Lycopene as Antioxidant for Type II Diabetes Mellitus

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Nutrition is of utmost importance in chronic disease management and has often been described as the cornerstone of a variety of non-communicable diseases. In particular, type II diabetes mellitus (T2DM) represents a prevalent and global public health crisis. Lycopene, a bright red carotenoid hydrocarbon found in tomatoes and other red fruits and vegetables, has been extensively studied for its biological activities and treatment efficiency in diabetes care. Epidemiological investigations indicate that lycopene has potential antioxidant properties, is capable of scavenging reactive species, and alleviates oxidative stress in T2DM patients.

Keywords: antioxidant ; complementary medicine ; lycopene ; oxidative stress

1. Introduction

Type II diabetes mellitus (T2DM), which accounts for 90% of diabetes cases, is a global public health crisis. The International Diabetes Federation (IDF) estimated that approximately 463 million adults worldwide are living with diabetes, and 4.2 million people died from diabetes in 2019 [1]. T2DM is a metabolic disease characterized by peripheral insulin resistance and impaired insulin secretion caused by dysfunction of the β-cell in the pancreas [2]. It is mostly seen in older adults, but it has increasingly affected children, adolescents, and younger adults as a consequence of rapid urbanization, unhealthy diets, and increasingly sedentary lifestyles. T2DM is often asymptomatic in the early stage and can remain undiagnosed for many years. Undiagnosed and poorly managed glucose levels are associated with life-threatening complications, such as cardiovascular disease (CVD), neuropathy, nephropathy, and retinopathy. Diabetes not only imposes a huge health burden but also has a substantial economic impact on countries and national health systems, due to the increased use of health services, loss of productivity, and the long-term support needed for the care and treatment of diabetic-related complications [3].

Numerous risk factors are known as contributors to the development of T2DM. Besides lifestyle and genetic factors, earlier epidemiological and animal studies have uncovered the impact of oxidative stress in the pathogenesis of T2DM and its complications [4][5][6][7]. In T2DM patients, hyperglycemia state favors free radical production through several pathways: activation of the polyol pathway, formation of advanced glycation end products (AGEs) and its receptors (RAGE), activation of the protein kinase C (PKC) pathway, and increased glucose influx through the hexosamine pathway. Overproduction of reactive species decreases antioxidant defense system and thus leads to the damage of redox equilibrium, subsequently increasing the risk of developing T2DM complications including heart disease, stroke, end-stage renal failure, blindness, and amputation [8].

2. Lycopene as Antioxidant

The antioxidant property of lycopene has been the main focus of research. The reactivity of lycopene with reactive species is related to its unique molecular and physical structure, including the highly conjugated double bonds which can be easily attacked by electrophilic reagents, and to a lesser extent influenced by either the presence of cyclic or acyclic end groups [9][10]. Among the carotenoids, lycopene is reported as the most efficient singlet oxygen ($^1O_2$) quencher [11] with the physical quenching rate constant (k_q) of $^1O_2 = 3.1 \times 10^{10}$ M^{-1} s^{-1}. The quenching rate was reported as two times higher compared to β-carotene and 10 times higher compared to α-tocopherol. A comparison of the $^1O_2$ quenching ability between lycopene and other carotenoids are described as: lycopene > y-carotene > astaxanthin > canthaxanthin > α-carotene > β-carotene > bixin > zeaxanthin > lutein > cryptoxanthin > crocin > α-tocopherol > lipoic acid > glutathione [12]. The density functional theory study conducted by Zhang et al. [13] applied the optimization configurations of the ground and excited states of lycopene and oxygen, respectively. Another study provided evidence for the high capability of lycopene in preventing nitrogen dioxide-induced oxidation of lipid membranes and subsequent cell death compared to β-carotene [13].

2.1. The Mechanisms of Action of Lycopene in Scavenging Reactive Species

Lycopene has been reported to reduce lipid peroxidation by acting as a chain-breaking antioxidant [14]. This antioxidative role can be seen through its reaction with peroxyl radicals, a reactive species produced in the process of lipid peroxidation that can destruct lipophilic sections. Lycopene is forming new chain-carrying peroxyl radicals that are highly stable than ROS.

