



Risk reduction and prevention of cardiovascular diseases: biological mechanisms of lycopene

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ABSTRACT

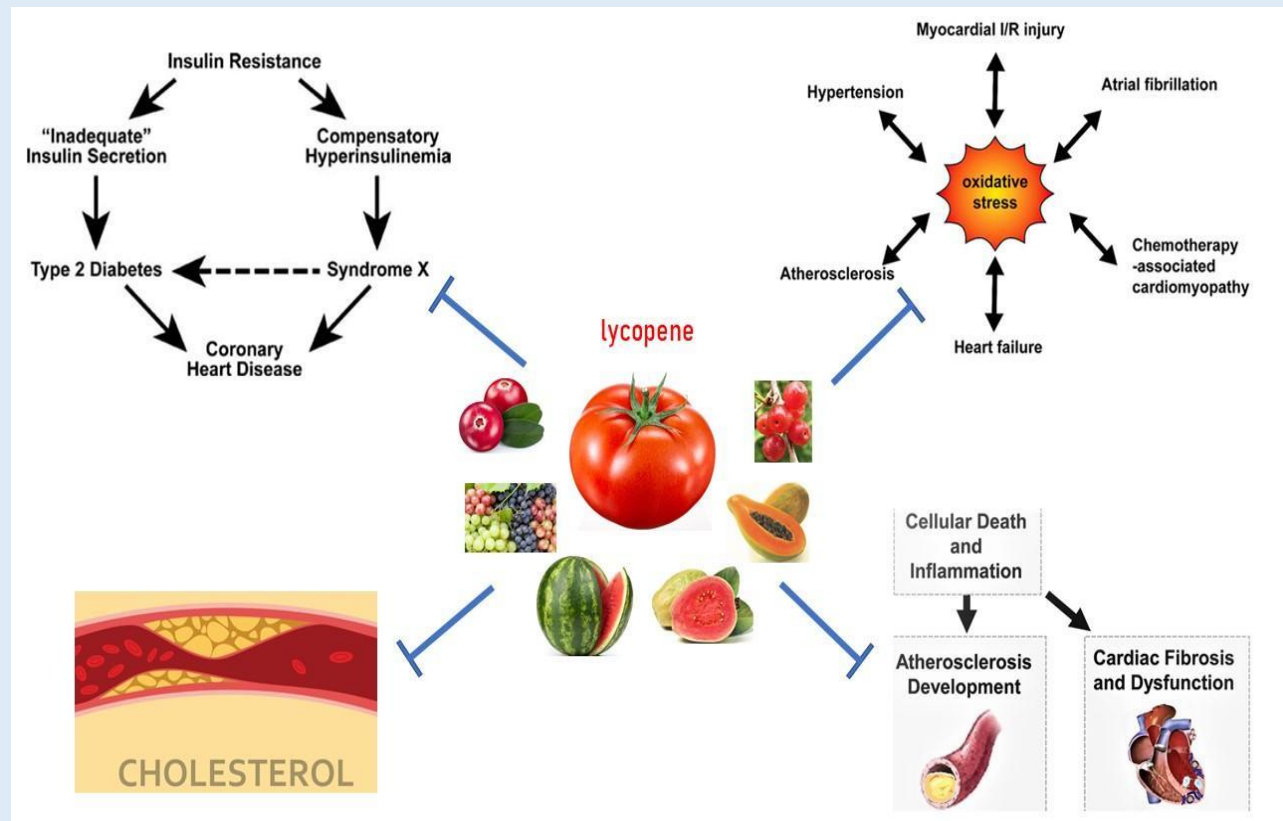
Background and aims: The conservational effects of dietary interventions as advantageous instruments in the primary and secondary prevention of cardiovascular disease (CVD) have gotten more attention in recent years. Numerous nutritional epidemiological studies have highlighted the ability of diets to decrease costly care and treatments as well as adverse side effects from standard treatments. Lycopene is a non-pro-vitamin A carotenoid that is present in tomatoes, processed tomato products, and different fruits like watermelon, autumn olive, gac, pink grapefruit, pink guava, papaya, sea buckthorn, and wolfberry. As one of the most powerful antioxidants among dietary tetraterpenoids, lycopene can also assist in lowering the risk of early death and extending life in patients with heart disease. By reducing the destructive effects of free radicals along with total and “bad” LDL cholesterol levels while increasing “good” HDL cholesterol, lycopene holds the power to reduce the risk factors of heart disease. Several studies have investigated a reduction of oxidized-LDL (oxLDL) cholesterol levels following lycopene consumption which supports these claims and suggests the conceivable function of lycopene in the blockage of oxidative stress-associated CVD. A negative correlation between serum lycopene concentration and mortality of people with metabolic syndrome was found.

