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Review Article

Beneficial Effect of Lycopene on Diabetes Mellitus and its Possible Mechanism: A Review

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ABSTRACT

Lycopene has received a lot of attention because of its benefits in various chronic diseases such as cancer, cardiovascular, neurodegenerative, and metabolic diseases such as diabetes. Various studies using cell culture, animals, and humans as subjects have proven the benefits of lycopene in diabetes, but none have yet explained its molecular mechanism in detail. Therefore, this study aims to summarize and describe the benefits of lycopene in diabetes mellitus and the potential underlying mechanisms. This study is a literature review that uses articles obtained from the PubMed and Google Scholar databases by entering the keywords lycopene, diabetes, oxidative stress, inflammation, apoptosis, and autophagy either separately or in combination to obtain a logical concept. There are 33 main articles summarized and discussed in this study. Lycopene shows potential use in the therapy and prevention of diabetes complications, particularly through its antioxidant and anti-inflammatory activities. Lycopene also increases insulin signaling activity via the PI3K/AKT pathway. Moreover, lycopene supplementation contributes to decrease apoptosis in brain cells and weakens apoptosis in podocytes through the autophagy process. Knowing these benefits, lycopene supplementation in diabetics needs to be considered, but further research is needed in the form of large clinical trials to prove the benefits of lycopene in diabetes and the optimal dosage required.

***Keywords*:** Lycopene, Diabetes, Oxidative stress, Inflammation, Apoptosis, Autophagy.

Introduction

Diabetes mellitus (DM) is a chronic and progressive metabolic disease characterized by symptoms of hyperglycemia, an increase in blood sugar levels, the progression of which can cause complications in internal organs, especially the nerves and blood vessels. The International Diabetes Federation in 2019 stated that around 463 million people (8.3% of the world's population) at the age of 20–79 years suffer from diabetes. If these trends continue, by 2045, this will rise to 700 million (9.6%).[1] During the past decades, the prevalence of DM has risen significantly, this is mainly due to the continued rise in the incidence of type 2 DM.[2] Thus, DM is a very common disease and may be considered a growing epidemic and important public health issue.[3,4] Globally, it is recognized as one of the most common chronic diseases associated with premature death and disability due to its long term complications.[3] The progression of DM due to uncontrolled hyperglycemia can cause complications, such as cardiac, cerebral, and vascular diseases (macrovascular complications) as well as neuropathy, nephropathy, and retinopathy (microvascular complications).[3,5] DM is a progressive disease. Although insulin and anti-diabetic drugs are usually effective, most therapies fail to control long-term hyperglycemia.[6] This can actually be overcome by increasing the dose of the drug, but the risk of side effects will also increase, especially in patients with impaired kidney function, it may cause problems.[6–8] In addition, it can also be treated with combination therapy, either with conventional anti-diabetic drugs from different groups or with natural bioactive compounds.[9–11] One of the natural bioactive compounds that has received much attention because it has great potential in the treatment and prevention of chronic diseases is lycopene.[12] Lycopene is a phytochemical from the carotenoid group that is lipophilic and is found naturally, especially in red plants such as tomatoes.[13] Among carotenoids, lycopene is the most potent antioxidant after astaxanthin.[14] Lycopene is able to neutralize reactive oxygen species (ROS) through scavenging and quenching activities. Lycopene is also very potent in targeting radical molecules that contain oxygen such as hydroxyl and nitrogen dioxide as well as thiyl radicals.[15] In removing singlet oxygen, lycopene is twice as good as β-carotene and much better than α-tocopherol (10 times more effective).[16] The large number of conjugated double bonds that lycopene has is the basis of its antioxidant properties.[17–19] Moreover, lycopene also has anti-inflammatory effects. Many studies have shown that lycopene shows potential beneficial effects in cancer and lifelong diseases, such as cardiovascular, neurodegenerative, and metabolic diseases which includes diabetes.[20–22] *In vitro* and *in vivo* studies show that lycopene has potential in diabetes therapy and prevention of disease progression associated with diabetes complications but have not yet explained its molecular mechanism in detail. Therefore, this literature review was made to summarize the results of studies (see Tables 1–4) related to the beneficial effect of lycopene in DM in the last decade and highlight several important molecular pathways (see Figure 1) involved such as oxidative stress, inflammation (nuclear factor-kappa B [NF-κB] pathway), insulin signaling (phosphatidylinositol 3-kinase [PI3K]/AKT pathway), apoptosis, and autophagy.

Materials and Methods

The research method used is a qualitative study with a literature study approach or literature review. We collect articles using the PubMed and Google Scholar search engines. The keywords used are "lycopene," "diabetes," "oxidative stress," "inflammation,"

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"apoptosis," and "autophagy." These keywords are used separately or in combination so that a logical relationship between concepts is obtained. The criteria for journals or articles are filtered based on literature titles, abstracts, and keywords. The journals or articles are then filtered again by looking at the entire text. The criteria for the journal or article selected are limited to articles containing the same keywords as the research topic, a full paper article in English published from 2011 to 2020, and an experimental study, including both *in vivo* and *in vitro* studies (not a review article).

Results and Discussion

We found 33 articles that match the keywords we used. Of the 33 articles, four were *in vitro* studies, one was a combination of *in vitro* and *in vivo*, 26 were *in vivo* studies in animals, and two were *in vivo* studies in humans. The results of the literature review are summarized and presented in Tables 1–4.

Lycopene ameliorates oxidative stress in DM

Excess production of free radicals and lack of the body's antioxidant system or what is known as oxidative stress can cause harmful oxidative damage to cells and tissues.[23] Sustained hyperglycemia causes an increase in free radical production (especially ROS) from glucose autoxidation and protein glycosylation.[24–26] The outcome of oxidative stress is modification or alteration of biomolecules (DNA, protein, lipid) structure and function leading to an alteration in cell signaling, cell cycle control, impairment of cell transport mechanism, and energy metabolism.[27] The role of oxidative stress in diabetes does not only promotes the onset of the disease but also exacerbates the disease's condition and associated complications.[28]

In DM, there is an increase of oxidative stress biomarkers (malondialdehyde [MDA], oxidized low-density lipoprotein [ox-LDL], and 8-hydroxydeoxyguanosine [8-OHdG]) with a decrease in several key endogenous antioxidants (superoxide dismutase [SOD], catalase [CAT], glutathione [GSH], glutathione peroxidase [GPx], and glutathione reductase [GR]).[29,30] Due to the highly reactive nature of ROS and its short half-life, it is easier to estimate oxidative stress in DM by measuring its oxidation target products, such as lipid peroxidation products (MDA, ox-LDL, and thiobarbituric acid reactive substances [TBARS]), oxidized proteins (protein carbonyl), and nucleic acid oxidation product (8-OHdG).[31] In a study conducted by Zhu *et al.,* administration of lycopene attenuates the increase in MDA and a decrease of SOD activity in the aorta of diabetic rats significantly and dose-dependently.[16] These results indicate that oxidative stress in the aorta is reduced in presence of lycopene. Oxidative stress in the aorta can cause endothelial dysfunction, an initiator and contributing factor to cardiovascular complications of diabetes.[16] Decreased MDA and increased SOD by lycopene treatment, as shown by Zhu *et al.*, are also consistent with many other studies[18,24,25,30,32–40]. A similar study conducted on patients with diabetes showed that lycopene supplementation (4 mg once daily for 3 months) can reduce oxidative stress, as seen from a decrease in MDA and xanthine oxidase levels and an increase in antioxidants such as SOD, GSH, GPx, and GR.[35]

Lycopene has a good antioxidant activity, especially against oxygen-derived radicals and has the highest singlet oxygen quenching capability among all carotenoids in biological systems.[18,22] The large number of conjugated double bonds in lycopene makes it a potent antioxidant because the delocalization of π electrons that occurs along the double bond allows the neutralization reaction of molecules containing unpaired electrons.[19,35] The radical neutralization reaction of lycopene can occur in various ways, including adding radicals to the polyene chain, electron transfer from lycopene to radicals, or eliminating hydrogen atoms from lycopene.[41] These three reactions are explained in succession as follows: (i) adding radicals to the polyene chain of lycopene: Lycopene + R• →R-Lycopene•, (ii) electron transfer from lycopene to the radical: Lycopene + R• →Lycopene$^{\bullet+}$ + R$^-$ and (iii) hydrogen elimination from lycopene: Lycopene + R• → Lycopene• + RH.[20]

