

REVIEW ARTICLE

The Effect of Strawberry on Type 2 Diabetes Mellitus: A Review

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ARTICLE INFO

Keywords:

Strawberry
Type 2 diabetes mellitus
Antioxidant

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Received: September 27, 2019

Revised: December 22, 2019

Accepted: January 2, 2020

ABSTRACT

Strawberry fruit has been studied to have a good effect on type 2 diabetes mellitus (T2DM). It has been demonstrated that interventions with various doses of strawberry fruit in preparations such as consumed intact, cooled, extracted and even processed in the powder can provide good benefits against T2DM and to improve insulin sensitivity, blood vessel inflammation and endothelial dysfunction and to reduce blood sugar. This review explains how the antioxidants in strawberries can directly affect type 2 diabetes mellitus biomarkers, especially in T2DM model mice and rats.

Please cite this article as: Putri MD, Wiboworini B, Dirgahayu P. The Effect of Strawberry on Type 2 Diabetes Mellitus: A Review. Int J Nutr Sci. 2020;5(1):1-6. doi: 10.30476/IJNS.2020.84050.1041.

Introduction

Diabetes mellitus (DM) is a chronic congenital disease caused by a deficiency in insulin production from pancreas, or by the ineffectiveness of insulin produced, resulting in an increase of blood glucose concentration (1). Type 2 Diabetes Mellitus (T2DM) is a disease that damages the regulation of blood glucose homeostasis in the body characterized by fasting blood glucose (FBS) levels above 126 mg/dL (2) stroke, peripheral neuropathy, renal disease, blindness and amputation. The best-known predictors of increased diabetes risk are elevated fasting plasma glucose, elevated 1- and 2-hour plasma glucose after an oral glucose tolerance test, obesity and evidence of impaired insulin action. However, the mechanisms by which people with impaired fasting glucose and/or abnormal glucose tolerance 'progress' to overt T2DM are not completely understood. Moreover, T2DM is

defined in a 'negative' sense (hyperglycaemia not accounted for by autoimmune destruction of islet cells or other known causes. T2DM contributes for more than 90% of patients with diabetes and causes microvascular and macrovascular complications (3).

In 2018, the World Health Organization (WHO) reported that the incidence of diabetes mellitus worldwide increased to more than 400 million population compared to 2016 (4). In 2014, it was recorded that T2DM affected 9% of the world's population, both in developed and developing countries, and directly caused 1.5 million deaths in just that year (5). In Indonesia, based on the 2018 Riskesdas data, the prevalence of Diabetes Mellitus based on doctor diagnoses in the population aged ≥ 15 years as Province based on blood tests has increased from 2013 to 2018, from 6.9% to 10.9% (6).

In T2DM, hyperglycemia is caused by the inability of insulin to mobilize blood glucose into cells due to

insulin receptor resistance. Hyperglycemia increases glucose auto-oxidation to form free radicals. In hyperglycemia, the formation of a free radical or Reactive Oxygen Species (ROS) came from glucose oxidation, non-enzymatic protein glycosylation, and oxidative degradation of glycosylated proteins (7). ROS is actually a natural by-product of various metabolic processes and produced at low levels during normal metabolism (8). Excessive oxidative stress levels due to abnormal glucose metabolism can be controlled by regulating food intake, especially foods that contain antioxidants (8).

Currently, there are many alternative therapies using nutrients for T2DM such as using juice that has been widely used because it is made from natural ingredients, safe for consumption, non-toxic, fewer side effects than synthetic sources and is easily available (9). A study revealed that the administration of strawberry juice that was orally administered at a dose of 1 ml/100g body weight/day in streptozotocin-induced diabetic rats for four weeks could reduce serum triglycerides (TG), blood glucose, serum insulin, total lipids (TL), total cholesterol (TC), low density lipoprotein (LDL) and malondialdehyde (MDA) (10). Other studies have shown that treatment with strawberry extract decreased serum lipid profile, liver function tests, also creatinine and caused a significant increase in antioxidant status in diabetic rats (11).

