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Tomato (*Solanum lycopersicum L.*) and Type 2 Diabetes

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Running title: **Tomato and diabetes**

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ABSTRACT

Since the late 1990s, various basic studies and clinical research have linked tomato to type 2 diabetes. This link, however, has yet to be understood and summarized. The present review systematically summarizes the effect of tomato on type 2 diabetes. The PubMed, Web of Science, and Embase databases were searched for reports published (in the English language)

from December 1999 to August 2017 using the keywords “tomato” and “diabetes.” Relevant references from particular publications were also considered. To date, studies in humans have not shown a significant relationship between tomato and the risk of type 2 diabetes, whereas mainstream *in vivo* system studies have generally shown that tomato or its bioactive compounds may have an anti-hyperglycemic effect. Nevertheless, tomato (fresh or cooked) has been found to be favorable for diabetic conditions because it decreases diabetes-induced oxidative stress, inflammation, accelerated atherosclerosis, and tissue (i.e., retinal, renal, and musculoskeletal) damage. Further studies in humans are very important toward elucidating the hypoglycemic response of tomato or its derived compounds in diabetic conditions.

Keywords: Tomato; type 2 diabetes; insulin resistance; anti-hyperglycemic effect; oxidative stress; inflammation; atherosclerosis

INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes, is a global health problem because the number of people with this illness has been growing yearly. Worldwide, the prevalence of diabetes mellitus among adults is approximately 8.5% (1). According to the World Health Organization website, from 2000 until 2012, diabetes mellitus has remained one of the top 10 leading causes of death in humans. Therefore, any research or report that examines an effective therapy or household remedy to manage or prevent diabetes is highly justified.

Given that synthetic anti-hyperglycemic agents may induce various side effects, the World Health Organization expert panel has recommended that anti-hyperglycemic foods and agents from plant origins be investigated, screened, and reported. In addition, diet is well-known to be intimately linked with the risk of type 2 diabetes and several studies support the hypothesis that many cases of type 2 diabetes could be prevented by following a healthy diet (i.e., a diet rich in vegetables) (2-5). The present work provides an important contribution in this context by systematically reviewing and summarizing the effect of tomato (*Solanum lycopersicum L.*), as one of the most edible vegetables in the world, and its bioactive compounds on diabetes, in particular type 2 diabetes.

Tomatoes have low amounts of carbohydrates and energy (~ 3.9 per 100 g) and are rich in potential antioxidants, such as lycopene, ascorbic acid, β -carotene, flavonoids (i.e., kaempferol), tocopherol, folic acid, and other small bioactive molecules (Figure 1); in addition, they contain a good amount of key minerals, such as potassium and magnesium (6-10). This inimitable composition is suggested to be favorable for diabetic conditions (6).

Therefore, since the late 1990s, various basic studies and clinical research have linked tomato to type 2 diabetes; this link, however, has yet to be understood and summarized both narratively and systematically. The present review summarizes the effect of tomato on diabetes, mainly type 2 diabetes. To achieve this, the PubMed, Web of Science, and Embase databases were searched for reports published (in the English language) from December 1999 to July 2017 using the keywords “diabetes” and “tomato.” Further, relevant references from specific published papers were reviewed and considered.

ANTI-HYPERGLYCEMIC EFFECT OF TOMATO

In general, a diet rich in vegetables has been suggested to be associated with a decreased risk of developing type 2 diabetes (11). However, a prospective cohort study on 35,783 women in the United States showed a poor association between dietary intake of lycopene-containing vegetables, such as tomato, and the risk of type 2 diabetes (12). In addition, supplementation with β -carotene, a red-colored pigment abundant in vegetables and fruits, including tomato, did not prevent type 2 diabetes in male smokers, and no correlation was found between serum levels of β -carotene and risk of type 2 diabetes (13).

A study by Upritchard et al. (2000) showed that the consumption of commercial tomato juice at 500 mL/day by diabetic patients (n = 57) for 4 weeks increased the plasma lycopene level but did not change the plasma glucose concentration (14). Similarly, a study on diabetic sand rats by Pollack et al. (1999) found that natural tomato extract at 0.2% did not lower the plasma glucose level (15).