Besides involving direct chain breaking[35], quenching[17], and scavenging,[18] the antioxidant activity of lycopene also involves activation of a transcriptional activator of antioxidant genes, nuclear factor erythroid 2-related factor 2 (Nrf2).[42] Under normal conditions, Nrf2 activity in the cytoplasm is suppressed by Kelch-like ECH-associated protein 1 (Keap1).[42] However, under conditions of oxidative stress, Nrf2 dissociates from its suppressor (Keap1) and translocates to the nucleus where it binds to MAF protein and then binds to antioxidant response elements (AREs) present in the promoter regions of the antioxidant genes.[42,43] The antioxidant genes activated by Nrf2 is approximately 23 genes, one example is the heme oxygenase 1 (HO-1) gene.[43] Heme catabolism is regulated by the heme oxygenase enzyme encoded by the HO-1 gene.[37] Free heme, which has pro-oxidant properties, is converted into iron, carbon monoxide (CO), and biliverdin by HO-1.[43] The physiological level of HO-1 modulates IL-10/1R pathway that has anti-inflammatory characteristics. Decreased levels of HO-1 mRNA in mice with streptozotocin-induced diabetic nephropathy (DN) can be increased with lycopene administration.[37] Besides the HO-1 gene, the genes coding for endogenous antioxidants such as SOD, CAT, GPX, GSH, and GR are also activated by Nrf2.[43] The levels of these endogenous antioxidants are reduced in DM; however, lycopene treatment can increase the levels of these endogenous antioxidants, as has been explained in the previous paragraph.

It has been reported that lycopene is one of the many health-promoting factors that can raise Nrf2 activity, and is probably the most active among carotenoids.[43,44] In diabetes there is dysregulation of the Nrf2 pathway that results in reduced Nrf2 levels and impaired translocation.[44–47] Dysregulated Nrf2 accelerates the occurrence of diabetic cardiomyopathy and nephropathy.[44] Although the direct effect of lycopene on Nrf2 levels in diabetes has not been investigated, the antioxidant activities of lycopene in diabetes possibly also involves Nrf2 activation. The mechanism that shows how lycopene reduces oxidative stress in diabetes is shown in Figure 1.

Lycopene ameliorates inflammation in DM

It is well known that the occurrence of insulin resistance in obesity and type 2 diabetes involves inflammation and activation of the immune system. Systemic inflammatory markers are closely related to the occurrence of type 2 DM and its macrovascular complications.[48] There have been many studies showing that lycopene has anti-inflammatory effects, this can be seen from the decreased levels of TNF-α, IL-1β, IL-6, CRP and decreased NF-κB activation. This statement is based on many studies, one of which is a study conducted by Zeng *et al.,* which showed that lycopene decreased serum IL-1β, TNF-α, and CRP elevations in HFD-treated mice and increased mRNA expression of IL-1β, TNFα, and CRP in the liver[49]. A recent study also showed that lycopene decreases TNF-α and CRP in type 2 DM rats.[30] A study conducted by Yin et al. found that lycopene decreased pro-inflammatory cytokines, such as TNF-α and IL-1β, and decreased NF-κB levels in the cerebral cortex and hippocampus of fructose-drinking rats given lycopene compared with those of fructose-drinking rats with insulin resistance.[50] In mice with STZ-induced DN, there was a significant increase in the expression of NF-κB and TNF-α in renal tissue, which was reduced by lycopene administration.[37] Another study by Tabrez *et al.* showed that lycopene inhibited NF-κB activation and MMP-2 production in HK2 cells.[38] This study was originally based on some literature reporting that ligand binding to RAGE triggers inflammation by activating MMP2 and NF-κB and the further production of cytokines that are regulated by NF-κB.[51] To confirm this assumption, ribosylation was performed on HK2 cells to initiate inflammation via the formation of AGE and RAGE expressions, and then the expression of NF-κB and MMP-2 was studied. The results showed that after 48 h of 20-mM ribose administration, the expression of NF-κB and MMP-2 increased significantly in HK2 cells, and 10 μM and 20μM of lycopene administration was proven to reduce NF-κB and MMP2 dose-dependently. These suggest that AGE–RAGE signaling activation that contributes to inflammation in HK2 cells was inhibited by lycopene treatment. Moreover, in this study, the administration of lycopene in ribose-treated rats decreased TNF-α, IL-1β, and IL-6 levels.[38] NF-κB downregulation is also consistent with the research conducted by Hussein et al.[32] and Icel *et al.*[52] The inflammatory process is closely

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related to NF-κB activation which is a molecular protein that plays a role in the regulation of functional DNA transcription.[53] The mechanism of lycopene to reduce inflammation in diabetes is shown in Figure 1.

Lycopene improves insulin signaling in DM via the PI3K/AKT pathway

Apart from being involved in cell proliferation and survival, the PI3K/AKT signaling pathway also regulates cellular metabolic functions, which include glucose and lipid metabolism and protein synthesis.[54] PI3K is one of downstream signaling pathways activated when insulin binds to the insulin receptor (IR).[55] Meanwhile, the primary downstream effector of the PI3K pathway is Akt (protein kinase B).[56] In pathologic conditions, such as obesity and diabetes, there is dysregulation of the PI3K/AKT pathway.[56,57]

The expression of IR, insulin-like growth factor 1 receptor, PI3K, and phosphorylated AKT (p-AKT) proteins in the hippocampus and cerebral cortex in the insulin-resistant fructose-drinking rats group was significantly lower than in the same group given lycopene.[50] These findings suggest that lycopene improves insulin signaling via upregulation of IR and the PI3K/AKT pathway. A recent study also showed that in high glucose conditions, lycopene was able to increase the expression of phosphorylated PI3K (p-PI3K) and p-AKT proteins in MPC5 podocytes compared with the untreated high-glucose group.[58] Another study also showed a significant reduction in p-AKT in untreated diabetic rats, which was increased by lycopene administration.[36] AKT as an important downstream effector of insulin signaling has an important role in various cellular functions, including glucose and lipid metabolism, cell hypertrophy, and cell proliferation, as well as programmed cell death (apoptosis).[36,57] In glucose metabolism, AKT as a biological regulator of insulin is involved in the translocation of glucose transporter type 4 (GLUT4) from the cytosol to the plasma membrane which mediates glucose uptake.[56] Activation of the PI3K/AKT pathway leading to translocation of GLUT4 appears to be one reason why lycopene, in several studies, exerts a hypoglycemic effect in diabetes. The hypoglycemic effect of lycopene is also related to its strong antioxidant properties and its effect that stimulates insulin secretion, increases repair or proliferation of β cells, liver glucokinase activity, and enhances insulin and adrenaline effects.[16,19] The mechanism that shows how lycopene improves insulin signaling via the PI3K/AKT pathway in DM that leads to glucose uptake via GLUT4 is shown in Figure 1.

The role of lycopene on apoptosis and autophagy in DM

Apoptosis and autophagy are found to be associated with DM.[59,60] The relative insulin deficiency in type 2 DM may be mainly due to apoptosis of pancreatic β cells secondary to increased glucotoxicity, lipotoxicity, chronic inflammation, and oxidative stress.[59] Interestingly, a recent in vitro study showed that lycopene treatment increased the proliferation of pancreatic β cells.[61] In addition to pancreatic β cells, apoptosis-associated DM also occurs in the brain.[62,63] Several studies have found the association between DM and central nervous system (CNS) disorder.[50,62,63] In DM, damage to CNS can also occur due to oxidative processes that results in long-term complications, morphological changes, and memory problems.[63,64] The hippocampus as part of the CNS and plays a role in memory function can be affected by DM.[65] A study by Soleymaninejad *et al.* found that there is higher neural cell death in the hippocampus of untreated diabetic rats than in diabetic rats treated with insulin or lycopene.[62] In that study, lycopene administration decreases the expression of the Bax gene that promotes apoptosis and increases the upregulation of Bcl-2 and Bcl-xL, the anti-apoptotic genes. This study suggested that lycopene can be used as a neuroprotective agent in the prevention of neurological damage caused by oxidative stress in DM. This findings are also consistent with the results obtained by Malekiyan *et al.* who also found a decrease in the apoptosis of nerve cells in the hippocampus after lycopene treatment.[63] Apoptosis and autophagic cell death share many of the regulator proteins and thus are not entirely distinct and can occur in both physiologic and pathologic conditions.[59] To some extent, autophagy can be protective because it is able to maintain cell integrity and intracellular homeostasis under conditions of metabolic stress. However, if excessive, it can lead to programmed cell death.[66] Autophagy with higher levels occurs in endothelial progenitor cells exposed to AGEs, however, giving lycopene can reduce this autophagy process as shown by the decrease in levels of autophagy-related proteins (LC3A/B, Beclin-1, PARP, and caspase-3).[66]

