

R E V I E W

The effects of catechins on related risk factors with Type 2 diabetes: a review

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Summary. Insulin resistance in patients with diabetes mellitus causes complications such as cardiovascular and renal diseases. Studies have shown that catechins can be effective in controlling hyperglycemia and preventing the complications of diabetes by improving insulin sensitivity and reducing the risk factors for Type 2 Diabetes Mellitus such as oxidative stress, dyslipidemia and obesity. The aim of the present study is a review of the studies conducted in the field of the effect of catechins on the improvement of the risk factors associated with Type 2 Diabetes Mellitus. This review study was conducted by searching in the databases of *Science Direct*, *Scopus*, *PubMed* and using the keywords, such as catechins, green tea, insulin resistance, diabetes mellitus, hyperglycemia, obesity, dyslipidemia and oxidative stress. In this study, articles published between the years 2000-2016, were used. The results of the review of the studies showed that the catechins and food containing them can improve hyperglycemia, oxidative stress, dyslipidemia and obesity in patients with Type 2 Diabetes Mellitus.

Key words: catechin, Diabetes Mellitus Type 2, dyslipidemia, obesity, oxidative stress

Background

Diabetes mellitus is one of the most common metabolic diseases. The prevalence of diabetes has increased dramatically in recent decades (1). Global diabetes prevalence increased from 4.3% (in 1980) to 9.0% (in 2014) in men, and from 5.0% to 7.9% in women. The number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014 (2). Lifestyle and changing dietary habits, which with the industrialization of society causes a wide range of diseases, are a major cause of the increasing prevalence of diabetes type 2 (3-5). Uncontrolled type 2 diabetes lead to complications, such as coronary ar-

tery diseases, peripheral vascular diseases, retinopathy, cerebral vascular diseases, neuropathy and nephropathy (6). Researchers attempt consistently in order to achieve a safe and efficient therapeutic approach for the treatment of type 2 diabetes. Many chemical agents are available for the control and treatment of diabetes, but to date, no full recovery of the disease has been reported. Furthermore, more oral drugs are costly and have side effects. On the other hand, numerous medicinal plants have been introduced that have shown the potential for reducing the blood glucose and preventing the complications of type 2 diabetes (7-10). Many of the properties of the medicinal herbs are originated from their active ingredients that mainly are classified

in the category of antioxidants. Catechin is one of the antioxidants contained in the medicinal plants that have potential for the treatment of type 2 diabetes.

A large number of interventions and epidemiologic studies reported that Catechin reduces the risk of chronic diseases such as cardiovascular disease (11). Some human and animal Interventional studies suggest that green tea extract or Epigallocatechin gallate (EGCG) can have beneficial effects on blood sugar control (12, 13). EGCG can cause removal of ROS and decrease oxidative stress (14). It is likely that catechins and their food sources prevent the complications of diabetes by reducing the expression of proinflammatory cytokines. While the beneficial effects of catechins in the health and treatment of diseases have been reported, but high doses of catechins may have side effects (15). Some animal studies have reported that taking high doses of catechin can induce oxidative stress in the liver and pancreas tissue (16).

Despite conflicting studies on the effects of catechin in the treatment of type 2 diabetes, limited review studies have been published in this area. So this review article has been designed in order to study the effects of catechin on the risk factors for type 2 diabetes.

Catechins and their sources

Catechins are considered as family polyphenolic antioxidants. Due to their carbon structure, Polyphenols are mainly divided into categories of phenolic acids, flavonoids and lignans. Flavonoids are the most abundant polyphenols in the diet. Flavonoids are divided into flavones, flavonols, isoflavones, anthocyanins, flavanols, the proanthocyanidins and flavanones. Some of these flavonoids are found only in a small number of foods. Soy in isoflavones, citrus fruits in flavanols citrus, fruits and vegetables in flavonols, are considered as their major food sources (17).

Catechins are considered as the most main flavones. Catechin types include: catechin, galocatechin, catechin-3-gallate, Gallocatechin 3- gallate, epicatechin, epigallo catechin, epicatechin 3- gallate, epigallo catechin-3-gallate. Green tea is considered as the richest source of catechins. Among the catechins, EGCG is the most abundant and strongest catechins in the green tea and includes 65% of the total content of catechin in green tea (18). In addition, catechins

are also abundantly found in chocolate. The content of polyphenols is different in types of chocolate, and dark, milk and white chocolates include the maximum value, respectively (19).