Tinkler and colleagues [14] conducted a physical chemistry technique based on singlet oxygen luminescence at about 1270 nm, and a biological cell membrane technique was used to study the quenching of singlet oxygen by lycopene bound to the surface of lymphoid cells. Interaction of lycopene with a peroxyl radical ($ROO^{\bullet}$) will result in adduct formation, the formation of resonance-stabilized carbon-centered radicals. This occurred when the peroxyl radical is attached to the polyene chain, the highly conjugated double bonds of lycopene forming a lycopene–peroxyl radical adduct (ROO–$lycopene^{\bullet}$) (Equation (1)) [14][15].

(1) $\text{Lycopene} + ROO^{\bullet} \rightarrow \text{ROO–lycopene}^{\bullet}$

The compound ROO–$lycopene^{\bullet}$ acts as pro-oxidant by reacting with oxygen to form a new lycopene–peroxyl radical (ROO–lycopene-$OO^{\bullet}$) (Equation (2)). Subsequently, this intermediate (ROO–lycopene-$OO^{\bullet}$) can serve as an initiator for lipid peroxidation by reacting with lipid (RH) (Equation (3)) and forming another peroxyl radical ($ROO^{\bullet}$) with oxygen (Equation (4)), which is more highly stable than ROS. Nevertheless, the peroxyl radical–lycopene adduct (ROO–$lycopene^{\bullet}$) may also be terminated by reacting with other peroxyl radicals to form an inactive end product (Equation (5)).

(2) $\text{ROO–lycopene}^{\bullet} + O_2 \rightarrow \text{ROO–lycopene–OO}^{\bullet}$

(3) $\text{ROO–lycopene–OO}^{\bullet} + RH \rightarrow \text{ROO–lycopene–OOH} + R^{\bullet}$

(4) $R^{\bullet} + O_2 \rightarrow ROO^{\bullet}$

(5) $\text{ROO–lycopene}^{\bullet} + ROO^{\bullet} \rightarrow$ inactive products

Lycopene's chain structure with an extensive conjugated polyene system has increased its ability in scavenging $^1O_2$ as shown in Equation (6) [16]:

(6) $^1O_2 + \text{lycopene} \rightarrow {}^3O_2 + {}^3\text{lycopene}$

$^3\text{lycopene} \rightarrow \text{lycopene} + \text{heat}$

It was also reported that lycopene reacts very rapidly with alkylthiyl radical ($RS^{\bullet}$) and glutathiyl radical ($GS^{\bullet}$) to generate lycopene-alkylthiyl radical adduct (RS-$lycopene^{\bullet}$) and lycopene-glutathiyl radical adduct (GS-$lycopene^{\bullet}$), at the absolute rate constant of 1.6×10^9 M^{-1} s^{-1} and 4.8×10^8 M^{-1} s^{-1}, respectively (Equation (7)).

(7) $\text{Lycopene} + RS^{\bullet} \rightarrow \text{RS–lycopene}^{\bullet}$

$\text{Lycopene} + GS^{\bullet} \rightarrow \text{GS–lycopene}^{\bullet}$

Lycopene in the process of scavenging radicals involves the electron transfer reactions as a result of the formation of lycopene cation radical ($lycopene^{+\bullet}$), anion radical ($lycopene^{-\bullet}$), or alkyl radical ($lycopene^{\bullet}$). For example, inactivation of nitrogen dioxide radical ($NO_2^{\bullet}$) and trichloromethylperoxyl ($CCl_3O_2^{\bullet}$) converts lycopene into radical cations (Equation (8)), whereas the interaction of lycopene with superoxide radical ($O_2^{\bullet-}$) forms lycopene anion radical [17] (Equation (9)).

(8) $NO_2^{\bullet} + \text{Lycopene} \rightarrow NO_2^{-} + \text{Lycopene}^{+\bullet}$

$CCl_3O_2^{\bullet} + \text{Lycopene} \rightarrow [CCl_3O_2^{-}\ \text{Lycopene}]^{\bullet} \rightarrow CCl_3O_2^{-} + \text{Lycopene}^{+\bullet}$

(9) $\text{Lycopene} + O_2^{\bullet-} \rightarrow \text{lycopene}^{\bullet-} + O_2$

Moreover, the formation of both lycopene adducts radical and lycopene cation radical is generated through the interaction between lycopene and the thiylsulfonyl radical ($RSO_2^{\bullet}$), at an absolute rate constant of 1.26×10^9 M^{-1} s^{-1}, as shown in Equation (10):

(10) $RSO_2^{\bullet} + \text{lycopene} \rightarrow [RSO_2^{-}\ \text{lycopene}]^{\bullet} \rightarrow RSO_2^{-} + \text{lycopene}^{\bullet+}$

