure, endothelial dysfunction, vascular remodeling, and sodium retention, consequently contributing to the development of hypertension (**Figure 2**). Possibly, green tea extract reduces the risk of hypertension by reducing vascular reactive oxygen species (ROS) formation and NADPH oxidase activity [37]. In rats, decaffeinated green tea extract stimulated the activation of the eNOS via the phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway [46].

Caveolin-1, the major negative regulator of eNOS activity, has its gene expression attenuated by green tea polyphenols via the activation of extracellular signal-regulated kinase 1/extracellular signal-regulated kinase 2 (ERK1/ERK2) and inhibition of p38 mitogen-activated protein kinase (MAPK) signaling pathways [47].

Another mechanism by which tea consumption can reduce the risk of hypertension is by inhibiting renin activity. The study conducted by Li et al. [48] showed that oolong and black tea extracts inhibited renin activity. The beneficial effect was attributed to thearubigins. However, monomeric catechins did not contribute to the inhibitory effect promoted by the tea extracts.

Endothelin-1 may contribute to hypertension by enhancing vascular superoxide anion production via ETA/NADPH oxidase. Evidence indicates that epigallocatechin gallate reduces endothelin-1 expression and secretion from endothelial cells, partly via Akt- and AMPK-stimulated forkhead box *transcription factor* class O1 (FOXO1) regulation of the endothelin-1 promoter [37].

Participants	Study type	Intervention	Outcomes	Ref.
4579 older Chinese (>60 years) without hypertension or antihypertensive treatment	Cross-sectional	Green tea (~90% of subjects) nonhabitual drinkers, l–5x/ week; ≥6x/week	Reduction of 16 and 22% with tea consumption 1–5 times per week and ≥6 times per week, respectively	[36]
20 subjects with T2D (mean 53 years old; BMI, 30 kg/m^2)	Parallel, double-blind, placebo-controlled	Decaffeinated green tea extract (400 mg/ day) or placebo for 12 weeks	No difference in blood pressure, anthropometric, and metabolic parameters when compared to placebo	[38]
100 mildly hypertensive patients with diabetes	Randomized clinical trial	3 g/150 mL of sour tea or 3 g/150 mL of green tea (3x/day) for 4 weeks	↓ Systolic and diastolic blood pressure in both groups	[39]
56 obese, hypertensive subjects	Double-blind, placebo-controlled trial	1 capsule (379 mg green tea extract) or placebo for 3 months	↓ Systolic and diastolic blood pressure compared with placebo	[22]
19 hypertensive subjects	Randomized, double-blind, controlled, cross-over study	Black tea (129 mg flavonoids) or placebo (2x/day) for 8 days	↓ Systolic (3.2 mmHg) and diastolic (2.6 mmHg) blood pressure and prevented blood pressure increase after a fat load	[40]
123 prediabetic subjects	Randomized controlled clinical trial	600 mL/day of green tea or control (warm water) for 14 weeks	↓ Mean arterial pressure ↓ Waist/hip ratio compared to control Did not affect fasting plasma glucose nor HbA1C level	[41]
1697 subjects (22–74 years)	Meta-analysis	Green tea (208 to 1344 mg/day of catechin) for 3–16 weeks	↓ Systolic (1.17 mmHg) and diastolic (1.24 mmHg) blood pressure, no effect of caffeine, effect of low catechin dose was greater than high catechin	[42]
971 overweight or obese subjects (29–54 years)	Meta-analysis	Green tea/ reen tea extract (320–1207 mg of catechin) for 3–16 weeks	↓ Systolic and diastolic blood pressure in normotensive and hypertensive subjects. Significant reduction only for low catechin dose (250 mg of EGCG/ day) and intervention ≥3 months Caffeine did not interfere with the results	[43]

BMI, body mass index; EGCG, epigallocatechin gallate; HbA1C, glycated hemoglobin A1C; T2D, type 2 diabetes; ↓, reduction.

Table 2.
Clinical trials showing the tea effect on blood pressure.

