



## Polyphenols and their effects on diabetes management: A review

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### Abstract

**Background:** Type 2 diabetes is a growing public health problem and is associated with increased morbidity and mortality. The worldwide prevalence of type 2 diabetes is rising. Polyphenols, such as flavonoids, phenolic acid, and stilbens, are a large and heterogeneous group of phytochemicals in plant-based foods. In this review, we aimed at assessing the studies on polyphenols and diabetes management.

**Methods:** A literature search in the PubMed, EMBASE, Scopus, and ISI Web of Science databases was conducted to identify relevant studies published from 1986 to Jan 2017.

**Results:** Several animal models and a limited number of human studies have revealed that polyphenols decrease hyperglycemia and improve acute insulin secretion and insulin sensitivity. The possible mechanisms include decrease in glucose absorption in the intestine, inhibition of carbohydrates digestion, stimulation of insulin secretion, modulation of glucose release from the liver, activation of insulin receptors and glucose uptake in insulin-sensitive tissues, modulation of intracellular signaling pathways, and gene expression.

**Conclusion:** Growing evidence indicates that various dietary polyphenols may influence blood glucose at different levels and may also help control and prevent diabetes complication. However, we still need more clinical trials to determine the effects of polyphenols-rich foods, their effective dose, and mechanisms of their effects in managing diabetes.

**Keywords:** Polyphenol, Blood glucose, Inflammation, Phytochemical, Type 2 diabetes

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### Introduction

Type 2 diabetes (T2D), a growing public health problem, is associated with increased morbidity and mortality. According to the report of International Diabetes Federation (IDF), the number of people with diabetes in the world will increase from 382 million in 2013 to 592 million by 2035 (1). In Europe, approximately 6% to 8% of the population suffer from diabetes, of them nearly 90% have T2D, making T2D the fastest enhancing disease in Europe and worldwide (2). Inflammation is a serious problem in patients with diabetes and plays an important role in the evolution of atherosclerotic process in non-insulin dependent diabetes mellitus (NIDDM), together with the known influence of glucose and lipid

metabolism pathology. Inflammation both increases the levels of circulating inflammatory cytokines and insulin resistance in the liver, skeletal muscles, and vascular endothelium (3).

Polyphenols are the most abundant antioxidants in the diet of humans. There are thousands of natural polyphenols in the plant kingdom (4). Polyphenols, such as flavonoids, phenolic acid, and stilbenes, are a large and heterogeneous group of phytochemicals in plant-based foods (tea, soy, coffee, cocoa, cereal grains, cinnamon, ginger, fruits, and berries). Polyphenols are classified into several categories based on the number of phenol rings and structural elements that bind these rings (4).

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#### ↑What is “already known” in this topic:

This research can be used by physicians, nutritionists, and diet therapists and by all people, especially those with diabetes and those suffering from insulin resistance, such as metabolic syndrome and polycystic ovary syndrome (PCOS).

#### →What this article adds:

The possible effect of polyphenol on diabetes management is already known, and this article adds to the previously known knowledge by summarizing the results of other researches on the effectiveness and mechanisms of polyphenols on diabetes management.

Growing evidence indicates that various dietary polyphenols may prevent diabetes. In this article, we will discuss some polyphenol-rich foods and their possible effect on blood glucose.

### Curcumin

Curcumin is a natural compound extracted from the root of *Curcuma Longa* and is the main component of the Indian curry spice. Curcumin has been consumed in the traditional Asian medicine for centuries because of its anti-inflammatory properties. Curcumin has also antioxidant and anticarcinogenic effects (5-7). Its anti-cancer activity is mainly attributable to the inactivation of hypoxia-inducible factor-1(HIF-1), as curcumin is known to downregulate HIF-1 $\alpha$  (8) and HIF-1 $\beta$  (9) and inhibit downstream actions, e.g. angiogenesis mediated by HIF-1. Also, it is able to selectively kill tumor cells or prevent tumorigenesis through interfering with many cellular pathways (6, 10). It represses nuclear factor- $\kappa$ B (NF- $\kappa$ B), inhibits adipogenic transcription factors and the cell cycle, and induces apoptosis (11-13). In colorectal cancer, curcumin treatment upregulates p53 expression (14). It has been reported that curcumin inhibits TNF- $\alpha$ -induced expression of Interleukin-1 beta (IL-1 $\beta$ ), IL-6, and tumor necrosis factor (TNF- $\alpha$ ) in human keratinocytes. It enhances the secretion of adiponectin (15), inhibits insulin-regulated glucose transporter 4 (GLUT4) translocation and glucose transport (16, 17). Some studies demonstrate that 10–25  $\mu$ M of curcumin efficiently inhibited the differentiation of mouse adipocytes. In concentrations of 10–50  $\mu$ M, curcumin is able to activate AMP-activated protein kinase (AMPK)(18) and it can also inhibit the activation of MAPK pathway, c-Jun N-terminal kinases (JNK), p38MAPK, and extracellular signal-regulated kinases (ERK) in adipocytes (19). Thus, it stimulates proliferation (20) but suppresses lipid accumulation and adipogenesis (21). However, conflicting data on how curcumin affects peroxisome proliferator-activated receptors (PPARs) ranges from direct activation to inhibition via AMPK (22-24). Interestingly,

curcumin applied at a half maximal inhibitory concentration (IC50) of 45  $\mu$ M can also interfere with cellular energy balance by inhibiting ATP synthesis at the mitochondrial membrane (25). Furthermore, it was illustrated that active spice-derived components such as curcumin suppress obesity-induced inflammatory responses in adipose tissue of obese mice. As a result, migration and release of monocyte chemoattractant protein-1 (MCP-1) and TNF- $\alpha$  were inhibited and MCP-1 was released from adipocytes (26). Beyond the anti-inflammatory properties, curcumin has also ameliorated diabetes in different mouse models; 200 mg curcumin/kg diet has improved insulin resistance and hyperglycemia in mice. Also, it elevated insulin level and lowered the free fatty acid, triglyceride, cholesterol, and glucose level in blood and reduced lipid oxidation (27). Further studies on curcumin has illustrated that it reduces macrophage infiltration into the white adipose tissue, induces the expression of adiponectin, and decreases NF- $\kappa$ B activity (28, 29). Administration of 500 mg/kg curcumin in diet leads to a decrease in body weight gain, adiposity, and expression of VEGF in mice (30). Antihyperlipidemic and antidiabetic effects were also seen in rats (31, 32) and hamsters (33). Taken together, these data indicated that curcumin can repress inflammation and obesity and improve the chronic condition in diabetes.