Materials and Methods

This review study has been conducted by searching scientific databases such as *Scopus*, *Science Direct*, *Pubmed*. Articles were searched using keywords: Catechins, green tea, insulin resistance, diabetes mellitus, hyperglycemia, obesity, dyslipidemia and oxidative stress in the articles published between from 2000 to 2016. In this study, a variety of studies, including interventional, cohort, case-control, cross-sectional and meta-analysis were reviewed. Based on the objectives of the study the articles were included. These objectives were: The effect of catechins on blood glucose, the effect of catechins on obesity, the effect of catechins on oxidative stress and the effect of catechins on dyslipidemia. At first, on the basis of titles related to the objectives of this study, the articles were reviewed. After studying abstract for eligibility, if it was qualified, the main body of the article was studied and analyzed. In the beginning, 534 articles, which were potentially associated with the objectives of the study were identified. After studying the full text of these articles, finally, 74 articles were included in this study.

Results

Catechins effect on hyperglycemia

In vivo studies have shown that green tea can improve insulin sensitivity (20). Animal studies have reported the hypoglycemic effect of green tea extract as a rich source of catechins (21). Epidemiological studies have reported that green tea consumption may reduce the risk of type 2 diabetes (22). A clinical trial study showed that supplementation with green tea extract reduces the glycated hemoglobin in people with abnormal blood sugar (23). It is reported that EGCG causes an increase in insulin sensitivity and facilitates entry of glucose into cells (24). Liu et al.'s study showed the EGCG supplementation for 12 weeks in

Table1. The effects of catechins on related risk factors with Type 2 diabetes

Variable	Catechins	Models	Effects	Reference
	Green tea-extract powder containing 544 mg polyphenols (456 mg catechins) for 2 months	Subjects with glucose abnormalities	Decrease in hemoglobin A1c level. No significant changes in FBS and Insulin resistance	(23)
	EGCG supplementation for 12 weeks	SAMP8 mice	Improved glucose homeostasis	(25)
Hyperglycemia	Green tea (containing 582.8 mg of catechins), 12 weeks	patients with type 2 diabetes	Decrease in hemoglobin A1c	(26)
	Green tea extract containing 856 mg of EGCG	obese individuals with type 2 diabetes	Decrease in HbA1C, HOMA-IR index and insulin level	(27)
	400 mg EGCG, twice daily, 8 weeks	Overweight or obese male subjects	No effect on insulin sensitivity, insulin secretion and glucose tolerance	(65)
	30 ml of EGCG-supplemented olive oil	Patients with early atherosclerosis	Decrease in inflammatory parameters: sICAM, white blood cells, monocytes, lymphocytes and platelets.	(66)
	high-fat diet containing 0.1%, 0.2%, or 0.5% EGCG (w/w), 25 weeks	non-obese type 2 diabetic GK rats	Decrease in OHdG and MDA by supplementation with EGCG at 0.1%. Significant reductions in the mRNA levels of genes related to inflammatory responses (IL-1 β , IL-6, IL-18, TNF- α , IFN- γ , MCP-1), 8-OHdG, and total MDA by EGCG supplementation at 0.1%.	(42)
Oxidative stress	Green tea extract for 8 weeks	Obese subjects with metabolic syndrome	Decrease in MDA and HNE	(67)
	high-dose green tea extract for day 28	Obese diabetic mouse	Decrease in sICAM-1	(68)
	Catechin-rich green tea (catechins 615 mg) beverage per day, 4 weeks	Postmenopausal women	Improved serum postprandial derivatives of reactive oxygen metabolites concentrations. A significant increase in serum postprandial thioredoxin concentrations	(69)
	0.1% EGCG for 34 weeks	Obese and diabetic C57BL/KsJ-db/db Mice.	Decrease in TNF- α . also, decreased the expression of TNF- α , interleukin (IL)-6, IL-1 β , and IL-18 mRNAs in the livers	(70)
	high-dose green tea extract (EGCG) at a daily dosage of 856.8 mg for 12 weeks	women with central obesity	Improve in weight loss, as well as decreases in BMI and waist	(72)
	Decaffeinated green tea extract (catechins 400 mg), twice daily for 6 weeks	overweight and obese men	Decrease in body-weight	(71)
Obesity	beverage containing 625 mg of catechins with 39 mg caffeine for 12 wk	overweight and obese adults	Decrease in total abdominal fat, subcutaneous abdominal fat area	(50)

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Table 1. The effects of catechins on related risk factors with Type 2 diabetes