Nutritional Content

Strawberry is an herbal genus in the family Rosaceae (called *Fragaria*), with more than 20 species with several levels of ploidy (12). Rosaceae is mostly a family of trees (plants), but while *Fragaria* is associated with apples, almonds, and various ornamental plants, the genus is genetically most similar to raspberries and roses. The edible red part is actually not a fruit in the botanical sense, but a receptacle of a flower. Receptacle is a flower base that develops into an edible part of strawberries. The fruit part is called achenes and is like seeds that appear on the surface (13) (13). Strawberry, which is widely cultivated today (*Fragaria x ananassa*), is an artificial hybrid between *Fragaria chiloensis* and *Fragaria virginiana* which are American octopus species (14). Overall, the taxonomy of strawberries was presented in Table 1.

Low total calorie content in 100 grams of strawberry only provides 32 kcal, that makes strawberries a healthy food choice. According to the data available in Table 2, strawberries contain sources of B vitamins, vitamins C and E, potassium, folic acid, carotenoids, and flavonoids such as

Table 1: Taxonomy of strawberry

Taxonomy	
Domain	Eukaryota
Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Dicotyledonae
Order	Rosales
Family	Rosaceae
Genus	<i>Fragaria</i>
Species	<i>Fragaria xananassa</i>

Source: CABI, 2019 (15).

pelargonidin, quercetin, and catechin. This fruit is also rich in manganese. Strawberry is also considered as a source of potassium, iodine, magnesium, copper, iron, and phosphorus (16). The antioxidant content in strawberries comes from achenes and flesh of the fruit. It was shown that although strawberries contain only 1% achene based on net weight (17), but achenes contribute to 81% of antioxidant capacity (TEAC) (18). Achene has been investigated to contribute a significant fraction to the content of phenolic acids and hydrolyzed tannins in all fruits (19). Strawberry is a fruit that is rich in phytochemical (ellagic acid, anthocyanins, quercetin, and catechin) and vitamins (ascorbic acid and folic acid) (20) a rich source of phytochemicals (ellagic acid, anthocyanins, quercetin, and catechin).

The main phenolic compounds in strawberries are anthocyanin, followed by flavonols, hydrolyzed tannins (ellagitannins and gallotannins), phenolic acids (hydroxybenzoic acid and hydroxycinnamic acid), and condensed tannins (proanthocyanidins). Anthocyanin is the most polyphenol mixture in strawberry, and more than 25 anthocyanin pigments have been supported in various varieties of strawberry by various research groups. Many studies reported anthocyanin compositions ranging from 150 to 800 mg/kg-1 of their net weight (16). The authors showed that in 3.6 ml strawberry juice, 194.35 ppm Anthocyanin, 5.24% wb Antioxidant and 0.129% wb total phenolic are found.

Antioxidant of Strawberry and Type 2 Diabetes Mellitus

Strawberry juice significantly inhibits free radicals (21) and reduces the proliferation of lipoprotein induced by ox-low-density in mouse aortic smooth muscle cells (22). Studies also revealed that cellular antioxidant activity (CAA) and oxygen radical absorption capacity (ORAC), among 25 fruits commonly consumed by citizens in the United States, strawberries were the largest contributors to the CAA diet (23). Meanwhile, the study also

Table 2: Nutrient composition of strawberries (Value per 100 g).

Nutrient	Unit	Raw Strawberry	Frozen (Unsweetened)	Sweetened whole
Energy	Kcal	32	35	78
Protein	g	0.67	0.43	0.52
Total lipid	g	0.3	0.11	0.14
Carbohydrate	g	7.68	9.13	21
Fiber	g	2	2.1	1.9
Total sugar	g	4.89	4.56	18.61
Water	g	90.95	89.97	78.05
Vitamin C	mg	58.8	41.2	39.5
Folate	µg	24	17	4
Total saturated fatty acids	g	0.015	0.006	0.007
Total monounsaturated	g	0.043	0.015	0.019
Total polyunsaturated	g	0.155	0.054	0.068
Cholesterol	g	0	0	0
Iron	mg	0.41	0.75	0.47
Potassium	mg	153	148	98
Zinc	mg	0.14	0.13	0.05

Source: Padmanabhan *et al.*, 2016 (16).

illustrated that when comparing ORAC activity among berries, the highest antioxidant activity was in strawberries, followed by black raspberries, blackberries, and red raspberries (24).