An in vitro study found that curcuminoids effectively enhanced the phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target acetyl-CoA carboxylase (ACC) in H4IIE rat hepatoma and Hep3B human hepatoma cells with 400 times (curcumin) to 100 000 times (tetrahydrocurcuminoids) the potency of metformin. These results suggest that AMPK mediated the suppression of hepatic gluconeogenesis and may be a potential mechanism mediating glucose-lowering effects of curcuminoids (34). In another study on 240 prediabetic adults, participants were given 250 milligrams of curcumin or a placebo every day for 9 months. After intervention, none of those taking curcumin developed diabetes, but 16.4% of the placebo

**Table 1.** Overview of recent clinical trials testing curcumin with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of curcumin
25 T2DM patients	200 mg curcumin (1000 mg Meriva)/d; 4 w	(36)	Improvement of diabetic microangiopathy
10/9 healthy participants	500 mg/6000 mg curcumin/d; 7 d	(37)	Decline of serum cholesterol and triglyceride levels (more pronounced at the lower dose than the higher); enhancement of antioxidant capacity
20 T2DM nephropathy patients	66.3 mg curcumin (1500 mg tumeric)/d; 2 m	(38)	Attenuation of proteinuria, TGF- $\beta$ and IL-8 levels
50 patients with osteoarthritis	200 mg curcumin (1000 mg Meriva)/d; 8 m	(39)	Decrease in inflammatory markers (IL-1 $\beta$ , IL-6, sCD40L, sVCAM-1, ESR)
21 patients with $\beta$ -thalassemia/Hb E	500 mg curcuminoids (357 mg curcumin, 107 mg demethoxycurcumin, and 36 mg bisdemethoxycurcumin)/d; 12 m	(40)	Improvement of oxidative stress markers including MDA, SOD, GSH-Px, and GSH in RBCs, and NTBI in serum
15/14/15 patients with ACS	45/90/180 mg curcumin (2/4/8 g curcuma extract)/d; 2 m	(41)	Trend of reduction in total cholesterol and LDL cholesterol level by low-dose curcumin
8/11 healthy participants	1/4 g curcumin/d; 6 m	(42)	No significant effect on serum cholesterol or triacylglycerol
60 T2DM patients	Group I received standard metformin treatment and group II metformin therapy with turmeric (2 g) supplements for 4 w	(43)	Reduction in lipid peroxidation, MDA, and enhanced total antioxidant status. Beneficial effects on dyslipidemia and decrease in hsCRP

ACS: acute coronary syndrome; T2DM: Type 2 diabetes mellitus; g: gram; d: days; w: weeks; m: months; TGF- $\beta$ : transforming growth factor beta 1; IL: interleukin; sCD40L: Soluble CD40 ligand; sVCAM-1: Soluble cell adhesion molecule-1; ESR: erythrocyte sedimentation rate; MDA: Malondialdehyde; hsCRP: high sensitive C-reactive protein; SOD: superoxide dismutase; GSH-Px: glutathione peroxidase; GSH: reduced glutathione; RBC: red blood cells; NTBI: non-transferrin bound iron

group did. In other words, curcumin was 100% effective in preventing Type 2 diabetes (35). Table 1 demonstrates recent clinical trials testing curcumin with respect to diabetic and inflammatory markers.

### Resveratrol

Resveratrol is a non-flavonoid polyphenol produced naturally by many plants including grapes, peanuts, cranberries, blueberries, and Japanese knotweed. The resveratrol content ranges from 50 to 100 µg/g in fresh grape skin and from 0.1 to 14 mg/l in red wine (44, 45). It is synthesized in plants in response to injury or fungal attack. Different studies have found that resveratrol has antioxidant and anti-inflammatory effects, ameliorating inflammation through counteracting with TNF- $\alpha$ -induced effects and declining mRNA expression and secreting different adipokines such as plasminogen activator inhibitor-1 (PAI-1), IL-1 $\beta$ , IL-6, IL-8, and MCP-1. Resveratrol and curcumin increase pancreatic  $\beta$ -cell function by inhibiting phosphodiesterase activity. They protect against  $\beta$ -cell dysfunction. In T2DM, cAMP plays an important role in glucose and incretin-stimulated insulin secretion as well as overall pancreatic  $\beta$ -cell health. A potential therapeutic target in managing T2DM is to regulate the activity of phosphodiesterases (PDEs), which degrade cAMP. Both resveratrol and curcumin have been reported to act as PDE inhibitors in various cell types, but it remains unknown whether they do so in pancreatic  $\beta$ -cells. Treating  $\beta$ -cell lines and human islets with these polyphenols has led to an increase in intracellular cyclic adenosine monophosphate (cAMP) levels. Resveratrol and curcumin increase pancreatic  $\beta$ -cell function through inhibiting phosphodiesterase activity and promote  $\beta$ -cell function across species by acting as direct PDE inhibitors in  $\beta$ -cells and islets. Treatment of mouse and human  $\beta$ -cells with resveratrol and curcumin resulted in a substantial reduction of PDE expression, particularly PDE3B, PDE8A, and PDE10A, which are known to be important in insulin signaling (46). Also, resveratrol and curcumin treatment showed a profound ability to directly inhibit PDE activity in  $\beta$ -cells of pancreas. As a result of PDE inhibition, resveratrol and curcumin treatment prevented the degradation of cAMP, leading to an increase in its intracellular levels. Subsequently, this allowed for activation of cAMP-dependent signaling pathways, augmenting

insulin secretion and  $\beta$ -cell function (46).