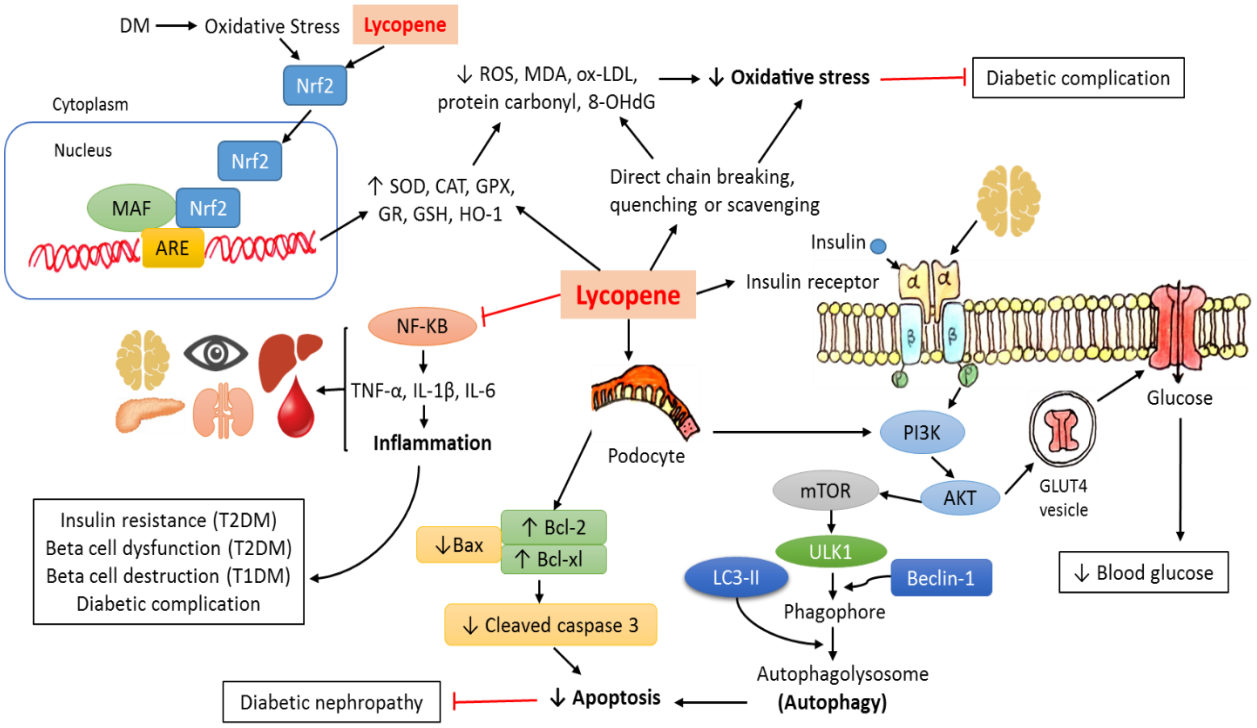

Figure 1: Proposed mechanism of how lycopene exerts beneficial effects on DM

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Table 1: Summary of results from *in vitro* studies

Author (Years)	Purpose	Research Method	Main Findings	Ref
Zeng *et al.* 2014	To investigate the effects of lycopene (Lyc) on the migration, adhesion, tube formation capacity, and p38 mitogen-activated protein kinase (p38 MAPK) activity of endothelial progenitor cells (EPCs) cultivated with high glucose (HG) and as well as explore the mechanism behind the protective effects of lycopene on peripheral blood EPCs.	• Mononuclear cells isolated from human peripheral blood • 6 groups: normal control (only M199 medium), mannitol (30 mmol/L of mannitol and M199 medium, osmotic control), HG group (33 mmol/L of glucose), and three Lyc groups according to dosage (each cultured with 33 mmol/L of glucose followed by Lyc at doses of 10, 30, and 50 µg/mL in M199 medium).	• ↑ Proliferative capacity of EPCs & ↓ apoptosis of EPC • ↑ The proliferation, migration, adhesion, and vasculogenesis capacity of EPCs • ↓ Phosphorylation of p38 MAPK.	[22]
Zeng *et al.* 2017	To investigate the molecular mechanism of Lyc on EPCs exposed to advanced glycation end products (AGEs).	• EPCs from SD rats bone marrow with T2DM • 7 groups: control, 200 µg/ml AGEs, AGEs + 10 µg/ml Lyc, AGEs + 20 µg/ml Lyc, AGEs + 30 µg/ml Lyc, AGEs + 40 µg/ml Lyc, AGEs + 50 µg/ml Lyc.	• ↑ Cell proliferation & increases the S phase of the cell cycle arrest • ↓ AGEs-induced apoptosis of EPC • ↓AGEs-induced autophagy flux in EPC (↓ PARP, Beclin-1, LC3A/B, Caspase 3) • ↓ AGEs-induced ROS generation and rescues mitochondrial membrane potential (MMP) in EPCs	[66]
Liu *et al.* 2020	To study the effects of Lyc on pancreatic α and β cells	• αTC1 and βTC6 cells • Cells in a 6-well plate were treated with various concentrations of Lyc (0, 2.5, 5, 7.5, 10 µmol/L) and DMSO as vehicle control for 24 h.	• ↑ Growth of β cells & the ratio of S phase • ↓ ROS levels and ↑ the ATP levels of β cells • ↑ mRNA expression levels of TNF-α, TGF-β, and HIF-1α in β cells	[61]
Wang *et al.* 2020	To explore the protective effect of Lyc on high glucose (HG) induced MPC5 podocyte apoptosis and the underlying mechanism	• MPC5 podocytes • 7 groups: normal (5.5 mM glucose), hypertonic (5.5 mM glucose + 19.5 mM mannitol), HG (25 mM glucose), HG + 3.125 mM Lyc, HG + 12.5 mM Lyc, low Lyc treatment group (3.125 mM Lyc), and high Lyc treatment group (12.5 mM Lyc).	• ↑ Cell viability in high lyc group (under HG condition) • ↑ Protein expression levels of nephrin and podocin (under HG condition) • ↓ Rate of apoptosis & ↓ protein expression level of Bax & cleaved caspase 3 and ↑ Bcl-2 • ↑ Protein expression levels of p-PI3K and p-AKT • ↑ The expression levels of autophagy-related proteins (LC3II/LC3I and Beclin-1)	[58]