Polyphenols play a role in reducing levels of free radicals such as superoxide, peroxy, alkoxy, and hydroxyl radicals by donating hydrogen atoms (25, 26). Provision of antioxidants and polyphenol compound components can capture free radicals, reduce oxidative stress and can reduce TNF- α expression. Phytochemical compounds are able to be manipulated by various mechanisms, so as to reduce the complications of diabetes through reducing oxidative stress, ROS and TNF- α (27). The polyphenol content in strawberries can increase glucose metabolism and peripheral glucose uptake in insulin-sensitive tissue by increasing translocation and GLUT4 activity and reducing oxidative stress and inflammation (28, 29).

The most common anthocyanins found in strawberries are glycosidic derivatives of pelargonidin and cyaniding (30). Anthocyanins are responsible for the red color in strawberries. The anthocyanin content of strawberries can reduce glycemia and increase insulin sensitivity in diabetic rats (31). This is because anthocyanin can increase insulin signaling by stimulating tyrosine phosphorylation from insulin receptors and by increasing glucose transporters that are insulin-regulated (GLUT4) expression in streptozotocin-diabetic mouse muscular tissues (28). Strawberry can also increase insulin sensitivity by increasing insulin signaling and glucose transport in skeletal muscle cells rangka (32).

Anthocyanins regulate carbohydrate metabolism in the body by upregulating GLUT4 translocation, increasing activation of PPAR γ (receptor-activated

peroxisome- γ receptors) in adipose tissue and skeletal muscle and increasing secretion of adiponectin and leptin. Anthocyanins can reduce insulin resistance in diabetes due to upregulation of GLUT4 gene expression, activation of AMP-activated protein kinases and downregulation of retinol 4 binding protein (RBP4) expression. Anthocyanin also increases the absorption and utilization of glucose by tissue in streptozotocin-induced diabetic rats, and protects pancreatic cells against necrosis caused by streptozotocin. Another reason that causes anthocyanins can lower blood sugar levels in rats that eat anthocyanin-containing foods compared to those that do not is because anthocyanins can inhibit intestinal α -glucosidase and pancreatic α -amylase (33).

Anthocyanins are glycosides consisting of aglycone components (anthocyanidins such as cyanidin, delphinidin, malvidin, peonidin, pelargonidin, and petunidin) and some are sugar (glucose, xylose, galactose, and arabinose) (34). It was shown that supplementing nutritional strawberry foods (2.35% freeze-dried strawberry powder in diet pellets (w/w), equivalent to two human servings of fresh strawberries (~ 160 g strawberries)) can reduce vascular inflammation and improve vascular dysfunction in diabetic rats and this is due to circulating metabolites that mediate the vascular effects of strawberry anthocyanin (35).

Other research on vitamin C content in strawberries shows that the administration of high doses of vitamin C (2 g/day) can improve the health of diabetics (7, 36, 37). Vitamin C has therapeutic potential for insulin sensitivity (38). Vitamin C conjugate bonds can stabilize radical electrons with electronic resonance which is then resolved by scavenging proteins. This neutralizes

oxidation that caused by radicals (39). Vitamin C helps prevent complications of T2DM by inhibiting the production of sorbitol. Sorbitol is a byproduct of sugar metabolism which will be accumulated in cells and contribute to the development of neuropathy and cataracts. Giving vitamin C 1000-3000 mg/day in diabetics can reduce sorbitol production. It is recommended for diabetics to consume lots of foods containing quite high vitamin C content such as strawberries, because it can prevent various diabetes complications (36).

Increased glycemic levels are mainly initiated by the beneficial effects of antioxidants on β cells. Vitamin C can reduce glucose toxicity and contribute in part to the prevention of decreasing β cell mass. Another explanation that vitamin C can reduce blood glucose levels is that plasma vitamin C levels play a role in modulating the action of insulin in diabetics. The increase in the action of insulin which is mediated by vitamin C is mainly caused by an increase in non-oxidative glucose metabolism (40).