Resveratrol effects on weight reduction induced by several mechanisms include increasing apoptosis, fat mobilization, fatty acids oxidation, lipolysis, and decrease in lipogenesis and adipogenesis. Table 2 displays an overview of recent clinical trials testing resveratrol with respect to diabetic and inflammatory markers.

### Cinnamon

with Type 2 diabetes through improving the ability to respond to insulin. A total of 8 meta-analysis clinical studies demonstrated that cinnamon or cinnamon extracts decrease fasting blood glucose levels (51). Cinnamon slows the rate of stomach emptying after eating. In the study of Hlebowicz et al., participants ate a cup of rice pudding with and without a teaspoon of cinnamon. Adding cinnamon decreased the rate of stomach emptying from 37% to 34.5% and significantly decreased the rise in blood sugar levels at 0 and 120 minutes compared to ingestion of the reference meal. Even less than half a teaspoon a day reduced blood sugar levels of patients with type 2 diabetes (52).

### Capsaicin

Capsaicin is an active component in chili peppers and is usually consumed as a spice, but it is also used for neurological disorders, such as diabetic neuropathy and tropical therapy of cutaneous allergy. Capsaicin specifically binds to ion channel, which is activated by several physical and chemical stimuli and causes pungent sensation in mammals (53). Moreover, studies illustrated that it can activate AMPK and suppress adipocyte differentiation in mouse adipocytes (54). In murine macrophages, capsaicin's anti-inflammatory action was shown by repressing the expression of proinflammatory gene inducible nitric oxide synthase (iNOS). It also represses cyclooxygenase 2 (COX2) activity, inhibits prostaglandin E2 (PGE2) production, and inactivates NF- $\kappa$ B by inhibiting (I $\kappa$ B $\alpha$ ) degradation (55). Also, it binds specifically to PPAR $\gamma$  and suppresses the production of TNF- $\alpha$ . Hence, capsaicin's anti-inflammatory effect is assumed to be mediated through activation of PPAR $\gamma$  and NF- $\kappa$ B (56, 57). Screening different plant extracts also determined its potential to activate PPAR $\alpha$  (58). In mouse adipocytes, capsaicin inhibits adipogenesis and decreases

Table 2. Overview of recent clinical trials testing resveratrol with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of resveratrol
11 healthy, obese males	150 mg resveratrol /d; 30 d	(47)	Decrease in metabolic rate, mimicking the effect of calorie restriction
10 T2DM patients	10 mg resveratrol /d; 4 w	(48)	Reduction of insulin resistance
10/10/10/10 healthy participants	0.5/1/1.5/2 g resveratrol /d; 29 d	(49)	Reduction of IGF-1 and IGFBP-3 in plasma and gastrointestinal symptoms on 2 highest dose levels
10 healthy participants	200 mg PCE (40 mg resveratrol )/d; 6 w	(50)	Suppression of oxidative and inflammatory stress markers including the reduction in ROS generation, the expression of p47phox, intranuclear NF- $\kappa$ B binding, the expression of jun-N-terminal kinase-1, inhibition of $\kappa$ B-kinase- $\beta$ , phosphotyrosine phosphatase-1B, and suppression of cytokine signaling-3 in mononuclear cells and plasma TNF- $\alpha$ , IL-6, and C-reactive protein

T2DM: Type 2 diabetes mellitus; d: days; w: weeks; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor binding protein 3; ROS: reactive oxygen species; NF- $\kappa$ B: nuclear factor- $\kappa$ B

**Table 3.** Overview of recent clinical trials testing capsaicin with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of capsaicin
18 healthymales	9 mg capsinoids; once (FDG-PET)	(69)	Activation of brown adipose tissue, enhancement in energy expenditure
25 healthy participants	1 g red pepper (1995 µg capsaicin, 247 µg nordihydrocapsaicin, and 1350 µg dihydrocapsaicin); once	(70)	Enhancement in energy expenditure and body temperature
12 healthy participants	26.6 mg capsaicin (5 g capsicum); once (OGTT)	(68)	Decrease in plasma glucose levels; increase in insulin levels
27 healthy participants	510 mg cayenne/510 mg cayenne t.w. green tea; once	(71)	Decrease of energy intake and hunger and enhancement in satiety (in combination with green tea)
36 healthy participants	33 mg capsaicin (30 g chili blend [55% cayenne chili])/d; 4 w	(72)	No change of metabolic parameters (plasma glucose, serum lipids, lipoproteins, insulin, metabolic rate)
14 healthy participants	400 µg capsaicin; once (glucose loading test)	(73)	Slight increase in glucose absorption and glucagon release
27 healthy participants	33 mg capsaicin (30 g chili blend [55% cayenne chili])/d; 4 w	(74)	Inhibition of oxidation of serum lipoproteins; no difference in the serum lipid, lipoproteins, total anti-oxidation status
36 healthy participants	33 mg capsaicin (30 g chili blend [55% cayenne chili])/d; 4 w	(75)	Attenuation of postprandial hyperinsulinemia