In contrast, lycopene also acts as a hydrogen donor to reduce the radical. This reaction is known as hydrogen abstraction, as shown in Equation (11) [18]:

$$(11)\ \text{Lycopene} + \text{ROO}^{\bullet} \rightarrow \text{Lycopene}^{\bullet} + \text{ROOH}$$

2.2. Synergistic Effect of Lycopene with Other Antioxidants

The reactivity of lycopene with ROS depends not only on their molecular and physical structure, but also on their location or site of action within the cells, concentration and the partial pressure of oxygen, as well as their ability to interact with others [19]. Lycopene is a highly lipophilic carotenoid located within the hydrophobic core of lipoprotein, therefore exerting higher capability in scavenging free radicals in a hydrophobic environment. However, as a lipid-soluble radical scavenger, lycopene has less interaction with aqueous phase radicals. It was suggested that the scavenging activity of lycopene in the lipoprotein particle can be maximized by its interaction with other carotenoids, for instance, α-tocopherol located near the membrane surface. Specifically, α-tocopherol scavenges lycopene-derived peroxyl radicals (ROO–lycopene–$OO^{\bullet}$) via hydrogen atom donation, giving rise to a relatively stable α-tocopherol radicals ($TO^{\bullet}$) (Equation (12)) [20]. Additionally, lycopene helps in repairing α-tocopherol radicals as shown in Equation (13) [21].

$$(12)\ \alpha\text{-TOH} + \text{ROO–lycopene–OO}^{\bullet} \rightarrow \text{ROO–lycopene–OOH} + \text{TO}^{\bullet}$$

$$(13)\ \text{Lycopene} + \text{TOH}^{+\bullet} \rightarrow \text{TOH} + \text{Lycopene}^{+\bullet}$$

On the other hand, α-tocopherol might play a role in regenerating intact lycopene by reducing lycopene cation radical ($TOH^{+\bullet}$) (Equation (14)) [22].

$$(14)\ \alpha\text{-TOH} + \text{Lycopene}^{+\bullet} \rightarrow \alpha\text{-TO}^{\bullet} + \text{Lycopene}$$

In this context, the synergistic effects between lycopene and α-tocopherol in different cellular locations have provided a greater resistance for lipid and lipoproteins against oxidative damage [23]. Synergistic interactions among lycopene and other carotenoids have also been demonstrated in multiple studies. For example, a study using multilamellar liposomes reviewed an inhibitory effect of lycopene and lutein towards diene hydroperoxides produced from linoleic methyl ester with 2,2′-azobis (2,4-dimethylvaleronitrile) (AMVN)-induced oxidation [24], whereas the interaction of lycopene and vitamin C, E, and β-carotene showed a high scavenging activity on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical than their individual antioxidant activity [25].

3. Lycopene Consumption and T2DM

3.1. Lycopene Status in T2DM Patients

The lycopene status of T2DM patients from different populations has been studied extensively by previous researchers. In a cross-sectional surveillance study, the lycopene level of 24,377 Korean adults (19–74 years) was assessed using 24-h dietary recall. The result showed the dietary lycopene intake was significantly higher in non-T2DM men compared to T2DM men [26][27]. In a case-control study, lycopene intake in T2DM patients was significantly lower compared to age-matched healthy controls. The study further explicated that subjects with proliferative diabetic retinopathy had significantly lower lycopene levels than subjects without diabetic retinopathy or with non-proliferative diabetes [28][29]. This result is in accordance with a community-based cross-sectional study in Australia, which demonstrated a significantly lower level of lycopene in the T2DM-retinopathy group [30][31]. Moreover, Ford et al. [32] reported that the United States (US) population with newly diagnosed T2DM had a significantly lower level of lycopene compared to the US adults with scarce glycemic control. Another study investigating the lycopene status among T2DM patients in Germany revealed the plasma concentration of lycopene was significantly lower in very old T2DM patients (mean age 75.7 ± 0.8 years) as compared to healthy controls. Also, a significant inverse correlation between age and the level of lycopene was reported in the study [33].

3.2. Animal Studies: Lycopene Effects on Glycemic Control and Oxidative Stress Biomarkers

The antidiabetic effect of lycopene has been studied in different animal models with various outcomes. In diabetic rat models (streptozotocin (STZ)-induced), oral administration of lycopene significantly decreased blood glucose levels [6][28][34][35][36][37][38][39][40][41][42][43][44][45][46], reduced HbA1c levels [6][7][40], and increased insulin concentrations [34][37][38][43][44].