Variable	Catechins	Models	Effects	Reference
	1 bottle oolong tea/d containing 690 mg catechins, for 12 wk	Healthy men	Decrease in Body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area	(49)
	High-catechin drink (886 mg catechins, 198 mg caffeine/day) for 90 days	overweight subjects	Decrease in intra-abdominal fat area, waist circumference, body weight, total body fat and body fat %	(53)
	Tea (4.5 g green tea/330 ml, 400 mg catechins)	patients with coronary artery disease	Improved levels of postprandial Pancreatic lipase, total cholesterol, HDL-C and LDL-C	(63)
	Green tea extract containing 1315 mg catechins (843 mg EGCG) for 12 month	postmenopausal women	Decrease in TC, LDL cholesterol and non-HDL cholesterol. No change in HDL-cholesterol concentration	(62)
Dyslipidemia	Catechins and EGCG 550 mg, for 56 days	Rats (Sprague Dawley)	cholesterol and LDL were substantially reduced	(73)
	EGCG 25mg/kg/day for 8 weeks	diabetic rats	Improved levels of serum triglyceride, HDL- and LDL cholesterol	(22)
	500 mg green tea extract, three times a day for 16-week	patients with type 2 diabetes and lipid abnormalities	Decrease in triglyceride, increase in HDL-cholesterol, Adiponectin, apolipoprotein A1 and apolipoprotein B100	(74)

SAMP8: senescence-accelerated mice prone 8; OHdG: 8-hydroxydeoxyguanosine; MDA: malondialdehyde; HNE: hydroxynonenals

mice can reduce the levels of FBS and fasting insulin by a change in the expression of GLUT4 gene (25).

A clinical trial conducted by Nagao et al. showed that the 12-week intervention of a catechin-rich drink, including green tea containing 528.8 mg of catechins than a green tea drink containing catechins can significantly reduce insulin levels in type 2 diabetic patients, although no significant difference was observed in fasting glucose levels and glycosylated hemoglobin (26). The results of the clinical trials conducted by Hsu et al. showed that 1500 mg of green tea extract supplementation (856 mg EGCG) for 16 weeks on obese people with type 2 diabetes can cause a significant reduction in fasting insulin, insulin resistance and glycated hemoglobin (27). On the other hand, some studies have reported failing to influence the catechin in improving the glycemic status. In an intervention cross-over study, Baer et al. showed that a five-day intervention using tea along with cat-

echins, on the healthy people cannot change a significant change in the levels of FBS, fasting insulin, area under the oral glucose tolerance curve and area under the insulin level curve (28). In addition, Toolsee et al. reported that intervention of 200 ml of green tea (containing 234 mg of EGCG) for 14 days in patients with pre-diabetes cannot have significant changes in fasting blood glucose and glycosylated hemoglobin (29). On the other hand, some studies have suggested that green tea can increase the level of FBS. A study by Josic et al. showed that an intervention of 300 mg of green tea compared to placebo (drinking water) can increase glucose levels after meals (Postprandial), although the increase in the levels of fasting insulin and area under the curve the blood glucose was observed (30). A meta-analysis of randomized controlled trials reported that the administration of green tea catechins with or without caffeine resulted in a significant reduction in fasting blood glucose (31).

Catechin effect on the oxidative stress

Hyperglycemia in type 2 diabetes causes several complications such as nephropathy, decreased insulin secretion from the pancreas, insulin resistance, retinopathy and cardiovascular disease. The major cause is side effects caused by oxidative stress hyperglycemia and leukocyte activity that causes inflammation (32). Recent studies have shown that hyperglycemia causes inflammation directly through increased pro-inflammatory cytokines such as IL-1 β , IL-6, IL8 and TNF- α (33, 34). Through apoptosis in the pancreatic Langerhans islet beta cells, cytokines cause an increase in capacity and a reduction in the risk of developing type 2 diabetes as well as a reduction in insulin secretion capacity (35). Several studies have reported that the expression of pro-inflammatory cytokines are induced by reactive oxygen species (ROS) and are followed by oxidative stress (36). By increasing the activity of mitochondrial respiratory chain, hyperglycemia induces production of ROS (37). On the other hand, antioxidants can reduce oxidative stress and inflammation. Studies show that among antioxidants, EGCG is one of the antioxidants that reduce the risk of cardiovascular disease (38). EGCG can clear ROS in in- vitro (39). In addition, EGCG can reduce the 8-hydroxy guanosine doxycycline (8-OHdG) as one of the DNA oxidation products (40). Through an effect on NF- κ B signaling pathway, EGCG reduces the production of inflammatory cytokines (41). Recently, an experimental study examined effects of EGCG supplementation in non-obese diabetic rats. The results of the study showed that EGCG supplementation can cause a significant reduction in oxidative stress markers such as 8-OHdG and Malondealdehyde (MDA). In addition, EGCG supplementation could cause a significant reduction in the level of inflammation-related genes mRNA (TNF- α , IFN- γ , IL-1 β , IL-6, IL-18, MCP-1), 8-OHdG and MDA in the peripheral leukocytes (42).