d: days; w: weeks; OGTT: oral glucose tolerance test

es the amount of intracellular triglycerides. Thermogenesis is enhanced by capsaicin (59). Through stimulating lipolysis and thermogenesis, capsaicin increases the energy expenditure in adipose tissue (60). More recently, it has been shown that capsaicin induces concentration-dependent (0.1–10 µM) upregulation of the mitochondrial UCP-2 (uncoupling protein 2), a mitochondrial protein transporter that separates oxidative phosphorylation from ATP synthesis with energy dissipated as heat and other genes involved in lipid catabolism in white adipocytes (61). Another study on adipocytes revealed that activation of VR1 by capsaicin concentrations, starting from 10 nM, promotes a calcium influx and prevents adipogenesis and obesity, which has also been confirmed in vivo (62). This property of capsaicin likely explains the activation of further downstream targets. In earlier studies on rats, it has been shown that capsaicin stimulates lipid mobilization from adipose tissue and decreases the perirenal adipose tissue weight and serum triglyceride concentration if added to 0.014% of the diet (63). This was also associated with an increased energy metabolism and an enhanced respiratory quotient (64). More investigations in mice suggest that capsaicin suppresses obesity-induced inflammation by modulating adipokine release. Also, it suppresses the expression and secretion of IL-6 and MCP-1 from obese adipose tissues, but increases adiponectin gene expression. Intraperitoneal administration of capsaicin (2 mg/kg bw) suppresses macrophage activation and decreases the release of proinflammatory mediators and stops their migration (57, 65). Capsaicin also counteracts the proinflammatory effects of saturated fatty acids through reduction in JNK activity, thus it may be regarded as a beneficial phytochemical for attenuating obesity-induced inflammation and obesity-related pathologies. In some studies, an increased fat oxidation (66) and a lowered fat intake (67) were observed in overweight participants treated with capsaicin. More recent studies investigating the effect of dietary capsaicin showed an effect on glucose and insulin. Capsaicin also seems to be involved in the regulation of energy expenditure and activation of brown adipose

tissue in humans (68). **Table 3** demonstrates recent clinical trials testing capsaicin with respect to diabetic and inflammatory markers.

### Catechins and Procyanidins

Catechins are flavanols that contain catechin (C), epicatechin (EC), galliccatechin (GC), epigallocatechin (EGC), and their gallates. Cocoa is very rich in catechins and flavanol-based oligomers known as procyanidins (76). Procyanidins positively affect inflammatory diseases, such as obesity and Type 2 diabetes. They can modulate inflammation through decreasing the expression of IL-6 and MCP-1 and increasing the production of anti-inflammatory adipokine and adiponectin (77). **Table 4** displays recent clinical trials testing catechin with respect to diabetic and inflammatory markers.

### Berberine

Berberine is a bitter compound found in the roots of several plants including goldenseal, barberry, and oregon grape. Studies have found that berberine can lower blood glucose. Chinese researchers compared berberine with metformin in a pilot study on 36 participants. They found that berberine (0.5 g 3 times a day) decreased blood sugar level just as well as metformin in 3 months. Berberine also significantly reduced fasting blood sugar and after meal blood sugar of patients (99). In the same study, researchers gave berberine (0.5 g 3 times a day) to 48 patients with diabetes for 3 months. They found that berberine decreased fasting and post meal blood glucose levels after 1 week. They also found that the patients' insulin resistance decreased to 45% (99). A meta-analysis on 14 studies involving 1068 participants has revealed that berberine effects are similar to those of metformin, glipizide, and rosiglitazone. These drugs are the most important diabetes drugs on the market (100). Most importantly, berberine has no serious side effects. **Table 5** demonstrates recent clinical trials testing berberine with respect to diabetic and inflammatory markers.



Table 4. Overview of recent clinical trials testing catechin with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of catechin
15 ow-ob participants	650 ml green tea (534 mg catechins t.w. 11.7 g inulin)/d; 6 w	(78)	Reduction of body weight, fat mass, body mass index, and blood pressure
64 ow-ob males	1060 mg GTE (424–753 mg EGCG t.w. 170–286 mg EGC, 85–784 mgEC)/d; 6 w	(79)	Reduction of body weight; no effect on blood pressure or biomarkers of metabolic function
80 T2DM patients	1500 mg GTE (856 mg EGCG)/d; 16 w	(80)	No significant effect in fasting glucose, HbA1c, hormone peptides, and plasma lipoproteins
19 healthy males	491 mg catechins t.w. oolong tea/d; 5 d	(81)	No effect on glucose metabolism
8 healthy participants	405 mg EGCG/d; 2 d	(82)	No influence on resting metabolism and the thermic effect of food
22 healthy pmp females	One group consumed a catechin-rich green tea (catechins 615 mg/350 ml) and another consumed a placebo (catechins 92 mg/350 ml) beverage per d for 4 weeks	(83)	Decrease in postprandial glucose concentrations, Inhibition of the increase in the serum concentrations of the derivatives of reactive oxygen metabolites
13/10 ob patients with MetS	4 cups green tea (440 mg EGCG t.w 220 mg EGC, 180 mg ECG, and 88 mg EC)/2 capsules GTE (460 mg EGCG t.w. 240 mg EGC, 120 ECG, and 50 mg EC)/d; 8 w	(84, 85)	Reduction of body weight, BMI, lipid peroxidation, and plasma serum amyloid alpha; no effect on inflammatory markers or features of MetS
47/49/43 ow participants	458 mg green tea catechins t.w. 104 mg caffeine/468 mg catechin t.w. 126 mg caffeine/886 mg catechins t.w.198 mg caffeine/d; 90 d	(86)	Reduction of intra-abdominal fat, waist circumference and body weight with highest dose, total body fat mass with low and medium doses; no effect on plasma HDL cholesterol and LDL cholesterol, triglycerides, and glucose levels
10 ow-ob males	300/600 mg EGCG/d; 3 d	(87)	No effect on energy expenditure; enhancement of postprandial fat oxidation only by low EGCG dose
10 healthy smokers	580 mg green tea catechins (102 mg EGCG, 77 mg EGC, 30 mg ECG, 129 mg GCG, 138 GC, 38 mg C)/d; 2 w	(88)	Enhancement of NO production, reduction of oxidative stress; decrease of MCP-1 level
100 tuberculosis patients	500 µg catechin extract 3×/week; 4 m	(89)	Reduction of oxidative stress with significantly decreased lipid oxidation and increased NO levels
46 ow-ob males	800 mg EGCG/d; 8 w	(90)	No effect on insulin sensitivity, insulin secretion, or glucose tolerance; reduction of diastolic blood pressure
23 T2DM patients	583 mg green tea catechins/d; 12 w	(91)	Decrease in waist circumference; increase in adiponectin and insulin levels; no effect on glucose and HbA1c
21 ob children	576 mg green tea catechins/d; 24 w	(92)	Decrease in waist circumference, systolic blood pressure, and LDL cholesterol
12/11 healthy males	3 capsules GTE (366 mg EGCG)/d; 1 d	(93)	Increase in fat oxidation during exercise; improvement in insulin sensitivity and glucose tolerance
60 with elevated blood glucose	GTE powder (456 mg catechins t.w. 102 mg caffeine)/d; 2 m	(94)	Reduction in HbA1c and diastolic blood pressure; no effect on weight, body fat, systolic blood pressure, HOMA index, serum lipid, and glucose level
29 healthy adults	500 mg green tea catechins/d; 4 w	(95)	Reduction in oxidized LDL cholesterol
16/17 T2DM patients	150/300 mg green tea catechins t.w. 75 mg of black tea theaflavins/d; 3m	(96)	No effect on HbA1c
19 ow-ob, pmp women	300 mg EGCG/d; 12 w	(97)	Reduction of heart rate and plasma glucose concentration in participants with impaired glucose tolerance
6 ow males	300 mg EGCG/d; 2d	(98)	Decrease in respiratory quotient; no effect on energy expenditure