Over 10 years, researchers observed a 39% decreased chance of premature death in individuals with the metabolic disease who had the highest blood concentrations of lycopene. Lycopene’s protective impacts are especially beneficial in those with low blood antioxidant levels or high levels of oxidative stress. This includes older adults, smokers, and

diabetic individuals or other vascular disorders. Lycopene intake has been thought to reduce the risk of obesity, insulin resistance, and diabetes mellitus.

Lycopene acts as an antihypertensive agent by impeding the angiotensin-converting enzyme and improving the production of nitric oxide (NO) in the endothelium. The purpose of this review is to summarize the possible mechanisms of lycopene in the prevention of CVD.

Keywords: Lycopene, Risk factors of heart disease, Antioxidants, Carotenoids, Cardio-metabolic, Insulin resistance



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INTRODUCTION

Worldwide, cardiovascular diseases (CVD) are the leading cause of death for adults over 60 years of age in both developed and developing countries. According to World Health Organization reports, the number of deaths is increasing annually [1]. Myocardial ischemia is a chronic, progressive disease, but can quickly become an acute and unstable emergency, typically due to an acute atherothrombotic event caused by plaque rupture [2].

Atherosclerosis is one of the non-communicable, multifactorial and immunoinflammatory diseases of the arteries driven by lipids. Common risk factors such as smoking, high blood pressure, diabetes, gender, age, and inflammation, which accelerate the penetration of lipids into the intima and the formation of coronary atherosclerotic plaques [2]. With arteriosclerosis, the elasticity of the coronary artery walls decreases and lipid deposits on the blood vessel walls lead to increased

blood pressure. To ensure a sufficient blood supply, the heart must consume excessive energy and work harder to defeat the increased resistance to blood flow, consequent of coronary artery stenosis [3].

At some point, the coronary blood flow cannot overcome high flow resistance in the narrow segment of the diseased blood vessel, and the heart wall will have varying degrees of myocardial ischemia [4]. Type 2 diabetes mellitus (T2DM) shortens life expectancy by up to 10 years, largely due to its effects on the microvasculature, such as retinopathy, neuropathy, nephropathy, and coronary arterial disease among other complications. Therefore, it is not surprising that CVD is the leading cause of death in T2DM patients [5]. Many studies propose that nutritional supplements play a pivotal role in the prevention of cardiovascular diseases. Therefore, a dietary intake of tomatoes and tomato products containing lycopene is associated with a decreased risk of cardiovascular disease [6].

RETRIEVAL OF PUBLISHED STUDIES

Pertinent studies were found for this systematic review by doing database searches using PubMed and Google Scholar. Articles published in English from scholarly, peer-reviewed publications were marked for additional evaluation using the search terms "lycopene" and "heart diseases."

Structural characterization of lycopene: As a carotenoid, lycopene contributes to the red color in plants like tomatoes by optical absorption with wavelength maximum at $\lambda = 444, 470, \text{ and } 502 \text{ nm}$ [7]. Lycopene is a linear polyene organic compound made up of forty carbon atoms, with the molecular formula $C_{40}H_{56}$ [8]. It contains eleven conjugated and 2 unconjugated double bonds, that interconvert to 5-cis, 9-cis, 13-cis, or 15-cis depending upon exposure to light, temperature, and

several different chemical reactions [8]. This unique polyene structure confers the ruby red color and antioxidant properties of lycopene. It has unique lipophilic properties, making it almost insoluble in ethyl alcohol, methyl alcohol, and water. Due to its acyclic structure and lack of ionic rings, lycopene lacks the activity of provitamin A, which is the reason for the difference in its biochemistry, compared to α and β carotene [8]. Carotenoids are a group of more than 1,100 triterpenoids, tetraterpenes, and pentaterpene lipophilic pigments (but mainly tetraterpenes) produced by plants, many bacteria, and fungi. However, carotenoids are not produced by humans and must be obtained completely through dietary sources [9]. Early publications indicated that the cis-isomer of lycopene is more absorbed by the lipid micelles, than the all-trans configuration [10].