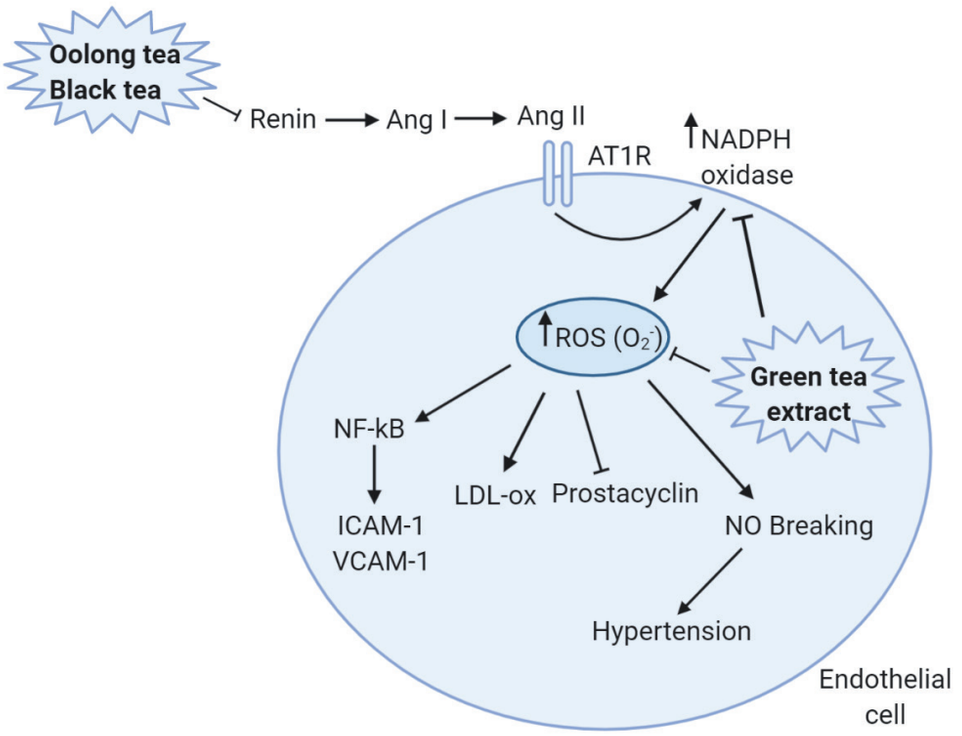

Figure 2.
In hypertension, there is excessive ROS generation in endothelial cells induced by angiotensin II. ROS excess can stimulate the NF-kB pathway and increase endothelial inflammation. ROS excess may also increase LDL-C oxidation and inhibit prostacyclin; superoxide anion reacts with NO to form peroxynitrite, which is cytotoxic. The NO loss may reduce vasorelaxation and contribute to endothelial dysfunction and hypertension. Green tea extract may inhibit the ROS production as well as Oolong tea and black tea may inhibit renin, and consequently angiotensin II. Ang II: angiotensin II; AT1R: angiotensin II type 1 receptor; ICAM-1: intercellular adhesion molecule 1; LDL-ox: oxidized LDL-C; NF-kB: nuclear factor kappa B; NO: nitric oxide; ROS: reactive oxygen species; VCAM-1: vascular cell adhesion molecule 1. →: stimulation; ⊥: inhibition.

5. Tea and insulin resistance/diabetes

Insulin resistance is a key feature of MetS and an important risk factor for CVD and T2D. Diabetes is a global health issue with high morbidity and mortality. The global prevalence of diabetes was 8.5% in 2014. In 2016, about 3.7 million deaths were caused by high blood glucose levels and diabetes. Almost half of the deaths caused by high blood glucose levels occur before the age of 70. T2D is linked to insulin resistance, altered lipid profile, hypertension, and endothelial dysfunction [49].

Recent evidence indicates that tea consumption improves insulin sensitivity and reduces the risk of T2D [9, 50]. Possibly, tea polyphenols act on gut microbiota, increase the probiotic species in the intestine, and attenuate the gene expression of enzymes involved in gluconeogenesis (phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase) and glucose production in the liver, mediated by AMPK activation [9].

In vitro, in vivo, and clinical studies have shown that green tea catechins, mainly EGCG, have various antidiabetic activities [50–53]. However, some studies have shown that there are no beneficial effects of tea on T2D [51, 52, 54, 55] (**Table 3**).

5.1 Molecular mechanisms of tea regulating insulin resistance/T2D

Green tea enhances glucose-stimulated insulin secretion through the cyclic adenosine monophosphate (cAMP)/Akt pathway. Moreover, EGCG could activate