Ow : overweight; ob: obese; pmp: postmenopausal; T2DM: Type 2 diabetes mellitus; MetS: metabolic syndrome; d: days; w: weeks; m: months; GTE: green tea extract; EGCG: epigallocatechin gallate; EGC: epigallocatechin; ECG: epicatechin gallate; EC: epicatechin; C: catechin; GC: gallo catechin; GCG: gallo catechin gallate; GA: gallic acid; t.w.: together with; HbA1c: hemoglobin A1c; BMI: body mass index; NO: nitric oxide; MCP-1: monocyte chemoattractant protein-1; HOMA: homeostatic model assessment

## Genistein

The isoflavone genistein is a naturally occurring phytoestrogen, which is particularly highly concentrated in soy and soy-derived products; its possible suitability as a pharmacological agent has been studied, as it has been illustrated that people in Asia consuming large amounts of genistein-rich soy products are seldom affected by prostate or breast cancer (104, 105) and Type 2 diabetes (106). In hypoxic conditions, genistein has been shown to suppress the HIF1 $\alpha$  expression, accumulation, and activation of ERK (107, 108). Also, genistein seems to provide a protective effect on myocardial and endothelial

cells, as it activates the exocytosis of the cardioprotective neuropeptide calcitonin gene-related peptide. This is due to vanillin receptor 1 (VR1)-mediated action, of which genistein is supposed to be a direct activator (109), apart from capsaicin and gingerol. In adipocytes, genistein acts as an anti-inflammatory substance, down-regulates leptin production in the presence of 50  $\mu$ M (110), induces apoptosis at 100  $\mu$ M (111), and also counteracts the antilipolytic action of insulin if used at concentrations higher than 12.5  $\mu$ M (112). This is probably due to PPAR $\gamma$ , to which genistein is a direct ligand and activator (113). However, the effect of genistein on differentiation of adipocytes has been illustrated with

**Table 5.** Overview of recent clinical trials testing berberine with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of berberine
36 T2DM patients	1.5 g/d berberine for 3 months	(99)	Decrease in HbA1c, fasting blood glucose, postprandial blood glucose, and TG
31 T2DM patients	3 extract of barberries vulgaris g/d for 3 months	(101)	Decrease in TG, TC, LDL, apo B, Glc, insulin and increase in total antioxidant capacity
69 T2DM patients	1000mg berberine, 1000 mg berberine and 210 mg silymarin for 4 m	(102)	Decrease in Glc, TC, TG, LDL, AST, ALT, Hb A1c
30 T2DM patients	2 mg barberries fruit extract /d for 2 m	(103)	Decrease in Glc and Hb A1c

T2DM type 2 diabetes mellitus; g: gram; d: days; m: months; TG: triglyceride; TC: total cholesterol; Glc: glucose; AST: Aspartate Aminotransferase; ALT: alanine aminotransferase; Hb A1c: hemoglobin A1c

**Table 6.** Overview of recent clinical trials testing genistein with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of genistein
23 patients with prostate cancer	30 mg genistein/d; 3–6 w	(123)	Reduction of blood cholesterol
43 healthy, ob, pmp females	60.8 mg genistein (t.w. 16 mg daidzein+3.2 mg glycitein)/d; 6 m	(124)	Enhancement of adiponectin serum levels
71 pmp osteopenic females	54 mg genistein/d; 24/36 m	(125)	Reduction of fasting glucose and insulin, HOMA-IR, fibrinogen and homocysteine after 24/36 months of treatment
30 pmp normo- and hyperinsulinemic females	54 mg genistein/d; 24 w	(126)	Reduction of fasting glucose in normoinsulinemic patients; reduction in fasting insulin, fasting C-peptide; improvement of HDL levels
32 healthy, pmp females	64 mg genistein (t.w. 63 mg daidzein and 34 mg glycitein)/d; 12 w	(127)	Enhancement in serum adiponectin levels; no effect on metabolic parameters
25 pmp females	2 mg genistein (t.w. 4.8 mg daidzein)/d; 6 m	(128)	No significant effect