In contrast, certain compounds in fresh or processed tomato have been determined to exert an anti-hyperglycemic effect. The oral administration of tomato extract lycopene (90 mg/kg of body weight) to streptozotocin (STZ)-induced hyperglycemic rats resulted in a decreased fasting serum glucose level (16). In humans, this therapeutic dose of lycopene is equivalent to ~ 14.5 mg/kg of body weight (17). The anti-diabetic effect of lycopene may be due to its antioxidant activity, which lowers the level of free radicals formed (16). The administration

of kaempferol, an antioxidant flavonoid found in tomato, to STZ-diabetic rats was found to normalize plasma glucose (18).

In addition, obese diabetic mice fed 13-oxo-9,11-octadecadienoic acid, a bioactive compound present in processed tomato juice, and an isomer of 9-oxo-10,12-octadecadienoic acid present in fresh tomato, at 0.02% to 0.05%, respectively, had lower plasma glucose (19). Moreover, the oral glucose tolerance test carried out in the same study showed that the plasma glucose level in mice fed 0.05% 13-oxo-9,11-octadecadienoic acid decreased more rapidly than that in normal mice (19). Mechanistically, 13-oxo-9,11-octadecadienoic acid increased the concentrations of insulin and adiponectin, an adipocytokine that ameliorates insulin resistance, in the tested diabetic mice compared with controls, which could have resulted in the observed anti-hyperglycemic effect of this compound (19). Additionally, 13-oxo-9,11-octadecadienoic acid is a potent activator of peroxisome proliferator-activated receptor α , a nuclear receptor with an anti-hyperglycemic effect (19). An *in vitro* study confirmed these findings in cultured adipocytes (20). Furthermore, long-term tomato intake by patients with type 2 diabetes resulted in decreased glycosylated hemoglobin levels (21). In these patients, an antioxidative stress effect (i.e., higher antioxidant enzyme activity and lower lipid peroxidation rates (22)) was observed after tomato consumption (21).

A very recent study conducted by Zidani et al. (2017) revealed that BALB/c male mice on high-saturated fat/high-cholesterol diets supplemented with dry tomato peels at 9 – 17% for 12 weeks had lower insulin resistance, as indicated by homeostatic model assessment-insulin resistance (HOMA-IR), and lower plasma glucose concentrations (23).

TOMATO PREVENTS OXIDATIVE DAMAGE IN DIABETIC CONDITIONS

Table 1 presents a summary of the studies performed on tomato and its derived compounds and their reported effects in preventing diabetes-induced oxidation. The data indicate that tomato (fresh or cooked) or its derived compounds, such as lycopene, kaempferol, and naringenin, show potent antioxidant effects against diabetes-induced oxidative stress. This antioxidant effect mainly occurs by enhancing the activities of antioxidant enzymes, increasing the level of non-enzymatic antioxidants, and decreasing the formation of reactive oxygen species (i.e., H₂O₂).

In obese mice, lycopene supplementation increased the concentration of adiponectin, an adipocyte-specific adipokine that effects insulin sensitization, in the blood and the mRNA expression of adiponectin in adipose tissues [\(24\)](#). The non-enzymatic glycosylation of proteins (glycation reaction), which occurs more rapidly in diabetic conditions, generates reactive oxygen species, such as superoxide ions, leading to cellular oxidative stress [\(25, 26\)](#). This state may occur in the pancreas, resulting in β -cell destruction and shifting the progress of insulin resistance toward insulin deficiency and other diabetic complications [\(26\)](#). Therefore, tomato and tomato extracts, which exhibit strong antioxidant activity, may inhibit the progression of type 2 diabetes by neutralizing the produced reactive oxygen species.

Another indirect mechanism by which tomato decreases oxidative stress and consequently diabetic complications is through the compounds it contains, which are able to chelate metals, such as copper, iron, lead, and mercury [\(27, 28\)](#). This chelating effect decreases the

likelihood of the subsequent Fenton's reaction, therefore decreasing the generation of the hydroxyl radical ($\bullet\text{OH}$) (29).

TOMATO AND DIABETES AS AN INFLAMMATORY DISEASE

A randomized controlled study (n = 106) on overweight or obese female university students in Iran showed that those who consumed tomato juice at 330 mL/day for 20 days had lower serum concentrations of tumor necrosis factor alpha, a cytokine that plays a major role in insulin resistance (30). Moreover, tomato extract inhibits the production of proinflammatory mediators, such as nitric oxide, tumor necrosis factor alpha, and monocyte chemoattractant protein-1, in co-cultures of 3T3-L1 adipocytes and RAW264 macrophages (31). In addition to its antioxidant activity, kaempferol has been identified as an anti-inflammatory flavonoid; its anti-inflammatory effect has been shown in various aging diseases, including diabetes (32).