Recent studies have shown that lycopene promotes autophagy to attenuate high glucose-induced apoptosis in MPC5 podocytes.[58] In that study, there was a decrease in Bax protein and cleaved caspase-3 and in contrast increases Bcl-2 protein. The underlying mechanism was investigated by examine PI3K/AKT signaling pathway and the levels of autophagy-related proteins (LC3II/LC3I and Beclin-1) by western blotting. And the PI3K (LY294002 [LY]) and autophagy inhibitor (3-methyladenine [3-MA]) were used to investigate the effects of lycopene on the PI3K/AKT signaling pathway and autophagy. The results showed that lycopene increases p-PI3K, p-AKT, LC3II/LC3I, and Beclin-1 protein expression. Finally, this study concluded that lycopene attenuates apoptosis in MPC5 podocytes due to high glucose condition by promoting the occurrence of autophagy through the activation of the PI3K/AKT signaling pathway.[58] The mechanism of how lycopene promotes autophagy and decreases apoptosis in DM is shown in Figure 1 Lycopene reduces oxidative stress in two ways. The first is through chemical reactions with free radicals involving direct chain breaking, quenching, and scavenging activities. The second is by activating Nrf2, which in turn will increase the body's endogenous antioxidants such as SOD, CAT, GPX, GR, GSH, and HO-1. Lycopene reduces inflammation in DM by inhibiting the activity of NF-κB and ultimately decreases proinflammatory cytokines (TNFα, IL-1β, IL-6) in the liver, eye, brain, pancreas, kidney and blood tissues. Inflammation contributes to insulin resistance and beta-cell dysfunction in T2DM, beta-cell destruction in T1DM, and DM complications. Lycopene upregulates insulin receptors and increases the expression of PI3K and AKT proteins (in brain cells) which are proteins involved in insulin signaling. The binding of insulin to its receptors will activate the PI3K/AKT pathway. AKT is an effector in translocating GLUT4 from the cytoplasm to the cell membrane. GLUT4 expression in the cell membrane will facilitate the entry of glucose into cells so that in turn, it can lower blood sugar. Lycopene also activates the PI3K/AKT pathway which leads to autophagy and decreased apoptosis in podocytes, which in turn, will inhibit the development of diabetic nephropathy. A black arrow indicates activation and a red line indicates inhibition. mTOR: mammalian target of rapamycin; ULK1: Unc-51 like autophagy activating kinase 1; MAF: musculoaponeurotic fibrosarcomaa (Figure 1).

Table 2: Summary of results from combined in vitro and in vivo study

Author (Years)	Purpose	Research Method	Main Findings	Ref
Tabrez *et al.* 2015	Investigates the effect of Lyc in downregulating the menace caused by ribose-induced glycation both *in vitro* and *in vivo*.	• HK2 cells, a primary human proximal tubular cell line and 40 male Wistar rats (200–230 g) • At 80% confluence, cells were exposed to 20 mM D-ribose, 20 mM D-ribose + 10 µM and 20 µM Lyc and 20 µM Lyc separately for up to 48 h • 5 groups of rats: normal control + normal saline i.p, ribose goup (3.2 g/kg) i.p. for 10 days, alloxan group (45 mg/kg), ribose-Lyc group (ribose 3.2 g/kg i.p for 10 days + Lyc 10 mg/kg p.o for 5 weeks), Lyc group (10 mg/kg) for 5 weeks.	• ↓ AGEs & RAGE in HK2 cells & renal tissue in rats • ↓ NF-κB & matrix metalloproteinase-2 (MMP-2) expression in HK2 cells dose-dependently • ↓ BW loss in rats • ↓ 24 h urine volume in rats • ↓ %HbA1c in rats • ↓ BUN and creatinine and normalized the GFR in rats • ↑ Serum SOD, GPx, CAT, and GSH • ↓ Serum carbonyl content and MDA • ↓ Serum TNF-α, IL-1β, and IL-6	[38]

RAGE: receptor for advanced glycation end products; BW: body weight; BUN: blood urea nitrogen; GFR: glomerular filtratio rate; IL-1β: interleukin-1β; IL-6: interleukin-6

Table 3: Summary of results from *experimental animal* studies

Author (Years)	Purpose	Research Method	Main Findings	Ref
Zhu *et al*. 2011	To investigate whether Lyc could lower oxidative stress and attenuate endothelial dysfunction in diabetic rats	• Eight-week-old male Wistar rats (190–220 g) • STZ 60 mg/kg i.p • 6 groups: control, control high Lyc-treated (60 mg/kg), diabetes mellitus (DM), diabetic low Lyc-treated (DM +	• ↑ Bodyweight • ↓ Fasting blood glucose • ↓ Plasma ox-LDL levels (dose-dependent) • Improved the ACh-induced endothelium-dependent	[16]

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		Lyc 10 mg/kg), diabetic medium Lyc-treated (DM + Lyc 30 mg/kg), diabetic high Lyc-treated (DM + Lyc 60 mg/kg) • 30 days	vasorelaxation in the aortic rings from diabetic rats • ↑ Aortic SOD activity • ↓ Aortic MDA level • ↓ The decreased NO levels and cNOS activity in the aorta (dose-dependent) • ↓ the increased of iNOS activity in aorta	
Ozmutlu *et al.* 2012	Investigating the detection of diabetes-related complications, and to determine the possible role of Lyc in diabetes complications regarding the effects of ACE activity	• Wistar-Albino male rats weighing 200–250 g • STZ 45 mg/kg i.p • 4 groups: control, diabetes, diabetes + Lyc 10 mg/kg, Lyc only (10 mg/kg). • 28 days	• ↓ Blood glucose • ↓ HbA1c • ↓ Blood ACE Activity	[12]
Aydin and Celik, 2012	To determine possible therapeutic effects of oral Lyc supplementation on plasma insulin levels, lipid peroxidation, blood glucose levels, and the antioxidant defense system of streptozotocin (STZ)-induced diabetic rats.	• Male Wistar rats, 2 months of age, and weighing 150–250 g • STZ 45 mg/kg i.p • 4 groups: control, diabetic, Lyc-supplemented diabetic (4 mg/kg BW), and Lyc-supplemented control (4 mg/kg BW) • 8 weeks	• ↓ Blood glucose • ↑ Plasma insulin concentrations • ↓ MDA level in brain tissue samples • ↑ CAT enzyme activity in the red blood cells and brain tissue sample • ↑ Total SOD activity in the brain tissue sample and plasma • ↓ GSH levels in plasma and brain tissue sample • ↑ GSH-Px activity in the erythrocytes and brain tissue sample • ↓ Plasma NO level • Stopped & ↑ the suppression of SOD, CAT, and GSH-Px mRNA transcription levels in brain tissue	[24]
Bayramoglu *et al*. 2013	To describe the effects of Lyc on the symptoms of STZ–induced diabetes in rats	• Sprague–Dawley rats weighing 190–210 g • STZ 50 mg/kg i.p • 3 groups: nondiabetic control, diabetic control rats received vehicle solution (olive oil 1 mL/kg BW); and diabetic rats treated with Lyc 2.5 mg/kg BW in vehicle solution. • 7 days	• ↓ Serum glucose • ↓ Total cholesterol (TC) and Total triglyceride (TG) • ↓ AST and ALT • ↑ Serum insulin level	[17]
Yegin *et al.* 2013	Researching the effect of	• Wistar–Albino rats aged 7–8 weeks,	• ↑ PON activity	[5]

	lycopene application on lipoprotein, paraoxonase (PON), and cytokines that are projected to be used in the diagnosis and treatment of diabetes by making experimental diabetes.	weighing 300 –350 g • STZ 45 mg/kg • 4 groups: control, diabetes, Lyc, diabetes-Lyc • 4 weeks	• ↓ HbA1c • ↓ TG level • ↑ Cholesterol • ↑ VLDL • ↑ LDL • ↓ HDL	
Yin *et al*. 2014	To investigate the effect of Lyc on learning and memory impairment and the possible underlying molecular events in fructose-drinking insulin-resistant rats	• Six-week-old male Wistar rats • 6 groups: control (normal drinking water), 10% fructose solution in drinking water for 16 weeks to develop insulin resistance, 10% fructose solution in drinking water for 16 weeks, and Lyc (4 mg/kg) for the last 10 weeks of the 16 weeks, Lyc only (4 mg/kg).	• ↓ The levels of plasma insulin and HOMA-IR • ↑ insulin receptor (IR), insulin-like growth factor-1 receptor (IGF-1R), PI3K, and p-AKT protein expression in the hippocampus and cerebral cortex • ↓ ROS, LPO, and carbonyl in both hippocampus and cerebral cortex • ↓ TNF-α, IL-1β and NF-κB in both hippocampus and cerebral coxtex • ↑ PPAR-γ protein expression in the hippocampus and cerebral cortex • ↓ AChE activity & ↑ Ach in the hippocampus and cerebral cortex.	[50]
Li *et al*. 2014	To study the effect of Lyc on ameliorating renal function of diabetic nephropathy	• Sprague-Dawley rats weighing 220–260 g • STZ 70 mg/kg • 4 groups: normal untreated, normal + Lyc 20 mg/kg per day, diabetes untreated, and diabetes + Lyc 20 mg/kg per day • 8 weeks	• ↓ BW loss in DM rats • ↓ BUN, 24 h urea protein, creatinine • ↓ Serum TG, TC, LDL, and ↑ HDL • ↓ MDA & ↑ SOD in renal tissue • Improves kidney histology of DM rats • ↑ p-Akt in renal tissue • ↓ Connective tissue growth factor (CTGF) in renal tissue	[36]
Guo *et al.* 2015	To highlight the therapeutic prospect of Lyc against STZ-induced kidney injury in mice.	• Male Kunming (KM) mice, one-month-age and weighing 18–20 g • STZ 60 mg/kg • 3 groups: (1) DN control, given the vehicle composed of 25% cremophor EL and 75% H2O2 emulsifier solution; (2) Lyc intake groups, given 40 and 80 mg/kg Lyc (3) normal	• ↓ Blood glucose level • Prevent BW loss • ↓ Proteinuria • ↓ Serum LDL-C and ↑ HDL-C • ↑ SOD and GSH-Px and ↓ MDA in kidney cells • ↓ Cell damages, necrosis, inflammatory infiltration, and repair basement membrane	[37]