In diabetes, the occurrence of insulin insufficiency and hyperglycemia can affect changes in almost all metabolic pathways. It was demonstrated that the ability of strawberry extract to reduce diabetes complications is mainly due to its antioxidant content, namely vitamin C. Strawberry can provide antioxidant and hypoglycemic effects from water (strawberry water extract: WES) and methanol extract (methanolic strawberry extract: MES) in diabetic rats induced alloxan at a dose of 50 mg/kg bw. This is because strawberry extract will restore the structural integrity of beta cells and mobilize synergistic action with insulin to reduce levels of hyperglycemia. Strawberry extract will also facilitate insulin secretion in the bound form to increase low insulin levels (32).

Anti-Diabetic Action of Strawberry

Insulin is a major determining factor in glucose homeostasis, however, other non-insulin-dependent mechanisms also play a role in regulating glucose homeostasis, such as antioxidants. The polyphenol content in strawberries has an effect on insulin levels related to pancreatic cell function and insulin secretion and peripheral tissue sensitivity and insulin independent mechanisms, such as impaired glucose absorption (41). The main phenolic compounds of quercetin in strawberries, namely ellagic acid, and catechin, in their pure form, have been reported to have antidiabetic activity. Studies in diabetic rats induced by streptozotocin and nicotinamide (STZ+Nic) proved that administration of aqueous (water) strawberry extract (2 g/kg/day), hydro-alcoholic strawberry extract (2 g/kg/day) and

alcoholic strawberry extract (2 g/kg/day) significantly increased PPAR- α expression which might be one of the factors to reduce serum triglyceride levels and significantly reduce regulation of TNF- α and IL6, thereby reducing serum triglyceride levels and inhibit lipogenesis, and with anti-inflammatory effect (11).

Hypoglycemic Activity of Strawberry

Studies on diabetic-induced diabetic rats showed that administration of 50 mg/kg of strawberry water extract and 50 mg/kg of methanol extract of strawberry for 45 days effectively reduced levels of free radicals produced based on examination of 1-diphenyl-2-picrylhydrazyl (DPPH) and 2-azinobis (3-ethylbenzothiazoli-ne-6-sulfonic acid) (ABTS) *in vitro*. This is due to the polyphenolic content of strawberries, which are mostly anthocyanin. The possible hypoglycemic mechanism of strawberry extract is due to the facilitation of insulin-mediated glucose absorption by cells. The extract can directly or indirectly increase insulin levels by existing pancreatic beta cells. Strawberry extract will restore the structural integrity of beta cells and mobilize synergistic action together with insulin to potentiate the reversal of hyperglycemic conditions. The extract will also facilitate insulin secretion in the bound form to reverse low insulin levels (32).

Other Studies

Whether strawberry supplementation with a nutritional dose can improve blood vessel inflammation and endothelial dysfunction in T2DM model mice is a question. Endothelial dysfunction plays an important role in the development of vascular complications and atherosclerosis in T2DM (42, 43). Evidences revealed that endothelial dysfunction associated with endothelium-dependent vasodilatation that is dependent on resistance arteries contributed to an increase in blood pressure in T2DM mice. The strawberries used were 2.35% freeze-dried strawberry powder which is equivalent to 2 servings of fresh strawberries at a human dose (± 160 g strawberries per day). After 10 weeks, mice given the strawberry intervention showed that strawberry supplementation could reduce blood vessel inflammation and endothelial dysfunction. In addition, arterial hypertension observed in the T2DM model reduced by the presence of strawberry supplementation (44).

Another study with the same dosage investigated the effect of strawberry supplementation on intestinal microbiota in general and specifically on T2DM mice model. Intestinal microbiomas play an important role in anthocyanin metabolism and are

one of the important mechanisms of anthocyanin properties in improving health status. It was shown that supplementation of strawberries with nutritional doses induced significant changes in the composition and functional potential of intestinal microbiomas in T2DM mice (35).

Conclusion

The available evidences on the effect of strawberry antioxidants would be of great interest in diabetes prevention and as hypoglycemic activity in T2DM. Anthocyanins in strawberries have a marked effect on anti-diabetic effects, decrease blood sugar, improve blood vessel inflammation and endothelial dysfunction. Giving the right dose can have a real effect, so that when applied to humans, it is expected to have an efficient effect. Anthocyanin as the majority group of antioxidants in strawberries was shown to have a promising effect on T2DM.

Conflict of Interest

None declared.

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