Furthermore, Navarrete et al. (33) found that aqueous extract of tomato inhibited the expression of interleukin-1 β , an inflammatory cytokine also known as leukocytic pyrogen, and tumor necrosis factor alpha (33). This may occur by inhibiting the activation of nuclear factor (NF)- κB , which could be very beneficial in chronic inflammatory conditions, including type 2 diabetes (33). A recent study by Roy et al. (2016) showed that naringenin (5-10 mg/kg), a flavonoid present in tomato skin, ameliorated diabetes-induced renal injury in Wistar rats (34). Moreover, this study revealed that the downregulation of transforming growth factor- β 1, a cytokine that is involved in cell growth and apoptosis, and interleukin-1,

a proinflammatory cytokine, via the modulation of oxidative stress correlated with decreased apoptosis (34). A very recent *in vivo* study showed that supplementation of a high-saturated fat/high-cholesterol diet in mice with different doses of dry tomato peels (9% and 17%) did not reduce the intensity of inflammation and steatosis, which could be a hepatic manifestation of insulin resistance (23).

ROLE OF TOMATO IN PREVENTING TISSUE DAMAGE IN DIABETIC CONDITIONS

Retinal Damage

In 1999, Pollack et al. found that natural tomato extract at 0.2% did not lower cataract development in diabetic sand rats (15). A meta-analysis by Valero et al. (2011) showed that the non-provitamin A/provitamin A carotenoids ratio was negatively linked with the risk of diabetic retinopathy (35).

Renal Damage

Intraperitoneal administration of naringenin (50 mg/kg daily for 7 days) decreased lipid peroxidation in kidney and liver tissues, as well as the degree of vacuolization in the liver, of alloxan-induced diabetic mice. Thus, naringenin could be very useful in ameliorating diabetes-induced renal damage in humans (36). A recent study by Roy et al. (2016) showed that naringenin (5-10 mg/kg), a flavonoid present in tomato skin, ameliorated diabetes-induced renal injury in Wistar rats (34). Moreover, this study revealed that the downregulation of transforming growth factor- β 1, a cytokine involved in cell growth and

apoptosis, and interleukin-1, a proinflammatory cytokine, via the modulation of oxidative stress correlated with decreased apoptosis (34).

Musculoskeletal damage

Streptozotocin-induced diabetic rats have decreased activities of total ATPases (Na (+)/K (+)-ATPase, Mg (2+)-ATPase, and Ca (2+)-ATPase in erythrocytes and tissues compared with normal rats (37). Kaempferol, a flavonoid found in tomato and other edible plants, given at 100 mg/kg of body weight restored these enzymatic activities in the same tested rats (37). In 2014, Michael et al. identified a small molecule in tomato called tomatidine, which inhibits skeletal muscle atrophy (38). Because skeletal muscle atrophy can be caused by diabetes (39), it can be hypothesized that tomatidine supplementation or tomato consumption could be beneficial for patients with diabetes mellitus.

ROLE OF TOMATO IN PREVENTING ATHEROSCLEROSIS IN DIABETIC CONDITIONS

Obese diabetic mice fed 13-oxo-9,11-octadecadienoic acid, a potent activator of peroxisome proliferator-activated receptor α derived from tomato juice, at 0.05% of their supplemented diet for 4 weeks had lower hepatic and plasma triglycerides (19). Accordingly, 13-oxo-9,11-octadecadienoic acid supplementation or tomato consumption may improve obesity-induced dyslipidemia and hepatic steatosis (19). Upritchard et al. (2000) showed that the consumption of commercial tomato juice at 500 mL/day by diabetic patients (n = 57) for 4 weeks increased the plasma lycopene level and the intrinsic resistance of LDL to oxidation similarly to

supplementation with a high dose of vitamin E (14). The consumption of tomato juice for 3 weeks inhibited platelet aggregation in patients with type 2 diabetes (40). Long-term tomato intake by patients with type 2 diabetes caused no change in their lipid profiles (triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein) or glycosylated hemoglobin levels (21).