Metabolites of lycopene: The initial catabolism of lycopene leads to the formation of lycopene-like substances or lycopenoids. One of the bioavailable metabolites of lycopene is APO-10'-lycopenoic acid, which is produced by the action of β -carotene oxygenase 1 (BCO1). The pharmacological dose of the putative lycopene metabolite APO10' lycopene acid (APO10) (10 mg per kilogram of feed) can improve insulin resistance and reduce inflammatory factors in mice on a high-fat diet [9].

Minerals and lycopene absorption: Divalent minerals (Ca^{2+} , Zn^{2+} , and Mg^{2+}) can impede the bioavailability of carotenoids (lutein, β -carotene, and lycopene) and intestinal absorption. After the extraction of lycopene from the food matrix, it is transferred to food fat and then to mixed micelles. A nutritional dose of Ca^{2+} may impair the dietary bioavailability of lycopene in healthy subjects. This inhibition could be because of Ca^{2+} altering the electrical charge of micelles. At concentrations between 50 and 100 mg/L, Zn^{2+} did not affect the solubility of

lycopene. However, at concentrations above 200 mg/L, Zn^{2+} did inhibit the bioavailability of lycopene. Similarly, at a concentration of 252 mg/L Mg^{2+} , the bioavailability of lycopene was halved [11].

Opuntia ficus-indica, an obscure source of lycopene:

Opuntia ficus-indica, a giant cactus with edible fruits, is one of the lesser-known sources of lycopene [12]. Cactus

fruits are utilized to treat various diseases and conditions, such as inflammation and hyperglycemia. Certain types of cacti have been shown to possess protective properties against atherosclerosis and CVD, diabetes, metabolic disorders, and cancer. After administering cactus fruit juice to rats with alloxan-induced diabetes, the researchers detected an improvement in the body's redox balance and antioxidant status [12].

Table 1. Lycopene content in different sources.

Food Sources	Contents (mg/100 g)	Reference
Sun-dried tomatoes	45.9 mg	[13]
Tomato puree	21.8 mg	
Rose hip	6.8 mg	
Guava	5.2 mg	
Watermelon	4.5 mg	
Fresh tomatoes	3.0 mg	
Canned tomatoes	2.7 mg	
Papaya	1.8 mg	
Pink grapefruit	1.1 mg	
Cooked sweet red peppers	0.5 mg	

Antioxidant activity of lycopene: Due to its abundance of conjugated dienes, lycopene has a powerful antioxidant capacity, with a unique ability to quench singlet-oxygen oxidation twice as much as β -carotene and ten times as much as alpha-tocopherol [14]. By the DPPH assay, the antioxidant capacity of the sample is defined as its ability to donate electrons to neutralize the DPPH radical. Evaluation of the tomato pomace extracts shows the percentage of inhibition of the DPPH radical varied between 17.1 ± 1.66 and $31.35 \pm 0.18\%$ [15]. In addition, the FRAP assays measure the reducing power of the extracts in terms of the reduction of ferric ions, respectively. According to some studies, tomato FRAP values range from 64.00 to 230.12 $\mu\text{mol TE}/100\text{ g}$ [16].

Lycopene also enhances the activity of superoxide dismutase (SOD) and glutathione peroxidase (G-Px), two of the most important antioxidative enzymes [17]. In the study by Zheng et al, on the rat cardiomyocytes line H9c2, petunidin and lycopene combined in various ratios induced cellular antioxidant activity, especially at a petunidin: lycopene ratio of 9:1. They also induced the activation of the intracellular antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and notably the Akt/Nrf2 pathway, which is a critical regulator of ROS-induced oxidative stress. Phytochemicals like lycopene can activate the Nuclear factor erythroid 2-related factor 2- (Nrf2) pathway to thus attenuate oxidative stress mediated by CVD [18].

In the case of myocardial ischemia-reperfusion injury in the H9C2 cell model, apoptosis was determined by flow cytometry, and the attenuation was found to be related to the inhibition of the expression of p-JNK, CHOP, and caspase-12 cellular apoptosis pathways [19]. Nrf2 is a key regulator for ARE (antioxidant response element). Electrophiles such as p-Coumaric acid, caffeic acid, and derivatives of β -carotene and lycopene can activate the Nrf2 signaling pathway [20].