Catechins effect on obesity

Through a variety of mechanisms, obesity causes the development of type 2 diabetes. In obesity, growing up in fat cells reduces the antilipolytic activity of insulin on the enlarged fat cells. The reduced antilipolytic activity of insulin increases the free fatty acid level in Free

fatty acid (FFAs) level in the blood circulation. High FFAs circulating in the blood, impair glucose metabolism and increase insulin resistance (43). Adipose tissue is a source of production of inflammatory cytokines. With the increase in the amount of fat tissue, production of inflammatory cytokine also increased. Inflammatory factors released from adipose tissue by reducing lipoprotein lipase activity and increasing the intracellular lipolysis, cause an increase in the level of FFAs in the blood circulation. In addition, adipokines can increase insulin resistance by different mechanisms (44).

Several epidemiological studies have shown that catechins may have anti-obesity effects (45, 46). There have been reports on inverse association between intake of catechins with body mass index (47). A cross-sectional study showed that tea consumption is inversely associated with BMI and waist size (48). A clinical trial showed a 12-week intervention of Oolong tea containing 690 mg catechins than the control group (Oolong tea containing 22 mg catechins) can cause a significant reduction in body weight, BMI and body fat tissue (49). Another study found that intervention of 625 mg of catechins along with 39 mg of caffeine for 12 weeks in adults obese can cause weight loss, total abdominal fat area and subcutaneous abdominal fat area compared to the placebo group (50). Another study found that green tea consumption along with resistance exercise increase lean body mass and waist circumference in addition to reducing body fat (51). A clinical trial study showed that administration of EGCG supplementation (300 mg daily) can decrease respiratory quotient compared to the placebo group (52). In a double blind clinical trial study, anti-obesity effects of catechin-rich drink on overweight subjects were studied. Results showed that consumption of catechin-rich drinks for three months can cause a significant reduction in body fat percentage, body weight, total body fat, body fat, intra-abdominal fat and waist circumference (53).

Catechins effect on dyslipidemia

Disturbances in the metabolism of fatty acids lead to increased levels of FFAs in the bloodstream and will be followed by high triglyceride accumulation in the tissues. Changes in the metabolism of fatty acids by pancreatic beta cell dysfunction and insulin resis-

tance induced in body tissues (such as liver, muscle) will develop type 2 diabetes (54,55). Dyslipidemia is abundantly found in patients with type 2 diabetes (56). Dyslipidemia in diabetic patients can underlie atherosclerosis and cardiovascular disease (57). Therefore, treatment of dyslipidemia in diabetic patients can prevent cardiovascular complications of the disease (58).

Recent studies indicate can be used as an effective and safe treatment to improve the lipid profile (59). It has been reported that the green tea, through reducing the amount of oxidized LDL, improves vascular performance (60). With the intervention of EGCG, decrease in MDA a major lipid peroxidation byproduct has been observed (61). A double blind clinical trial study has investigated the effect of supplementation of catechin-rich green tea extract on lipid profiles in postmenopausal women. The results of the study showed that the intervention of green tea extract containing 1315 mg for one year can cause a significant reduction in the level of total cholesterol, LDL cholesterol and non-HDL cholesterol (62). Another study examined the effect of tea containing 400 mg of catechin on lipid profile changes after breakfast in coronary artery disease patients. The results of the study showed that the catechin-rich green tea after breakfast can cause control level of Serum triglycerides, total cholesterol, HDL-C, LDL-C and pancreatic lipase (63). Recently, the results of a systematic review study showed that consumption of 107- 856 mg/day EGCG for 4 to 14 weeks can reduce LDL-C (64).

Conclusions

The studies reviewed suggest that catechins can be used as an auxiliary treatment for controlling blood sugar and risk factors associated with type 2 diabetes (Obesity, Dyslipidemia, Oxidative stress).

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