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		control (non-diabetic mice) given an equivalent volume of the vehicle. • 8 weeks	• Cytoarchitectural reinstatements, including augmented organelles and mitochondria, replenished endochylema, reduced collagen and cytokine deposits • ↓ NF-κB and TNF-α in kidney tissue • ↑ Intrarenal HO-1 mRNA expression	
Daniel *et al*. 2015	Assessed the effects of Lyc on kidney antioxidant enzymes activities and functions in STZ-induced diabetic Wistar rats	• Wistar rats • STZ 60 mg/kg • 6 groups: normal control (olive oil 0.5 ml/kg BW), diabetic control (olive oil 0.5 ml/kg BW), diabetic + Lyc 10 mg/kg BW, diabetic + 20 mg/kg BW of Lyc, diabetic + 40 mg/kg BW of Lyc, diabetic + glibenclamide 2 mg/kg BW • 4 weeks	• ↓ Blood glucose • ↓ MDA level and ↑ SOD, CAT, and GPx in kidney tissue. • ↑ Serum sodium ion and ↓ serum urea level • Improves renal architecture as reflected by reduced glomerular and tubular necrosis	[18]
Eze *et al*. 2015	To investigate the hypoglycaemic potential of lycopene in STZ-induced diabetic Wistar rats.	• Wistar rats • STZ 60 mg/kg • 6 groups: normal control + 0.5 ml/kg BW of olive oil, diabetic control + 0.5 ml/kg BW of olive oil, diabetic + 10 mg/kg BW of Lyc, diabetic rats + 20 mg/kg BW of Lyc, diabetic rats + 40 mg/kg BW of Lyc, diabetic + 2 mg/kg BW of glibenclamide • 4 weeks	• ↓ Fasting blood glucose • ↑ Serum insulin level • ↑ The activity of hepatic glucokinase	[19]
Ozmen *et al*. 2016	To evaluate the effects of caffeine and lycopene on STZ-induced DM in rats.	• Sprague-Dawley rats weighing 125–150 g and aged 2 months • STZ 50 mg/kg • 6 groups: caffeine 10 mg/kg/d, caffeine (10 mg/kg/d) + STZ on 31th day, Lyc 10 mg/kg/d, Lyc 10 mg/kg/d + STZ on 31th day, normal control, diabetic (STZ) group • 40 days	• ↓ Vacuolization in the pancreas • Prophylactic effects in the insulin-secreting cells • ↓ Blood glucose levels • ↓ Glycosuria	[11]
Eze et al. 2016	Investigating the ameliorative effect of Lyc on liver glucokinase and enzymes activity in STZ-induced diabetic Wistar rats.	• Adult albino wistar rats • STZ 60 mg/kg • 6 groups: normal control (0.5 ml of olive oil); diabetic control (0.5 mL of olive oil); while group III-VI received (10, 20 and 40 mg/kg of Lyc and 2 mg/kg BW glibenclamide)	• ↓ Blood glucose level • ↑ The activity of liver glucokinase • ↓ Serum AST & ALT	[26]

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		respectively. • 4 weeks		
Uçar *et al*. 2017	To identify the effect of furan on the ovary of non-diabetic and diabetic female rats, and to show whether these adverse effects can be cured by Lyc and on the tissue damage, whether the level of oxidative stress and DNA damage in the rat' ovary can be decreased	• Female Wistar–Albino rats (300–320 g) • 8 groups: control (1 mL of 0.9% NaCl saline), Lyc 4 mg/kg BW, furan 40 mg/kg BW, 40 mg/kg furan + 4 mg/kg BW of Lyc, diabetic control+ STZ, diabetic + Lyc 4 mg/kg BW, diabetic (STZ) + furan 40 mg/kg BW, diabetic + furan 40 mg/kg + Lyc 4 mg/kg BW • 28 days	• ↓ The ovarian tissue damage • ↓ MDA level • ↑ CAT, SOD, GPx, and GST enzymes activities in ovary tissue	[39]
Zeng *et al.* 2017	Investigated the effect of Lyc on insulin resistance and elucidated the possible mechanisms.	• C57 mice (6–8 week old) high-fat diet (HFD)-fed mice • Protocol 1: 4 groups: control normal diet (10% of total calories from fat), HFD (45% of total calories from fat), L-Ly (HFD containing 0.05% Lyc), H-Ly (HFD containing 0.1% Lyc). • Protocol 2: 3 groups: HFD (45% of total calories from fat); H-Ly: HFD containing 0.1% lycopene; H-Ly + STAT3: HFD containing 0.1% Lyc, mice were injected with adenovirus carrying STAT3 through caudal vein before the administration of HFD. Mice in HFD and H-Ly were injected with empty adenovirus.	• ↓ FBG • ↓ Plasma insulin elevation • Inhibit the decrease of hepatic glycogen content • ↓ Serum IL-1β, TNFα, and CRP • ↓ Hepatic mRNA expression of IL-1β, TNFα, and CRP • ↓ Serum and hepatic levels of TC, TG, LDL, and ↑ HDL • ↓ Srebp-1c mRNA and protein expression in the liver • ↓ mRNA levels of ACC-1 and FAS in liver • ↓ Protein expression and phosphorylation of STAT3 in the liver	[49]
Assis *et al.* 2017	To investigate the changes promoted by the long-term treatment of STZ-diabetic rats with yogurt enriched with curcumin, Lyc, or bixin, individually, or as mixtures, on various biomarkers related to the metabolic and oxidative disturbances observed on the experimental model of type 1 DM	• Streptozotocin (STZ)-diabetic rats (T1DM model) • 8 groups: normal rats + yoghurt, diabetic rats + yoghurt, diabetic rats + insulin, diabetic rats + curcumin, diabetic rats + bixin, diabetic rats + curcumin + bixin, diabetic rats + Lyc, diabetic rats + curcumin + Lyc • 50 days	• ↓ Plasma glucose level • ↓ TG, TC, and ↑ HDL levels • ↓ Plasma ox-LDL and TBARS • ↑ Plasma PON1 activity • ↓ Hepatic level of TBARS and PCO • ↑ Hepatic SOD, CAT, GPx, and nonprotein sulfhydryl groups (NPSH) levels	[40]
Soleymaninejad *et al.* 2017	To evaluate the effects of antioxidants Lyc and insulin on histological changes and expression of Bcl-2 family genes in the hippocampus of STZ-induced type 1	• Male wistar rats weighing 200–250 g, aged 8–10 weeks old • 6 groups: untreated diabetic, diabetic + insulin + protamine (NPH), diabetic + Lyc 4 mg/kg/BW, diabetic + insulin + Lyc, control, and Lyc control groups.	• ↓ Blood sugar • ↓ BW loss • ↓ Neuronal cell death in the hippocampus • ↓ Bax gene (mRNA) level in hippocampus	[62]