As one of the most powerful antioxidants, lycopene has also demonstrated protective effects on kidney cells in an experimental diabetes model, suppressing the nuclear factor- κ B signaling pathway, thereby decreasing inflammation and alleviating oxidative stress [21]. A study by Bazyel, et al. revealed that on the PC12 cell line treated with the high-glucose, lycopene administration had inhibitory effects on oxidative DNA damage, caspase-3, and apoptosis [21]. Regarding its effect on autophagy, lycopene in H9C2 cardiomyocytes has been shown to prevent cell apoptosis, which is caused by oxidative stress from increased autophagy. Lycopene can reduce cell death by increasing AMPK-mediated autophagy in cardiomyocytes H9C2 induced by hypoxia/reoxygenation [22]. Experiments on the human macrophage cell line THP1 (human leukemia monocytic cell line) have shown that lycopene dosed at 0.5–2 mM can significantly inhibit apoptosis and oxidative stress induced by 7-ketocholesterol (7-KC). Additionally, it dose-dependently reduced the production of ROS and the formation of 8-hydroxydeoxyguanosine (8OHdG) induced by oxysterol. In addition, certain concentrations of lycopene decreased the expression of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, thereby reducing intracellular total cholesterol levels in THP1 macrophages [23]. Lycopene can downregulate cyclooxygenase-2 (COX2), inducible nitric oxide synthase (iNOS), and TNF α (Tumor necrosis factor- α) in LPS-stimulated RAW264.7 cells and suppress the inflammation due to its

immunomodulatory properties [24]. Lycopene treatment of endothelial progenitor cells (EPC) resulted in increased proliferation and decreased apoptosis and autophagy. These effects of lycopene in proliferation and apoptosis signaling are particularly important in vascular disorders, such as coronary heart disease [25].

In ischemia-reperfusion injury, cell models have shown an increase in 8-hydroxy-2'-deoxyguanosine (8-OHdG), a critical biomarker of oxidative stress in cardiomyocytes. 8-OHdG down-regulates mtDNA transcription and leads to dysfunctional mitochondria. Lycopene can inhibit excessive mtROS production and restore transcription factor A mitochondrial (TFAM). It also suppresses 8-OHdG expression to protect cardiomyocytes from damage caused by oxidative stress caused by ischemia-reperfusion [26].

A recently published study revealed that a lycopene-supplemented diet in rats could be effective in the control of metabolic syndrome induced by a high-fructose diet. Lycopene is involved in the prevention of hypertension, maintenance of lipid homeostasis, decreasing insulin resistance, and subsequently, regulation of blood glucose levels [27].

Lycopene's most advantageous properties are emphasized within the context of CVD. By preventing lipid peroxidation and LDL fractionation, it plays a protective role in the initiation and development of atherogenesis [28]. It prevents the oxidation of LDL cholesterol, as well as it also decreases overall cholesterol levels. Researchers observed reduced cholesterol synthesis (by up to 60–70%) in cultures of macrophages in patients who had received 60 mg a day for 3 months of lycopene by inhibiting HMG-CoA reductase [28]. The consumption of 22 mg lycopene in soy germ-fortified juice for eight weeks has an anti-oxidative effect on LDL [29]. Lycopene is transported by lipoproteins in the bloodstream and is actively absorbed by adipocytes. In patients with familial

hypercholesterolemia, lycopene lowers blood cholesterol via inhibiting the mRNA synthesis of the proprotein convertase subtilisin/Kexin type 9 (PCSK9) mutant gene. In addition to its role in lipid metabolism, PCSK9 is also implicated in the control of inflammation, blood pressure, and insulin homeostasis [30]. Watermelon powder consumption in rats changes liver gene expression; it then follows that the expression of fatty acid synthase and the enzyme responsible for fatty acid storage will subsequently be reduced [31]. Lycopene is mostly deposited in adipose tissue and has been shown to reduce the secretion of inflammatory cytokines by adipocytes; Therefore, reducing the risk of diseases associated with dyslipidemia and obesity [32]. In mice fed a high-fat, high-fructose (HFFD) diet, it was found that lycopene therapy reduced weight gain and liver weight [33].