Ob: obese; pmp: post-menopausal; d: days; w: weeks; m: months; t.w.: together with

inconsistent results; this is in part due to contradictory actions of genistein with respect to applied concentrations (110, 111, 113-119). In a study, streptozotocin-diabetic rats that received a daily intraperitoneal injection of 1 mg/kg bw showed a hypoglycemic effect (120). In a study on mice, 2 and 4 g genistein/kg diet significantly decreased fat pads, cholesterol, and lipid levels. Moreover, it inhibited mRNA expression of PPAR $\gamma$ , leptin, and TNF $\alpha$  and also increased mRNA expression in case of PPAR $\alpha$ , AMPK, and adiponectin in adipose tissue (121). Furthermore, it enhanced the expression of genes involved in fatty acid oxidation, and at the same time, activated expression of UCP2, which mediates proton leakage by uncoupling ATP synthesis. This lowered

metabolic efficiency may also account for the reduced fat accumulation and weight gain in animals receiving a daily genistein dose of about 200, 400, or 800 mg/kg of the body weight (117). Similar to resveratrol, genistein administration decreased the ATP level in adipocytes (122). Recent clinical trials on genistein in males showed an increase in adiponectin levels and a decrease in cholesterol and insulin levels, with doses that can easily be obtained by a soy rich diet. Table 6 displays recent clinical trials testing genistein with respect to diabetic and inflammatory markers.

### Combined effects of natural products

**Table 7.** Overview of recent clinical trials testing quercetin with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of quercetin
20 athletes	1000 mg quercetin t.w. 1000 mg Vitamin C, 40 mg niacinamide 120 etc.; once	(133)	No postexercise inflammation or immune changes
334/333 non-smoking, un-treated sarcoidosis patients	500/1000 mg quercetin (t.w. 125/250 mg Vit. C and 5/10 mg niacin)/d; 2 w	(134)	Little reduction in HDL cholesterol level and IL-6
12 sarcoidosis patients	2000 mg quercetin within 24 h	(135)	Increase in TAC, decrease in serum MDA, TNF $\alpha$ /IL-10 and IL-8/IL-10 ratio, no effect on serum glutathione
6 healthy females	150 mg quercetin; once	(136)	No changes for respiratory quotient, resting energy expenditure, pulse or blood pressure
38/40 healthy females	500/1000 mg quercetin/d; 12 w	(137)	No influence on innate immune function or inflammatory markers IL-6 and TNF- $\alpha$ or body fat
93 ow patients with MetS	150 mg quercetin/d; 6 w	(138)	Reduction of blood pressure, plasma oxidized LDL, and TNF- $\alpha$ (dependent on apolipoprotein E genotype)
20 rheumatoid arthritis patients	498 mg quercetin (t.w. 399 mg Vit. C)/d; 4 w	(139)	No significant change of inflammation markers in blood
93 ow with MetS	150 mg quercetin/d; 6 w	(140)	Reduction of blood pressure, serum HDL-cholesterol, and oxidized LDL plasma concentration; no effect on TNF- $\alpha$
35 healthy participants	50–150 mg quercetin/d; 2 w	(141)	No effect on TNF- $\alpha$ and oxidized LDL- concentration; no significant change of body composition, resting energy expenditure serum lipids, and lipoproteins
47 T2DM patients	Received oral quercetin (250 mg/d) or identical placebo (cellulose) capsules for 8 w	(142)	Improvement of TAC and reduction of serum concentration of atherogenic oxidized LDL

Ow: overweight; MetS: metabolic syndrome; T2DM: Type 2 diabetes mellitus; d: days; w: weeks; t.w.: together with; IL: interleukin; TNF $\alpha$ : tumor necrosis factor  $\alpha$ ; TAC: total antioxidant capacity; MDA: Malondialdehyde

Some studies propose that the anti-inflammatory and antidiabetic impacts of these natural products could be achieved even if fewer doses are used in combination. These combinations synergistically enhance their anti-inflammatory activity and the therapeutic effect on inflamed adipose tissue. Resveratrol and quercetin in combination activated caspase-3 in human pancreatic carcinoma cells (129), inhibited lipid accumulation, declined the expression of PPAR $\gamma$ , and enhanced apoptosis in 3T3-L1 mouse adipocytes. The effect was more than the expected additive response (130). Another study demonstrated that genistein and resveratrol in combination have a more potent impact on inhibiting adipogenesis and stimulating apoptosis (at dose 100  $\mu$ mol/L genistein +100  $\mu$ mol/L resveratrol) and promoting lipolysis (at dose 25  $\mu$ mol/L genistein +25  $\mu$ mol/L resveratrol) in 3T3-L1 mouse preadipocytes and mature adipocytes than each of these compounds alone (131). It was also reported that the combined treatment of primary human adipocytes with low concentrations of genistein, quercetin, and resveratrol suppressed lipid aggregation in maturing adipocytes, declined cell viability, and stimulated apoptosis, whereas the treatment of the compounds alone had no apoptosis inducing impact (132). Hence, possible toxic impacts could be prevented by decreasing the dosage of each single natural compound. In general, with respect to the data from clinical studies, a combination of several phytochemicals seems to exceed the effect of single administration. Thus, in patients with T2DM or other inflammatory diseases, a more comprehensive knowledge on reasonable combinations of the mentioned phytochemicals can be useful. Interestingly, many natural products contain a well-established combination of several phytochemicals like green tea, grapes, or other fruits, and vegetables. Table 7 shows recent clinical trials testing quercetin with respect to diabetic and inflammatory markers.

### Ginger (*Zingiber Officinale* Roscoe)

The main pharmacological actions of ginger include immunomodulatory, antitumorogenesis, antiinflammatory, antiapoptosis, and antiemetic. Ginger has different components such as gingerols, shogaols, paradols, gingerdiols, etc.