Besides the glucose-lowering and insulin-elevating effects, animal studies also demonstrated that lycopene prevents oxidative damage in diabetic rat models. The antioxidant effect mainly occurs by enhancing the activities of antioxidant enzymes and increasing the level of non-enzymatic antioxidants. Indeed, the mechanism of action of lycopene is probably

not only attributed to its scavenging mechanism, but rather due to the molecule itself to induce enzymatic defenses. Overall, such effect was accompanied by a decrease in the formation of ROS (H_2O_2) [26], reductions in MDA concentrations [6][39][43][44][47][48][49][50], and elevation of enzymatic antioxidants [26][30][35][39][40][41][42][43][44][45][46][48][49].

3.3. Human Studies: Lycopene Effects on Glycemic Control

In 2010, Li et al. [29] demonstrated that HbA1c was negatively correlated with lycopene. Coyne et al. [50] reported a significant reduction in plasma glucose and fasting insulin concentrations with increased serum lycopene in T2DM patients. However, She et al. [51] did not find a significant association between HbA1c and lycopene level in a sample of 40 T2DM participants. Bose and Agrawal [52] observed no significant changes in FBG and HbA1c levels for T2DM patients following a 30-day supplementation of ripe cooked tomatoes (200 g tomatoes/day). Similarly, Upritchard et al. [4] supplemented T2DM patients with 500 mL of tomato juice along with Vitamin E and C for 4 weeks, and reported that lycopene supplementation did not affect plasma glucose concentration. Very recently, HbA1c and FPG levels were found to decrease significantly with the higher lycopene intake [53]. The combined application of cross-sectional, case-control, prospective cohort, and randomized placebo-controlled trials generated a discrepancy in outcomes. This disagreement has been attributed to the wide selection of food sources to represent the lycopene intake in the model, disease state, and the sample size of the study.

4. Human Studies: Lycopene Effects on Oxidative Stress Biomarkers and Risk of T2DM

Lycopene-based dietary therapy indicated a significant role in the reduction of oxidative damage and improvement of LDL oxidation. Accordingly, Singh [54] conducted a 3-month-long study to investigate the effect of lycopene administration (4 mg once daily) in T2DM subjects. The levels of MDA, SOD, GPx, GSH, glutathione reductase (GR), and xanthine dehydrogenase (XOD) were determined in blood samples to evaluate the oxidant–antioxidant status. The study revealed significant elevations in the SOD, GSH, GPx, and GR, and a further decrease of MDA and XOD levels in the lycopene-ingesting T2DM patients in comparison to T2DM patients who did not receiving lycopene. Likewise, long-term supplementation of 200 g cooked tomatoes per day in T2DM patients showed significant improvement in the levels of antioxidant enzymes (SOD, GSH, GPx, and GR) and decreased lipid peroxidation rate (MDA level) after 30 days of tomato supplementation [52]. Neyestani et al. [5] demonstrated that administration of 10mg/day of lycopene for 8 weeks significantly increased the serum lycopene levels in T2DM patients, further preventing oxidative damage by inhibiting MDA-LDL formation and increasing TAC level. In addition, to investigate the synergic effects of lycopene and other antioxidants on oxidative stress, 57 T2DM patients were randomized to receive tomato juice (500 mL/day) supplementation along with vitamin E (800 U/day) and vitamin C (500 mg/day), or placebo treatment for 4 weeks [52]. The finding indicated that short-term supplementation of commercial tomato juice increased plasma lycopene levels nearly three folds, and the intrinsic resistance of LDL to oxidation by 42% in well-controlled T2DM, which were almost as effective as supplementation with a high dose of vitamin E. Conclusively, supplementation of lycopene in the short and long term attenuates oxidative damage by increasing the antioxidant enzyme level and reducing lipid peroxidation rate in the individual with T2DM.

On the contrary, some studies reported null effects of lycopene on T2DM. For example, a prospective study in Korea failed to show a correlation between dietary lycopene and the incidence of T2DM, even though lycopene intake was significantly higher in non-diabetic subjects than in diabetic patients [27]. In a European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort study (n = 37,846), Sluijs et al. [55] demonstrated that lycopene intake was not associated with a reduced risk of T2DM. A similar result was depicted in a nested case-control study [56]. After 10 years of follow-up, the study showed no prospective association between baseline plasma lycopene, as assessed by using FFQ, with the risk of T2DM in middle-aged and older women from the United States. Another prospective study demonstrated that dietary lycopene did not reduce the risk of T2DM in a Finnish cohort of men and women [57]. In Asia, a cross-sectional study of the Chinese urban population also reported that lycopene has no protective role on T2DM [51].