Experimental studies conducted by Yin et al. indicate that lycopene can increase antioxidant enzyme activity and regulate glucose and lipid metabolism in streptozotocin-induced diabetic rats [34]. They found that the glycolipid metabolism of T2DM rats significantly improved after 10 weeks of lycopene treatment, indicating that lycopene has beneficial effects on lipid and glucose metabolism. Also, this effect is dose-dependent and works best at 20 mg/kg [34]. Lycopene, like atorvastatin, can fill the binding pocket of the PCSK-9 crystal structure, preventing its worst catalytic activity of LDL-receptor degradation or recycling at low rates [35]. The anchored structures of Lycopene-PCSK-9 and atorvastatin-PCSK9 complexes surrounded by hydrophobic residues were determined. The binding energies (ΔG values) of both complexes (-493.93 Kcal/mol and -524.61 Kcal/mol, respectively) also corroborated the similar mode of action of lycopene and atorvastatin [35]. Lycopene can compete with cholesterol to be dissolved into the micelles by bile salts, which leads to a reduction in the expression of Niemann-

Pick C1-like1 in Caco-2 cells of the intestine epithelium and restricts the absorption of cholesterol [36]. Following 4 weeks of treatment with lycopene microspheres in atherosclerosis-induced rodents, the serum total cholesterol, low-density lipoprotein cholesterol levels, and the cholesteryl ester content of the aorta were significantly reduced [37].

Lycopene and blood pressure: There is substantial evidence suggesting that the daily consumption of vegetables and fruits decreases blood pressure. This hypotensive effect is often ascribed to the pivotal role of natural antioxidants, such as lycopene and other phytochemicals, in improving vascular function [38]. However, there are contradictory findings regarding lycopene supplements and blood pressure. A significant reduction in blood pressure has been shown in several studies when tomato extract or tomato juice is taken every day for at least 4 weeks, while other studies have shown no effect [38]. In 2019, Wolak et al. demonstrated that treatment with 15 or 30 mg of supplemental lycopene for eight weeks resulted in significant reductions in mean systolic blood pressure in hypertensive patients [39]. A study by Frosini et al. indicated that treating hypertensive rats with an aqueous extract of tomatoes or captopril for four weeks both led to an outstanding decrease in blood pressure [40]. Angiotensin II (Ang II) can be used to induce hypertension in rats, as it activates both NADPH and NADH oxidase. It has also been shown to increase intracellular O_2^- formation by almost 3 times in rat aortic vascular smooth muscle cells treated with Ang II for 5 hours, leading to endothelial dysfunction [40]. Losartan, an AT1 receptor blocker, inhibits these destructive effects. Similarly, lycopene treatment in rats given Ang- II can effectively prevent the increase in systolic blood pressure, but there

is no effect in rats with normal blood pressure [40]. These findings support the antihypertensive capacity of lycopene without causing hypotension. Interestingly, lycopene also increases sensitivity to sodium nitroprusside (SNP), a medication used to lower blood pressure [41]. Several plant-based bioactive substances have been identified as useful for preventing and reducing some common CVD risk factors, such as high blood pressure. Grape seed extract, cocoa, berberine, aged garlic extract, beetroot juice, resveratrol, green tea, ascorbic acid, pycnogenol, olive oil, and lycopene are all plants nutrients with studied anti-hypertensive effects [42]. According to the Functional Food Center (FFC), functional foods (FF) are natural or processed foods containing biologically active compounds in non-toxic and effective amounts that promote health, reduce the risk of chronic diseases, including cardiovascular diseases, and manage their symptoms [43]. In one of the randomized, single-blinded cross-over studies, short-term supplementation of tomato pastes while fasting over one week did not significantly affect diastolic BP; However, following a fatty meal, it did cause a modest decrease in diastolic blood pressure, suggesting an acute effect when food causes deleterious vascular effects [44]. Similarly, a new meta-analysis that summarized all these results found a significant impact of lycopene on systolic blood pressure, but not on diastolic blood pressure [44]. Flow-Mediated Dilatation (FMD) is an ultrasound-based approach for assessing the endothelium's ability to dilate in response to increased shear stress. The nitrates in tomatoes and other vegetables improve the function of the vascular system, including FMD. In addition to nitrates, lycopene and potassium (a mineral abundant in tomato products) play a key role in tomato products' ability to have a vasodilatory impact [44]. A randomized, double-blinded, placebo-controlled study comparing 7