Ginger is the underground stem of the plant *Zingiber Officinale* and most likely originates from southern china. Gingerol has been identified as a major bioactive component. Moreover, 6-gingerol, with a concentration of about 1.3–1.9 mg/g ginger, is the most abundant component in the ginger extract, which has been known to have a strong anti-inflammatory activity (143, 144). Gingerols also possess immunosuppressive (145) and antitumor-promoting properties. They inhibit the expression of COX-2 through inhibiting p38 MAPK and NF- $\kappa$ B activation (146) and decrease TNF- $\alpha$  expression, inflammation, and tumor promotion after application to the skin of mice (5, 147). Also, it has recently been reported that 6-gingerol can upregulate HIF-1 $\alpha$  during mouse embryogenesis and prevent developmental disorders

in the context of hypoxia (148). However, PPAR $\gamma$  is not affected by gingerol, which contradicts other phytochemicals (149). Treatment of mouse adipocytes with gingerol increased differentiation and enhanced insulin sensitive and glucose uptake; hence, it is expected to improve the diabetic state as well (150). Moreover, 6-gingerol at concentrations of 10 and 25  $\mu$ M was shown to have additional effect on the regulation of adipocyte function through inhibiting TNF- $\alpha$ -mediated decrease of adiponectin expression in mouse adipocytes via inhibiting JNK phosphorylation (149). Because of its structural homology to spice-derived compound capsaicin, gingerol is a further VR1 agonist (151), which might play a role in suppressing inflammatory responses of adipose tissue in obesity (152). In a study, animals that were fed a high-fat diet showed a significantly increased serum insulin concentration and better glucose tolerance if their diet was enriched with 2% ginger (153). In a similar study, the daily intraperitoneally administration of raw ginger extract (500 mg/kg bw) significantly decreased serum glucose, triacylglycerol, and cholesterol levels and reversed diabetic proteinuria (154). A recent in vivo study using high-fat fed mice showed that after adding 0.05% 6-gingerol supplementation to the mice diet, their body weight gain and adiposity in association with a modified cholesterol metabolism and fatty acid oxidation significantly decreased (155). However, to obtain an equivalent content of 6-gingerol, consumption of about 2.5 g/day of fresh ginger rhizome per kg bw (a 30 g mouse consuming 3 g/day) is necessary. Also, the administration of a ginger extract to diabetic rats (200 mg/kg bw) reduced their blood glucose levels and affected intra and extramitochondrial enzyme activities (156).

These animal studies show that ginger possesses hypocholesterolemic, hypolipidemic, and hypoglycaemic potential, and thus may be of value in humans. There are only few recent clinical trials focusing on the applicability of gingerol for the treatment of diabetes or related purposes in humans. Recent studies have found that consuming gingerol with the doses between 100 mg and 3 g can lower eicosanoid and lipid levels (157). In Arablou et al. study, 70 diabetic patients were enrolled and consumed 1600 mg ginger versus 1600 mg wheat flour for 12 weeks; and they found that ginger decreased C-reactive protein and prostaglandin E2 (significantly), fasting plasma glucose, hemoglobin A1C, insulin, and HOMA index compared to placebo group. However, there were no significant differences in tumor necrosis factor  $\alpha$  between the 2 groups (158). In another study, Mahluji et al. found that taking 2 g of ginger per day for 2 months has no effect on FPG and HbA<sub>1C</sub>, but can decrease serum insulin and HOMA. This difference is attributable to longer duration of study (159). Bordia et al. observed no significant changes in blood sugar levels in healthy individuals and patients with CAD and Type 2 diabetes with or without CAD after receiving 3g ginger for 3 months (160). Thus, ginger can probably reduce C-reactive protein, prostaglandin E2, blood glucose, insulin levels, and improve insulin sensitivity patients with

**Table 8.** Overview of recent clinical trials testing ginger with respect to diabetic and inflammatory markers

Treatment group	Dose; duration	Ref.	Effect of ginger
16 healthy participants	2 g ginger extract/d; 28 d	(161)	Reduction in PGE2 and other eicosanoids
45 patients with hyperlipidemia	3 g ginger/d; 45 d	(162)	Decrease in triglyceride, cholesterol, LDL, VLDL
35/35 healthy participants	300/600 mg NT (t.w. GA)/d; 24 w	(163)	Ineffective in causing weight loss or in suppressing food intake
64 T2DM patients	2 g ginger extract/d/2 m to NIDDM patients	(159)	Reduction in HbA1c, HOMA, Improvement in lipid profile
70 T2DM patients	1.6 g ginger extract/d/3 m to NIDDM patients	(158)	Reduction in CRP, FBS, HbA1c, HOMA Index, serum insulin, and improvement in lipid profile
41 T2DM patients	received 2 g/day of ginger powder supplement or lactose as placebo for 12 w	(164)	Reduction in FBS, Hb A1c, apolipoprotein B, apolipoprotein B/apolipoprotein A-I and MDA, increase in apolipoprotein A-I
88 T2DM patients	received 3 one-gram capsules containing ginger powder, whereas the PG received 3 one-gram/day microcrystalline-containing capsules for 8 w	(165)	Decrease in FBS, fasting insulin level, and HOMA.

T2DM: Type 2 diabetes mellitus; g: gram; d: days; w: weeks; m: months; t.w.: together with; NIDDM: noninsulin-dependent diabetes mellitus; PGE2: Prostaglandin E2; HbA1c: hemoglobin A1c; HOMA: homeostatic model assessment; CRP: C-reactive protein; FBS: fasting blood sugar; MDA: Malondialdehyde

Type 2 diabetes. Table 8 displays recent clinical trials testing ginger with respect to diabetic and inflammatory markers.

### Effect of phytochemicals on adipose tissue inflammation and diabetes

Adipocytes are the place for energy storage and they produce cytokines including interleukin IL-1 $\beta$ , IL-6, TNF- $\alpha$ , MCP-1, leptin, adiponectin, and many other molecules; thereby, they are referred to as adipokines. In the context of inflammation, the adipose tissue is infiltrated through macrophages, and it also releases proinflammatory mediators, produces reactive oxygen species, and stimulates T-cell responses for successful defense against invading organisms.