Participants	Study design	Outcome	Ref.
13 normal subjects and 11 prediabetic subjects	Randomized, double-blind, placebo-controlled crossover study Placebo, low dose of black tea polyphenol (110 g) or high dose (220 g) of polyphenol + sucrose (50 g) Samples collected at 0, 30, 60, 90, and 120 min from tea intake	Low dose and high dose of polyphenol reduced incremental blood glucose area under the curve (AUC) compared with placebo in both normal and prediabetic subjects. No significant difference between low dose and high dose of polyphenol	[56]
92 subjects with T2D and lipid abnormalities	Double-blinded, randomized and placebo-controlled clinical trial 500 mg green tea extract (3x/day) or control (cellulose) for 16 weeks	↓ Triacylglycerols ↓ HOMA-IR ↑ HDL-C ↑ GLP-1	[57]
49 subjects with T2D (average age of 65 years; median duration of diabetes, 6 years) 80% of them using hypoglycemic medication	A double-blind, placebo-controlled, randomized trial Placebo, 375 mg or 750 mg/day for 3 months	Extract of green and black tea did not show a hypoglycemic effect	[54]
Overweight or obese male subjects (40–65 years)	Placebo-controlled, randomized trial 400 mg capsules of EGCG or placebo (lactose)—2x/day for 8 weeks	No effect on insulin sensitivity, insulin secretion, or glucose tolerance	[55]
1584 subjects	Meta-analysis Green tea catechins with or without caffeine ≥12 weeks <12 weeks	↓ Fasting blood glucose Glucose-lowering effect was observed when follow-up ≥12 weeks	[58]
30 subjects with T2D	Randomized controlled trial 600 mL/day of black tea or 200 mL/day of black tea for 12 weeks	↓ HbA1C with 600 mL/day ↓ Pro-inflammatory $CD3^+$ $CD4^+$ $IL\text{-}17^+$ cells	[59]
56 obese, hypertensive subjects	Double-blind, placebo-controlled clinical trial 1 capsule/day (379 mg of green tea extract) or placebo for 3 months	↓ Systolic and diastolic blood pressure ↓ Fasting serum glucose ↓ Insulin resistance (HOMA-IR) ↓ TNF-α and CRP ↓ Total antioxidant status ↓ Total cholesterol, LDL-C, and triacylglycerols ↑ HDL-C	[22]
68 overweight subjects with T2D (20–65 years)	Randomized, double-blind, placebo-controlled clinical trial 1500 mg of decaffeinated green tea extract/day or placebo (cellulose) for 16 weeks	↓ HbA1C, ↓ HOMA-IR, ↑ ghrelin, ↓ waist circumference	[60]

Participants	Study design	Outcome	Ref.
66 subjects with T2D (32–73 years)	Randomized controlled trial Green tea extract (456 mg catechin)/ day or control (just followed) for 2 months	Blood glucose, HbA1c, insulin levels, and HOMA-IR did not differ from the control group	[61]

CRP, C-reactive protein; HbA1C, glycated hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance index; GLP-1, glucagon-like peptide 1; LDL-C, low-density lipoprotein cholesterol; TNF, tumor necrosis factor; T2D, type 2 diabetes; ↓, Reduction; ↑, increase.

Table 3.
Studies that showed the effect of tea on insulin resistance and diabetes.

AMPK to improve the shutdown of the insulin stress signal pathway caused by serine phosphorylation of insulin receptor substrate-1 (IRS-1), improving insulin resistance [50]. High plasma glucose level increases ROS production, while EGCG improved insulin resistance by scavenging ROS. ROS plays a key role in increasing JNK and IRS-1 serine phosphorylation and reducing the transduction of insulin signal [62]. Green tea catechin increases insulin sensitivity by directly activating peroxisome proliferator-activated receptor (PPAR) γ [50]. In addition to insulin sensitivity, EGCG can also inhibit glucose absorption by competitively binding with the sodium-glucose transporter-1 (SGLT-1) in intestinal epithelial cells and enhance glucose uptake in muscles and adipocytes via enhancement of the GLUT4 expression [44, 53].

Most studies showing the beneficial effects of EGCG on glucose homeostasis were performed in vitro. EGCG showed an insulin-like activity through the reduction of gluconeogenic enzymes (glucose-6-phosphatase and PEPCK) in hepatocytes by suppressing their gene expression [51, 52]. In myocytes, green tea or EGCG stimulates GLUT4 translocation and glucose uptake via the PI3-kinase/Akt signaling pathway; alternatively, muscle glucose uptake occurs via AMPK [52]. In laboratory animals, EGCG improved insulin sensitivity in peripheral organs and inhibited gluconeogenesis [51]. In humans, EGCG can protect pancreatic β cell from cytokines, inhibiting the NF-kB activation [63]. Tea also reduces carbohydrate absorption by inhibiting α-amylase, β-glucosidase, and sodium-glucose transporters [51, 56].

Black tea rich in theaflavins decreases the risk of T2D by inhibiting obesity through AMPK phosphorylation and promoting the browning of white adipose tissue [50]. The pro-inflammatory cytokines TNF-α and interleukin (IL)-1 are involved in obesity-associated insulin resistance and T2D. Black tea consumption has a potential role in downregulating serum TNF-α and IL-1 levels and upregulating IL-10, an anti-inflammatory cytokine [63].

6. Conclusion

Tea contains polyphenols that may provide an important source of dietary antioxidants in humans. Moderate consumption of tea seems to reduce the risk of MetS and/or MetS-related diseases. EGCG, the main catechin in tea, presents major health benefits. Green tea seems to have the best potential antioxidant effects when compared to other teas. It is worth mentioning that most of the studies have not demonstrated toxicity due to tea consumption or supplementation; however, further research, especially in humans, should be conducted to confirm this property and evaluate the underlying mechanisms of action.

Conflict of interest

The authors have no conflict of interest to disclose.

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