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	diabetic rats.		• ↑ Bcl-2 and Bcl-xL gene (mRNA) levels in hippocampus	
Hussein *et al.* 2018	To investigate the possible beneficial effect of Lyc against deleterious effect of diabetic nephropathy induced in male rats through investigation of blood glucose, kidney functions, inflammatory and oxidative stress biomarkers.	• White male albino rats of 5–6 weeks old and weighing 180–200 g • STZ 50 mg/kg BW i.p • 4 groups: normal rats (buffer citrate), DN rats, DN + insulin (2U/rat /day/i.p), DN + Lyc 20 mg/kg BW/day p.o).	• ↓ Serum glucose, urea, creatinine and, kidney tissue L-MDA concentrations • ↓ NF-κB gene expression in kidney tissue • ↑ SOD activity and GSH level in kidney tissue	[32]
Eze *et al.* 2018	To evaluate the capacity of Lyc against diabetes-induced oxidative damage in Wistar rats.	• Wistar rats of both sexes (20 males and 10 females) weighing 150–200 g • STZ 60 mg/kg • 6 groups: non-diabetic rats + 0.5 ml/kg olive oil, diabetic rats + 0.45 ml/kg olive oil, diabetic rats + 10 mg/kg of Lyc, diabetic rats + 20 mg/kg of Lyc, diabetic rats + 40 mg/kg of Lyc, diabetic rats + glibenclamide 2 mg/kg. • 4 weeks	• ↓ Blood glucose concentration • ↓ Serum levels of cortisol and MDA • ↑ Serum endogenous enzymes (SOD, CAT, GPx)	[25]
Karahan *et al.* 2018	To determine the effects of Lyc on oxidative DNA damage levels in experimental diabetic rats	• Wistar-Albino male rats weighing 200–250 g • STZ 45 mg/kg • 4 groups: control (physiological serum), diabetes, diabetes + lyc 10 mg/kg/day, lyc 10 mg/kg/day • 28 days	• ↓ Blood glucose and %HbA1c • ↓ Blood 8-OHdG levels	[29]
Zheng *et al.* 2019	To study the antioxidative and anti-inflammatory effects of Lyc on type 2 diabetes mellitus (T2DM) rats, anticipating a complementary strategy for the prevention of long-term complications of T2DM	• Sprague-Dawley rats (180– 220 g) aged 6 weeks • 5 groups: high fat (HF), DM, DM + 5 mg/kg Lyc, DM + 10 mg/kg BW of Lyc, and, DM + Lyc 15 mg/kg BW.	• ↓ FBG & HOMA-IR, ↑ FINS • ↑ T-AOC, SOD, CAT, and GPx in serum and pancreas • ↓ MDA level in serum and pancreas • ↓ Serum GHb, Gly-LDL, and ox-LDL. • ↓ Serum TNF-α and CRP	[30]
Icel *et al.* 2019	To determine the effects of Lyc treatment in the prevention of diabetes-associated inflammatory response and oxidative stress in an experimental model.	• Male albino Wistar rats (250–280 g) • Alloxan 120 mg/kg i.p • 3 groups: healthy, control group (alloxan-induced diabetic rats), and, Lyc group (alloxan-induced diabetic rats + Lyc 4 mg/kg/d for 3 months).	• ↓ FBG • ↓ MDA, TOS, OSI, NF-κB, and TNF-α levels in eye tissue • ↑ tGSH &TAS in eye tissue • ↓ Damage to the optic nerve (histology)	[52]
Eze *et al.* 2019	To gain information on basic changes in hematological parameters as	• Male Wistar weighing 150–200 g • STZ 60 mg/kg • 6 groups: negative control (olive oil),	• Improves hematological indices (↑ PCV, Hb, RBCs, MCV, MCH, MCHC)	[13]

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	markers for safety since anemia as a complication in diabetic chemotherapy has been reported	diabetic rats + olive oil at 0.5 ml/kg, comparative control (glibenclamide at 2 mg/kg), and three experimental groups of Lyc at 10 mg/kg, 20 mg/kg and 40 mg/kg per os • 28 days.	• Improves immune status (↑ WBCs and lymphocyte counts, ↓ neutrophils, ↓ neutrophil-lymphocyte ratio, and platelet counts, ↑ blood total protein and globulin levels)	
Yin *et al.* 2019	To explore the influence of Lyc on the metabolism of glycolipid in type 2 diabetes.	• Male Sprague-Dawley rats (180–220 g) • 70 rats: 60 rats fed with HFD, 10 rats normal feed (normal control) • 50 rats in the HFD group were randomly selected to be given 1% STZ solution (pH 4.5, 25 mg/kg BW) i.p. • 10 rats in HFD and normal control group: citric acid buffer. • 4 groups: control group (DM), high dose (20 mg/kg Lyc) of intervention group (DM+H), low dose (10 mg/kg) of Lyc intervention group (DM + L), high-fat control group (HF) • 10 weeks	• ↓ FBG, lipid in blood and liver, glycosylated Hb, HOMA-IR, and ↑ plasma insulin • ↑ SOD and GSH-Px and ↓ MDA in pancreatic tissue • ↓ BW loss	[33]
Saracoğlu *et al.* 2019	To demonstrate the cardioprotective and antioxidative role of Lyc on furan-caused cardiotoxicity models in diabetic rats	• Male Wistar albino rats (300–320 g), aged 120 days. • STZ 55 mg/kg • 5 groups: normal control + corn oil 1 ml/kg BW, diabetic control + corn oil 1 mL/kg BW/d, diabetic + Lyc 4 mg/kg BW, diabetic + furan 40 mg/kg BW, diabetic + furan 40 mg/kg BW + Lyc 4 mg/kg BW. • 28 days	• ↑ CAT, GPX, GST, SOD, and ↓ MDA level in the heart • Improves histology (less edema in connective tissue and degenerative changes in cardiac muscle cells).	[34]
Malekiyan *et al.* 2019	To investigate the effect of Lyc, insulin, and their co-treatment in preventing apoptosis, on the levels of total antioxidant capacity (TAC) and MDA activity, within the hippocampus of STZ-induced diabetic rats	• Adult male Wistar rats • STZ 60 mg/kg i.p • 6 groups: non-diabetic (control), control + Lyc 4 mg/kg/d, diabetic control, diabetic + Lyc 4 mg/kg/d, diabetic + insulin 1-2 U/d, diabetic + Lyc 4 mg/kg/d + insulin 1-2 U/d • 8 weeks	• ↑ TAC in blood & ↓ MDA in the hippocampus • AO & TUNNEL staining: ↓ cell apoptosis in the hippocampus	[63]
Figueiredo *et al.* 2020	To investigate the effects of the treatments with Lyc or metformin, alone or in combination, on glycoxidative stress biomarkers and antioxidant defenses in diabetic rats	• Male Wistar rats (*Rattus norvegicus*) • STZ 40 mg/kg • 6 groups: normal + yogurt, diabetic + yogurt, diabetic + 250 mg/kg metformin in yogurt, diabetic + 45 mg/kg Lyc in yogurt, diabetic + 250 mg/kg metformin +	**Lyc alone**: • ↓ Food intake, water intake, and urinary volume • ↓ The weight loss of skeletal muscle (soleus & EDL muscle) • ↓ Postprandial glycemia & fasting glycemia	[6]

		45 mg/kg Lyc in yogurt, diabetic + 4U insulin. • 35 days	• ↓ Plasma TG & TC • ↓ Plasma level of PCO, AGEs, ↑ the activity of PON1 • ↑ The activity of SOD, CAT, GSH-Px, GSH-Rd, NPSH in the liver & kidney • ↓ PCO & AGEs in the liver, ↓ PCO, AGEs & TBARS in the kidney **Lyc + Metformin:** synergistic effect (better outcome)

ACh: acetylcholine; AChE: acetylcholinesterase; NO: nitric oxide; NOS: nitric oxide synthase; cNO: constitutive nitric oxide synthase; iNOS: Inducible nitric oxide synthase; ACE: angiotensin-converting enzyme; AST: aspartate amino transferase; ALT; alanine amino transferase; PON: paraoxonase; PON-1: paraoxonase-1; LDL: low-density lipoprotein, VLDL: very low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment insulin resistance; FINS: fasted Insulin; LPO: lipid peroxidation; PPAR-γ: peroxisome proliferator-activated receptor gamma; GST: glutathione S-transferase; FBG: fasting blood glucose; CRP: C reactive protein; Srebp-1c: sterol regulatory element-binding protein-1-c; STAT3: signal transducer and activator of transcription 3; ACC-1: acetyl-CoA carboxylase; FAS: fatty acid synthase; PCO: protein carbonyl; NPSH: nonprotein sulfhydryl; T-AOC: total antioxidant capacity; TAS: total antioxidant status; TOS: total oxidative stress; OSI: oxidative stress index; PCV: packed cell volume; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; Hb: hemoglobin; RBCs: red blood cells; WBCs: white blood cells.