5. Mechanisms of Action of Lycopene in T2DM

Lycopene could diminish oxidative damage by scavenging oxidized species and enhancing the antioxidative enzyme activity in T2DM, as evidenced in the animal experiments, and observational and epidemiological studies. It has been proposed that overproduction of ROS could downregulate the antioxidant defense mechanisms, leading to oxidative imbalance. Accordingly, lycopene treatment could upregulate the expression of CAT, SOD, and GPx, and reduce the levels of MDA in the pancreatic tissues [49], in the diabetic kidney [28], and in the furan-induced ovarian tissue injury [45]. Another study found that lycopene attenuates oxidative stress by decreasing serum Ox-LDL and liver thiobarbituric acid

reactive substances (TBARS), and increased the levels of CAT and non-protein sulfhydryl groups in the liver of diabetic rats [30]. Additionally, the interaction between AGEs and its receptor, RAGEs, has been implicated in the oxidative stress-induced phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) (PI3K/Akt) signaling activation. Treatment of lycopene (20 mg/kg/day) for 8 weeks has been shown to promote Akt phosphorylation in diabetic renal tissue [28]. Similarly, 10mg/kg/d of lycopene supplementation for 5 weeks decelerated the ribose-induced AGE formation in HK2 cells and rat kidneys, thereby downregulating the expression of RAGE and protecting against diabetic nephropathy [57].

Moreover, it has been shown that vascular endothelial dysfunction and the number of endothelial progenitor cells (EPCs) are important risk factors for the development of vascular complications in T2DM. Zeng et al. [58] reported that lower cell proliferation, migration, adhesion, and in vitro vasculogenesis capacity, as well as increased EPC's apoptosis, were observed in the high glucose rats group. Lycopene treatment inhibits high glucose-induced EPC injury by inhibiting ROS generation and downregulating phosphorylation of p38 mitogen-activated protein kinases (p38 MAPK). Lycopene also protects EPCs from apoptosis and oxidative autophagy induced by AGEs, as demonstrated in the T2DM rats [59]. Furthermore, lycopene supplementation (4 mg/kg) for 3 months prevents diabetic retinopathy by decreasing TNF-κB and TNK-α level and increasing total glutathione levels (TGSH) and total antioxidant status (TAS) [60]. Also, supplementation of lycopene-rich tomato extract at a concentration of 0.2, 0.4, and 0.8% may dose-dependently inhibit cataractogenesis by reducing aldose reductase activity and upregulating lens protein and GSH levels [46].

Guo et al. [47] suggested that lycopene upregulated heme oxygenase-1 (HO-1) mRNA levels in the diabetic kidneys, thereby maintaining kidney metabolic homeostasis. Notably, HO is a vital enzyme in heme catabolism that mediates the anti-oxidative and anti-inflammatory characteristics through modulating the interleukin 10 receptor 1 (IL-10/1R) pathway. The antioxidative effect of lycopene is also evident in the reduction of 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels. The reduction was typical after the treatment with low, medium, and high doses (10, 20, 40 μM) of lycopene under high glucose conditions, demonstrating that lycopene scavenged free radicals, indirectly alleviating oxidative stress [61].

It is worthwhile to mention that lycopene is able to not only increase the peripheral antioxidative capacity, but also preserve glycemic control and protect against obesity in T2DM. Long-term hyperglycemic and insulin resistance could lead to glucose utilization disorders, which in turn causes excessive accumulation of FFAs and lipids in the bloodstream [62]. Lycopene intervention was demonstrated to regulate the metabolism of glycolipid in diabetic rats by decreasing FBG, glycosylated hemoglobin (GHb), and glycated low-density lipoprotein (Gly-LDL) levels. Lycopene has been proven to improve glucose metabolism by reducing Ox-LDL, thus reducing the occurrence of autonomic oxidation of glucose and lipid peroxidation reaction [45]. Li et al. [28] reported that lycopene acts as a lipid-lowering agent that significantly decreases total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), while at the same time increasing high-density lipoprotein cholesterol (HDL-C) in diabetic renal tissues. Lastly, lycopene treatment has been reported to reduce vacuolization of the islets of Langerhans and the loss of insulin-secreting cells leading to reduced blood glucose levels in diabetic rats [38].

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