mg of lycopene with a placebo showed that lycopene improved the production of NO and thus endothelium function in patients with cardiovascular disease. In comparison to day 1, CVD patients treated with lycopene had lower central and peripheral diastolic blood pressures on day 56 (peripheral diastolic BP 2.9 mm Hg lower, 95% CI (Confidence interval): -5.5 to -0.2, $P = 0.03$; and central BP 3.3 mm Hg lower, 95% CI: -6 to -0.5, $P = 0.02$); however, these changes were not considered significant compared to placebo [45]. Epidemiological studies have also demonstrated a relationship between being overweight/obese and hypertension. The renin-angiotensin-aldosterone system is activated by serum uric acid [46]. Lycopene is a natural antioxidant that reduces oxidative stress and free radicals produced by angiotensin-II by inhibiting the activity of the angiotensin-converting enzyme. Researchers studied the relationship between serum uric acid, serum lycopene, and hypertension in overweight people. Hypertension was found to be strongly positively linked with serum uric acid, whereas serum lycopene has a negative correlation. Furthermore, in overweight or obese adults, there was a strong link between blood lycopene to serum uric acid ratio and hypertension [46].

Diabetes alters vascular elasticity, raising blood pressure and increasing the risk of heart disease. Moreover, high blood glucose levels activate diacylglycerol (DAG), which activates a few isozymic forms of protein kinase C (PKC), leading to the development of various vascular dysfunctions [47]. In addition, hyperglycemia can cause the proliferation of vascular smooth muscle cells (VSMC), further increasing the possibility of cardiovascular disease. In conclusion, diet-based treatment strategies are expected to show excellent activity in laboratory animals and clinical trials. It was shown that tomato and lycopene are significantly

effective against cardiovascular dysfunction and related metabolic syndrome [47]. Consuming carotenoids, such as lycopene during pregnancy is confirmed to protect against pregnancy-induced hypertension [48].

Lycopene in protection against diabetes: According to epidemiological studies, consuming lycopene lowers the chance of developing diabetes and obesity. Studies on male C57BL/6J mice reveal that the lycopene derivative apo-10'-lycopeneoenoic acid improves glucose intolerance. However, some researchers have discovered that giving lycopene to obese animals had no impact on their body weight or obesity index. These discrepancies can be explained by different doses (2, 4, 10 mg/kg, and 15 mg/kg), durations of treatment (four, 12 weeks, and 24 weeks), or animal models or dietary supplements [49]. An animal study that was designed by Zhaohui et al. in 2016 demonstrated that lycopene improves insulin sensitivity by inhibiting STAT3/SREBP-1C-signaling in mice given a high-fat diet [50].

When lycopene participates in biological oxidation reactions and the capture of free radicals, it is irreversibly degraded, forming end products that get excreted from the body. Consequently, it is likely that processes like aging and diseases that are connected to oxidative stress such as atherosclerosis, diabetes, and cancer could be accompanied by lycopene depletion and the development of lycopene deficiency [51]. Diabetic rats induced by streptozotocin were treated with lycopene (45 mg/kg) or metformin (250 mg/kg) alone or mixed with yogurt for 35 days. Metformin is the drug of choice for the treatment of type 2 diabetes and lowers blood glucose levels by inhibiting the production of glucose by the liver hepatocytes, mainly through the inhibition of gluconeogenesis [51]. Lycopene appears to be beneficial for the treatment of advanced glycation-related metabolic disorders. This combination of lycopene and

metformin improved glucose tolerance and lipid profiles, reduced biomarkers of oxidative damage, and increased paraoxonase 1 activity. Combination therapy also resulted in further decreases in postprandial glycemia and production of AGEs [52]. In obese mice induced by an HFFD, lycopene inhibited lipid accumulation in adipose tissue by reducing the expression of adipogenic genes, including FAS, ACACA, PPAR γ , PPAR G, and SREBP1 C, and increasing the expression of genes related to lipolysis, including mitochondrial functional genes [53]. Moreover, lycopene improves insulin resistance in white adipose tissue and reduces inflammation in white adipose tissue (WAT), the intestines, and plasma [53]. HFFD evoked an inflammatory response in WAT, increased the RNA expression that handles the production of leptin, and further elicited insulin resistance, while reducing the mRNA expression of glucose transporters (GLUTs) in WAT. According to this experimental study, lycopene might be a nutritional preventive strategy to combat obesity [53]. Lycopene has an anti-anemic effect and improves the immune system of diabetic rats in a manner that is not dose-dependent. Additionally, it reduced the neutrophil and platelet count while stabilizing albumin and globulin levels [53]. Lycopene can activate erythropoiesis, which is associated with the maturation factor, such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin- (IL-) 3, stem cell factor (SCF), IL-1, IL-6, IL-4, IL-9, IL-11, insulin growth factor-1 (IGF-1), and erythropoietin (EPO) [53].