Table 4: Summary of results from human studies

Author (Years)	Purpose	Research Method	Main Findings	Ref
Singh *et al.* 2012	To study the ameliorative properties of Lyc in diabetic patients by measuring oxidative stress biomarkers	• 50 diabetic patients of both sexes, age 35–55 years • 3 groups: normal healthy subjects (control), diabetic patients, 4 mg Lyc ingested diabetic patients. • 3 months	• ↓ Serum MDA levels • ↓ Plasma XOD levels ↑ SOD levels • ↑ Blood GSH, GR, and GPX levels	[35]
Badkook *et al*. 2012	To investigate the effect of a high monounsaturated fatty acid (MUFA) diet alone or with combined vitamin E and C, or Lyc intake on oxidative stress in type 2 diabetes in Saudi Arabia	• Type 2 diabetic patients (n=48) • 20 weeks (5 consecutive intervals): interval 1 (olive oil), interval 2 (olive oil + Vit E and C), interval 3 (washout period, only olive oil), interval 4 (40 g of tomato paste daily: 12 mg Lyc/day)	↑ Total plasma antioxidant status	[23]

Conclusion

Lycopene has beneficial effect in DM and has the potential to be used as a therapy and prevention of DM complications through its antioxidant and anti-inflammatory activity, activation of the PI3K/AKT pathway, anti-apoptotic effect, and its effect against autophagy. Lycopene supplementation in diabetics needs to be considered because of its broad benefits in DM. Further research is needed in the form of large clinical trials to prove the beneficial effects of lycopene in DM and the optimal dose needed.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. International Diabetes Federation - Facts & figures [Internet]. [cited 2020 Nov 25]. Available from: https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html
2. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: Systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. Lancet. 2011;378(9785):31-40.
3. Lovic D, Piperidou A, Zografou I, Grassos H, Pittaras A, Manolis A. The Growing Epidemic of Diabetes Mellitus. Curr Vasc Pharmacol. 2019; 18(2):104-109.
4. Gupta A, Behl T, Sachdeva M. Key milestones in the diabetes research: A comprehensive update. Obes Med. 2020; 17:100183.
5. Yegin SÇ, Yur F, Ceylan E. Effect of lycopene application in rats with experimental diabetes using lipoprotein, paraoxonase and cytokines. J Membr Biol. 2013; 246(8):621-626.
6. Figueiredo ID, Lima TFO, Inácio MD, Costa MC, Assis RP, Brunetti IL, Baviera AM. Lycopene improves the metformin effects on glycemic control and decreases biomarkers of glycoxidative stress in diabetic rats. Diabetes, Metab Syndr Obes Targets Ther. 2020; 13:3117-3135.
7. Cahn A and Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care. 2016; 39(Suppl 2):S137-S145.
8. Akhter MS and Uppal P. Toxicity of Metformin and Hypoglycemic Therapies. Adv Chronic Kidney Dis. 2020; 27(1):18-30.
9. Prabhakar P, Kumar A, Doble M. Combination therapy: A new strategy to manage diabetes and its complications. Phytomed. 2014; 21(2):123-130.
10. Venkatakrishnan K, Chiu HF, Wang CK. Popular functional foods and herbs for the management of type-2-diabetes mellitus: A comprehensive review with special reference to clinical trials and its proposed mechanism. J Funct Foods. 2019; 57:425-438.
11. Ozmen O, Topsakal S, Haligur M, Aydogan A, Dincoglu D. Effects of caffeine and lycopene in experimentally induced diabetes mellitus. Pancreas. 2016; 45(4):579-583.
12. Ozmutlu S, Dede S, Ceylan E. The effect of lycopene treatment on ACE activity in rats with experimental diabetes. JRAAS - J Renin-Angiotensin-Aldosterone Syst. 2012; 13(3):328-333.
13. Eze ED, Afodun AM, Kasolo J, Kasozi KI. Lycopene improves on basic hematological and immunological parameters in diabetes mellitus. BMC Res Notes. 2019; 12(1):1-6.
14. Cho KS, Shin M, Kim S, Lee SB. Recent advances in studies on the therapeutic potential of dietary carotenoids in neurodegenerative diseases. Oxid Med Cell Longev. 2018; 2018:1-13.
15. Böhm F, Edge R, Truscott TG. Interactions of dietary carotenoids with singlet oxygen (1O2) and free radicals: Potential effects for human health. Acta Biochim Pol. 2012; 59(1):27-30.
16. Zhu J, Wang CG, Xu YG. Lycopene attenuates endothelial dysfunction in streptozotocin-induced diabetic rats by reducing oxidative stress. Pharm Biol. 2011; 49(11):1144-1149.
17. Bayramoglu A, Bayramoglu G, Senturk H. Lycopene partially reverses symptoms of diabetes in rats with streptozotocin-induced diabetes. J Med Food. 2013; 16(2):128-132.
18. Ejike DE. Effect of Lycopene on Altered Kidney Antioxidant Enzymes Activity and Functions in Streptozotocin-Induced Diabetic Wistar Rats. Cell Biol. 2015; 3(1):1.
19. Eze E, Mohammed A, Tanko Y, Ahmed A, Rabiu K. Hypoglycaemic Effect of Lycopene in Streptozotocin-Induced Diabetic Wistar Rats. Br J Med Med Res. 2015; 7(9):762-770.
20. Przybylska S. Lycopene – a bioactive carotenoid offering multiple health benefits: a review. J Food Sci Technol. 2019; 55(1):11-32.
21. Li N, Wu X, Zhuang W, Xia L, Chen Y, Wu C, Rao Z, Du L, Zhao R, Yi M, Wan Q, Zhou Y. Tomato and lycopene and multiple health outcomes: Umbrella review. Food Chem. 2021; 343:128396.
22. Zeng Y, Mu G, Huang S, Zeng X, Cheng H, Li Z. Effects of lycopene on number and function of human peripheral blood endothelial progenitor cells cultivated with high glucose. Nutr Res Pract. 2014; 8(4):368-376.
23. Badkook M, McCullough F, Ahmed N. Effect of a high monounsaturated fatty acid diet alone or with combined vitamin e and C, or lycopene intake on oxidative stress in patients with type 2 diabetes mellitus. Br J Diabetes Vasc Dis. 2012; 12(2):81-86.
24. Aydin M and Çelik S. Effects of lycopene on plasma glucose, insulin levels, oxidative stress, and body weights of streptozotocin-induced diabetic rats. Turkish J Med Sci. 2012; 42(SUPPL.2):1406-1413.
25. Ejike DE, Adam MA, Sheu OS, Nganda P, Iliya E, Moses DA, Alfred OO, Karimah MR. Lycopene attenuates diabetes-induced oxidative stress in Wistar rats. J Diabetes Endocrinol. 2018; 9(2):11-19.
26. Ejike DE and Yusuf T. Effects of Lycopene on Liver Markers and Glucokinase Activity in Experimentally-induced Diabetes Mellitus Rat Model. J basic appl Res. 2016; 2(3):353-362.
27. Newsholme P, Cruzat VF, Keane KN, Carlessi R, De Bittencourt PIH. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem J. 2016; 473(24):4527-4550.
28. Ighodaro OM. Molecular pathways associated with oxidative stress in diabetes mellitus. Biomed Pharmacother. 2018; 108:656-662.
29. Karahan F, Dede S, Ceylan E. The Effect of Lycopene Treatment on Oxidative DNA Damage of Experimental Diabetic Rats. Open Clin Biochem J. 2018; 8(1):1-6.
30. Zheng Z, Yin Y, Lu R, Jiang Z. Lycopene Ameliorated Oxidative Stress and Inflammation in Type 2 Diabetic Rats. J Food Sci. 2019; 84(5):1194-1200.
31. Bigagli E and Lodovici M. Circulating oxidative stress biomarkers in clinical studies on type 2 diabetes and its complications. Oxid Med Cell Longev. 2019; 2019:1-17.
32. Hussein SA, Hassanein MR, Awadalla MA. Lycopene and its Potential Role in Diabetic Nephropathy Induced in Rats. Benha Vet Med J. 2018; 34(3):26-41.
33. Yin Y, Zheng Z, Jiang Z. Effects of lycopene on metabolism of glycolipid in type 2 diabetic rats. Biomed Pharmacother. 2019; 109(74):2070-2077.
34. Saracoğlu G, Baş H, Pandır D. Furan - induced cardiotoxicity in diabetic rats and protective role of lycopene. J Food Biochem. 2019; 2018:1-9.
35. Singh K and BS B. Ameliorative Effect of Lycopene on Lipid Peroxidation and Certain Antioxidant Enzymes in Diabetic Patients. J Diabetes Metab. 2012; 03(06):202.
36. Li W, Wang G, Lu X, Jiang Y, Xu L, Zhao X. Lycopene ameliorates renal function in rats with streptozotocin-induced