### Hypoxia

Obesity decreases tissue mass access to oxygen (166-169). In mitochondria, reactive oxygen species (ROS) production elevates because of hypoxia (170), and consequently, compensatory angiogenesis is induced. This action leads to a reduction of adiponectin expression and secretion and an increase of proangiogenic genes including leptin, IL-6, and the vascular endothelial growth factor (VEGF) by adipocytes (171). It also stimulates expression of IL1 $\beta$ , IL-6, and TNF- $\alpha$  in macrophages (172). Hence, hypoxia is another key player with the potential to activate such inflammatory cascades in adipose tissue. Evidence for this hypothesis was provided previously when it was shown that hypoxia occurs in the adipose tissue of different obese mouse models and contributes to the endocrine dysregulation (172-174). However, it is unclear whether hypoxia in adipocytes triggers the inflammatory cascade per se without interfering with immune cells or other parameters.

Immune cells are known to invade adipose tissue. In adipose tissue, the interaction of immune cells with adjacent adipocytes increases the inflammation. These cells may also directly induce expression of proinflammatory genes by hypoxia (174-182). Some polyphenols as resveratrol, quercetin, and catechins are present at higher concentrations in red grapes. The balance of con-

sumed versus stored energy is represented through the AMP; ATP ratio can be assessed by the AMPK, which plays a central role in the regulation of glucose and lipid metabolism. Its overactivation by high AMP and low ATP levels, respectively, enhances cellular energy levels through suppressing anabolic energy consuming pathways (synthesis of lipids, glucose, and protein) and stimulating energy producing catabolic pathways (the uptake and oxidation of glucose and fat).

One of the important polyphenols mechanisms of action is the activation of PPAR- $\gamma$ , which has regulatory effects on metabolism and inflammatory processes.

PPAR $\gamma$  is restricted largely to adipose tissue and, to a much lesser extent, to immune cells. It is an activator of adipogenesis, as it induces fatty acid synthesis and storage, and thus it is likely inhibited by AMPK (18, 183, 184). Also, PPAR $\gamma$  represses the expression of inflammatory genes as iNOS suppresses transcription factors AP-1 and NF- $\kappa$ B, modulates MAPK activity, and influences glucose uptake (185). Hence, PPAR $\gamma$  is a suitable target for medical intervention, and PPAR $\gamma$ -activating pioglitazone is a well-known antidiabetic drug for treatment of T2DM (186).

These pathways are activated in adipose tissue. Also, JNK is activated by insulin but mediates feedback inhibition of insulin signaling, and thus contributes to insulin resistance (187). The insulin/IGF-1 signaling plays a role in developing cancer and T2DM (188). Sugar-rich food in Western diet induces insulin. The resulting insulin/IGF-1 signaling (IIS) activates the phosphatidylinositol 3-kinase (PI3K) and Akt kinase that mediate the suppression of transcription factors of the Forkhead box O (FoxO)(189), which are supposed to prevent uncontrolled inflammatory response (190), indicating a link between Western diet and development of civilization diseases like cancers and T2DM (188).

### Conclusion

In this review, we discussed the effects of polyphenols on blood glucose and diabetes complications and mechanisms of their actions. To answer these questions, we focused on specific food sources rich in dietary polyphenols.



Interaction of phytochemicals with receptor PPAR $\gamma$  has been shown for resveratrol, genistein, curcumin, capsaicin, catechins, and quercetin however, they had contradictory effects as well (191-193). The phytochemicals were all seemed to activate AMPK or affect inflammatory cascades via proteasomal activation as well as inactivation of key transcription factors, and this may explain most of the properties attributed to PPAR $\gamma$  interaction. Genistein, resveratrol, catechin, quercetin, and curcumin inhibit the respiratory chain and ATP synthetase at the inner mitochondrial membrane (25, 114). Overproduction of ROS via the mitochondrial electron transfer chain is the link between several independent molecular mechanisms (AGE formation, the polyol and hexosamine pathway flux, PKC activation and NF- $\kappa$ B activation) implicated in diabetic side effects (194). Considering the central role of reactive oxygen substances (ROS) (194), the hypoxia-induced ROS production at the mitochondrial electron-transport chain and the subsequent activation of the inflammatory response, it can be stated that polyphenols, as antioxidants, have a beneficial role in improving diabetes side effects (170). Furthermore, comparing traditionally produced food to modern food, phytochemicals may have probably been produced formerly in plants to a much higher amount than in today's industrialized and standardized agricultures because of a lack of stress via pathogens or pests. Thereby, future studies may also take into account different genetic predispositions for some of these compounds if testing their value as a platform for drug development or diet supplements. Animal and human studies have shown that polyphenols, foods, or beverages rich in polyphenols have reduced postprandial and fasting hyperglycemia and improved acute insulin secretion and insulin sensitivity. The possible mechanisms include a decrease in glucose absorption in the intestine and suppression of carbohydrate digestion, stimulation of insulin secretion from the pancreatic  $\beta$ -cells, modulation of glucose release from the liver, activation of insulin receptors and glucose uptake in the insulin-sensitive tissues, modulation of intracellular signaling pathways, and gene expression. Gut microbiota improvement by polyphenols could be an interesting target for exploring the potential role of polyphenols in metabolic balance and weight loss (195). The positive effects of polyphenols on glucose homeostasis have been found in a large number of in vitro, animal models, and some human trials. To confirm the implications of polyphenol consumption in preventing insulin resistance, Type 2 diabetes, and metabolic syndrome, more human trials with well-defined diets, controlled study designs, and investigation of molecular pathways involved in glucose homeostasis are needed. However, a limitation in clinical studies is the heterogeneous bioavailability and rapid metabolism of polyphenols.

### Conflict of Interests

The authors declare that they have no competing interests.

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