Lycopene's powerful hematoprotective effects increase its therapeutic effectivity, which has been observed through increased pancreatic protection in diabetes. This is important because common anti-diabetic drugs, like metformin interfere with the absorption of vitamin B12 [54]. Therefore, the use of lycopene in integrative medicine will help reduce the side effects and toxicity associated with conventional

diabetes treatment [54]. In Streptozotocin diabetic rats, curcumin and carotenoids (lycopene and bixin) were shown to improve several biomarkers associated with oxidative stress and cardiovascular risk [54]. In people with diabetes or obesity, consuming yogurt fortified with lycopene improved glucose and lipid metabolism and attenuated inflammation and oxidative stress [54]. The effects of lycopene in diabetes mellitus depend on its antioxidant potential, which attenuates endothelial dysfunction by reducing both the oxidative stress in the aorta and the levels of oxidized-LDL (ox-LDL). A recent study showed that lycopene treatment reduced both vacuolization of the islets of Langerhans and loss of insulin-producing cells in STZ-diabetic rats, resulting in better control of blood glucose levels compared to untreated diabetic rats [55]. Gliclazide, another diabetic medication, can significantly reduce blood glucose levels in diabetic animals. The hypoglycemic activity of gliclazide in rats is interceded by blocking K⁺ channels in β -cells of the pancreas [55]. Lycopene has a supportive effect when combined with gliclazide, which has been demonstrated in rats and rabbits. The liver appears to be an insulin-dependent tissue involved in glucose and lipid homeostasis, which is usually severely affected by diabetes. Lycopene can exert its hypoglycemic activity by increasing the activity of hepatic glucokinase and by stimulating the release of insulin from pancreatic beta cells to result in elevated serum insulin levels [56]. Lycopene significantly promotes the renovation of liver enzymes and reduces histopathological abrasions caused by a high-fat diet (HFD). In addition, lycopene significantly increased the expression of insulin receptor substrate 2 (IRS 2) by 25%. Insulin resistance surged significantly in HFD fed rats compared to the control group. Treatment with lycopene significantly decreased this ratio by 62% when compared to the HFD control group [57]. In T2DM rats, lycopene decreased glycated hemoglobin by two mechanisms: first, by improving

insulin resistance and thereby reducing blood glucose levels; second, by acting as a reducing agent, thereby suppressing the earlier non-enzymatic glycosylation reactions [58].

Decrease of oxidative stress and inflammation by

lycopene: Inflammation is known to contribute to the development and occurrence of many non-communicable diseases, such as cardiovascular disease, neurodegenerative disease, and type II diabetes [59]. To prevent mild chronic inflammation and maintain overall health, epidemiological evidence suggests exercise, a healthy weight, avoiding smoking, and eating a balanced diet rich in fruits, grains, and vegetables [59]. Due to its strong ability to neutralize free radicals, it is believed that lycopene can provide assessable protection against cancer, atherosclerosis, diabetes, and other inflammatory diseases. Many reports describe the beneficial role of lycopene in the endothelial activity of nitric oxide synthase and the normalization of nitric oxide levels in coronary arteries, blockage of the mevalonate pathway of cholesterol biosynthesis, and recuperation of endothelial function and inflammatory damage [60]. In their 2004 study on rats, Hassan and Edrees demonstrated that biochemical alterations in the activities of heart-specific enzymes LDL, CK, ALT, and AST caused by the consumption of oxidized frying cottonseed oil were ameliorated when lycopene was added to their diets [61]. Plasma lycopene levels and conjugated dienes, primary products of lipid oxidation, have a significant negative correlation. Dietary carotenoids significantly help reduce oxidative modification of LDL *in vivo* [51,62–64]. When severe oxidative stress occurs, the body's normal physiological system is disrupted, thus requiring the addition of antioxidants to eliminate the formation of free radicals. Many *in vitro* and *in vivo* reports indicate that the supplementation of lycopene can positively affect the progress and outcomes of CVD [65–70]. In the

recent intervention study by Colman-Martinez et al., it was shown that tomato juice supplements rich in lycopene can significantly reduce inflammatory markers such as CRP, IL-6, ICAM-1, and VCAM-1, encouraging the consumption of immunonutrients like lycopene as well as berries, ω -3 and ω -6 polyunsaturated fatty acids, vitamins E, A, C, and D, and coenzyme Q10 [71].