diabetes. Int J Clin Exp Pathol. 2014; 7(8):5008-5015.
37. Guo Y, Liu Y, Wang Y. Beneficial effect of lycopene on anti-diabetic nephropathy through diminishing inflammatory response and oxidative stress. Food Funct. 2015; 6(4):1150-1156.
38. Tabrez S, Al-Shali KZ, Ahmad S. Lycopene powers the inhibition of glycation-induced diabetic nephropathy: A novel approach to halt the AGE-RAGE axis menace. BioFactors. 2015; 41(5):372-381.
39. Uçar S and Pandir D. Furan induced ovarian damage in non - diabetic and diabetic rats and cellular protective role of lycopene. Arch Gynecol Obstet. 2017; 296(5):1027-1037.
40. Assis RP, Arcaro CA, Gutierres VO, Oliveira JO, Costa PI, Baviera AM, Brunetti IL. Combined effects of curcumin and lycopene or bixin in yoghurt on inhibition of LDL oxidation and increases in HDL and paraoxonase levels in streptozotocin-diabetic rats. Int J Mol Sci. 2017;18(4):332.
41. Belter A, Giel-Pietraszuk M, Oziewicz S, Chomczyński P, Barciszewski J. [Lycopene–occurrence, properties and applications]. [Likopen–wystepowanie, właściwości oraz potencjalne zastosowanie.]. Postepy Biochem. 2011; 57(4):372-380.
42. Nabavi SF, Barber AJ, Spagnuolo C, Russo GL, Daglia M, Nabavi SM, Eduardo Sobarzo-Sánchez. Nrf2 as molecular target for polyphenols: A novel therapeutic strategy in diabetic retinopathy. Crit Rev Clin Lab Sci. 2016; 53(5):293-312.
43. Pall ML, Levine S. Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors. Sheng Li Xue Bao. 2015; 67(1):1-18.
44. Kumar H, Kim IS, More SV, Kim BW, Choi DK. Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases. Nat Prod Rep. 2014; 31(1):109-139.
45. Tan Y, Ichikawa T, Li J, Si Q, Yang H, Chen X, Goldblatt CS, Meyer CJ, Li X, Cai L, Cui T. Diabetic downregulation of Nrf2 activity via ERK contributes to oxidative stress-induced insulin resistance in cardiac cells in vitro and *in vivo*. Diabetes. 2011; 60(2):625-633.
46. Bitar MS and Al-Mulla F. A defect in nrf2 signaling constitutes a mechanism for cellular stress hypersensitivity in a genetic rat model of type 2 diabetes. Am J Physiol - Endocrinol Metab. 2011; 301(6):1119-1129.
47. Siewert S, González I, Santillán L, Lucero R, Ojeda MS, Gimenez MS. Downregulation of Nrf2 and HO-1 expression contributes to oxidative stress in type 2 diabetes mellitus: A study in Juana Koslay City, San Luis, Argentina. J Diabetes Mellit. 2013; 3(2):71-78.
48. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014; 105(2):141-150.
49. Zeng Z, He W, Jia Z, Hao S. Lycopene Improves Insulin Sensitivity through Inhibition of STAT3/Srebp-1c-Mediated Lipid Accumulation and Inflammation in Mice fed a High-Fat Diet. Exp Clin Endocrinol Diabetes. 2017; 125(9):610-617.
50. Yin Q, Ma Y, Hong Y, Hou X, Chen J, Shen C, Sun M, Shang Y, Dong S, Zeng Z, Pei J, Liu X. Lycopene attenuates insulin signaling deficits, oxidative stress, neuroinflammation, and cognitive impairment in fructose-drinking insulin resistant rats. Neuropharmacology. 2014; 86:389-396.
51. Fukami K, Yamagishi SI, Coughlan MT, Harcourt BE, Kantharidis P, Thallas-Bonke V, Okuda S, Cooer ME, Forbes JM. Ramipril inhibits AGE-RAGE-induced matrix metalloproteinase-2 activation in experimental diabetic nephropathy. Diabetol Metab Syndr. 2014; 6:86.
52. Icel E, Icel A, Uçak T, Karakurt Y, Elpeze B, Keskin Çimen F, Süleyman H. The effects of lycopene on alloxan induced diabetic optic neuropathy. Cutan Ocul Toxicol. 2019; 38(1):88-92.
53. Didonato JA, Mercurio F, Karin M. NF-κB and the link between inflammation and cancer. Immunol Rev. 2012; 246(1):379-400.
54. Abeyrathna P and Su Y. The critical role of Akt in cardiovascular function. Vascul Pharmacol. 2015; 74:38-48.
55. Gardner DG, Shoback D. Greenspan's Basic & Clinical Endocrinology. McGraw-Hill. 2018.
56. Bathina S and Das UN. Dysregulation of PI3K-Akt-mTOR pathway in brain of streptozotocin-induced type 2 diabetes mellitus in Wistar rats. Lipids Health Dis. 2018; 17:1-11.
57. Huang X, Liu G, Guo J, Su ZQ. The PI3K/AKT pathway in obesity and type 2 diabetes. Int J Biol Sci. 2018; 14(11):1483-1496.
58. Wang Q, Li RUI, Xiao ZHI, Hou CUN. Lycopene attenuates high glucose - mediated apoptosis in MPC5 podocytes by promoting autophagy via the PI3K/AKT signaling pathway. Exp Ther Med. 2020; 20(3):2870-2878.
59. Demirtas L, Guclu A, Erdur FM, Akbas EM, Ozcicek A, Onk D, Turkmen K. Apoptosis, autophagy & endoplasmic reticulum stress in diabetes mellitus. Indian J Med Res. 2016; 144(4):515-524.
60. Turkmen K. Inflammation, oxidative stress, apoptosis, and autophagy in diabetes mellitus and diabetic kidney disease: the Four Horsemen of the Apocalypse. Int Urol Nephrol. 2017; 49:837-844.
61. Liu W-H, Wang Q-N, Zhou Y, Wang Y-J, Tong Z. Divergent effects of lycopene on pancreatic alpha and beta cells. Sheng Li Xue Bao. 2020; 72(2):133-138.
62. Soleymaninejad M, Joursaraei SG, Feizi F, Jafari Anarkooli I. The Effects of Lycopene and Insulin on Histological Changes and the Expression Level of Bcl-2 Family Genes in the Hippocampus of Streptozotocin-Induced Diabetic Rats. J Diabetes Res. 2017; 2017:4650939.
63. Malekiyan R, Abdanipour A, Sohrabi D, Anarkooli IJ. Antioxidant and neuroprotective effects of lycopene and insulin in the hippocampus of streptozotocin-induced diabetic rats. Biomed Rep. 2019; 10(1):47-54.
64. Rahmeier FL, Zavalhia LS, Tortorelli LS, Huf F, Géa LP, Meurer RT, Machado AC, Gomez R, Fernandes MC. The effect of taurine and enriched environment on behaviour, memory and hippocampus of diabetic rats. Neurosci Lett. 2016; 630:84-92.
65. Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and Cognitive Impairment. Curr Diab Rep. 2016; 16(9):87.
66. Zeng YC, Peng LS, Zou L, Huang SF, Xie Y, Mu GP, Zeng XH, Zhou XL, Zeng YC. Protective effect and mechanism of lycopene on endothelial progenitor cells (EPCs) from type 2 diabetes mellitus rats. Biomed Pharmacother. 2017; 92:8694.