Further, lycopene reduces malonyldialdehyde, a biomarker of lipid peroxidation (35). A randomized, single-blinded, and controlled clinical trial by Cuevas-Ramos et al. (2013) showed that overweight women (mean body mass index = 27.6 ± 5.0 kg/m², n = 41) who consumed raw tomato (300 g daily for 2 weeks) had higher levels of high-density lipoprotein cholesterol (41).

In contrast, patients with type 2 diabetes who consumed 200 g of raw tomato daily for 8 weeks had higher serum levels of apoA-I, the main apoprotein in high-density lipoprotein, and lower systolic and diastolic blood pressure (6). This effect is favorable toward delaying the progression of cardiovascular risk in those patients (6). A newly published study by Zidani et al. (2017) indicated that dry tomato peels have an anti-atherogenic effect (23). In this study, dry tomato peels supplemented at 17% of the diet for 1 year decreased the levels of total cholesterol, low-density lipoprotein, and triglycerides, and increased the levels of high-density lipoprotein in mice fed a high-saturated fat/high-cholesterol diet (23). Because of their lipophilicity, lycopene and other carotenoids in tomato are transported by low-density lipoproteins, which may impede the oxidation of these cholesterol related to disease risk, and hence reduce the risk of atherosclerosis (14, 23, 42). In addition, lycopene suppresses the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), an

enzyme involved in cholesterol synthesis (43, 44). Lycopene was found to increase the activity of the macrophage LDL receptor in vitro, similarly to the effect of fluvastatin, a drug used to treat hypercholesterolemia (44). In agreement with these findings, males supplemented tomato's lycopene at 60 mg day⁻¹ for 3 months had lower plasma LDL cholesterol by approximately 14% (44).

CONCLUSION

Studies in humans (4 studies) have revealed that tomato does not ameliorate insulin resistance, whereas the corresponding studies in rodents (5 studies) have shown that certain compounds in fresh or processed tomato exert an anti-hyperglycemic effect. In addition, tomato (fresh or cooked) is favorable for diabetic conditions because it decreases diabetes-induced oxidative stress (9 studies), inflammation (6 studies), accelerated atherosclerosis (8 studies), and tissue (e.g., retinal, renal, and musculoskeletal) damage (8 studies). However, further studies in humans are important toward clarifying the hypoglycemic response of tomato in diabetic conditions. At present, our laboratory is performing a clinical study to explore the short-term effect of tomato on insulin resistance markers (fasting serum glucose, insulin, and glycated hemoglobin (HbA1c)).

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Legends

Table 1: Studies conducted on tomato and its derived compounds and their reported antioxidant effects in diabetic conditions.

Affecter (<i>Tomato or tomato-derived compound</i>)	Dose	Duration	Population	Antioxidant effect	Reference
Tomato-extract lycopene	90 mg/kg of body weight	Single dose	Streptozotocin-induced diabetic rats	(-) H ₂ O ₂ formation (+) Catalase, superoxide dismutase, and glutathione peroxidase	(16, 45)
Natural tomato extract	0.2% of the diet	5 weeks	Diabetic sand rats	(+) Glutathione	(15)
Ripe cooked tomato	200 g of ripe tomatoes (cooked)/day	60 days	Patients with type 2 diabetes	(+) Superoxide dismutase, glutathione peroxidase, glutathione reductase. (-) Lipid peroxidation	(21)
Cooked tomato	200 g/day	30 days	Patients with type 2 diabetes	(+) Superoxide dismutase, glutathione peroxidase, and glutathione reductase (-) Lipid peroxidation	(46)
Tomato-derived lycopene	30 mg/day	4 weeks	Obese patients	(+) Plasma carotenoids	(47)
Kaempferol	100 mg/kg of body weight	45 days	Streptozotocin-induced diabetic rats	(+) Glutathione peroxidase, catalase, and glutathione-S-transferase. (+) Antioxidant status	(18, 32)
Naringenin	(5-10 mg/kg)	10 weeks	Diabetic Wistar rats	(+) Superoxide dismutase, catalase, and glutathione enzyme. (-) Tissue malondialdehyde	(34)
Dry tomato peels	9% or 17% of the diet	12 weeks	BALB/c male mice	(+) Plasma lycopene concentration	(23)

(-) decrease; (+) increase