According to research, lycopene inhibits cardiac hypertrophy-induced pressure overload and improves cardiac dysfunction. The decrease in left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) with the increase in fractional shortening (FS%) further confirmed the role of lycopene in heart remodeling. In addition, lycopene treatment significantly reduced the increase in BNP caused by pressure overload [72,73]. Obesity contributes directly to incident cardiovascular risk factors including metabolic dysregulation like insulin resistance and hypertension. Obesity-related adipokines, including leptin, adiponectin, pro-inflammatory cytokines like IL-6 and TNF- α , and monocyte chemoattractant protein-1 (MCP-1) are also produced by adipose tissue [74]. Therefore, increased generation of these products occurs in obese patients. Patients with chronic heart failure have been found to have increased levels of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), which suggests inflammation is correlated with disease severity. Interestingly, a study showed pro-inflammatory cytokines induce myocardial contractile depression, especially by fluctuating calcium homeostasis and handling. Consequently, myofibril sensitivity to Ca²⁺ decreases due to decreased systolic Ca²⁺ inflow and reuptake by SERCA2 [74]. After tissue injury, inflammation is a pivotal physiological response in the healing process, but excessive inflammatory reactions can lead to left ventricular (LV) hypertrophy and cardiomyopathy progression. Thus, natural anti-inflammatory therapeutic strategies are being highlighted, and lycopene displays such anti-

inflammatory properties [69]. The potent antioxidant properties of lycopene enable the prevention of atherosclerosis progression and thrombotic complications [75]. Five key mechanisms have been uncovered in explaining the antiatherogenic properties of lycopene: i) prevention of endothelial injury; ii) inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase and thus, inhibiting cholesterol synthesis, inhibiting LDL oxidation, and renewing HDL functionality; iii) maximization of cholesterol efflux; iv) suppressing pro-inflammatory cytokines; and v) regulating signaling pathways correlated to cellular proliferation and apoptosis and inhibiting foam cell creation. Mitogen-activated protein kinase (MAPK) and Protein Kinase B (AKT) are the important signaling pathways that contribute to oxidative stress-induced hypertrophy [76]. In cultured cardiomyocytes, lycopene can inhibit pressure overload-induced cardiac hypertrophy by mitigating ROS production as well as mitochondrial oxidative stress by suppression of ROS-dependent MAPKs (ERK1/2, p38, and JNK1/2) and Akt/GSK-3 β signaling pathways [75]. The advantageous impact of the broad group of hypocholesterolemia medications (i.e. statins family) on morbidity and mortality in patients who have cardiovascular diseases has been firmly proven in a variety of experimental studies and clinical trials [76]. In addition to the hypocholesterolemic effects of statins, they have been shown to possess anti-inflammatory activities through the inhibition of cytokine production. Similarly, lycopene has antioxidant and antithrombotic activities and exhibits an immunomodulatory effect. Therefore, it may be hypothesized that simvastatin and lycopene applied together will exert a synergistic influence on the inflammatory response [76].

One of the adverse consequences of inflammation is excessive production of abnormal collagen and a decrease of normal elastin. Imbalances in these two

major proteins lead to arterial stiffness. Due to lycopene’s powerful antioxidant and anti-inflammatory status, it is not surprising that some *in vitro* studies have suggested that lycopene also has an anti-atherogenic function. However, clinical studies have not displayed a significant impact of oral consumption of lycopene on arterial elasticity [77,78].

Percutaneous coronary intervention (PCI), a procedure to open blocked coronary arteries, activates the inflammatory cascade and increased plasma C-

reactive protein (CRP) concentrations and myocardial ischemia may repeat in these patients [79]. Lycopene consumption significantly inhibited the increase of Creatine kinase-MB, following the PCI procedure compared to the control. Therefore, lycopene can be beneficial in protecting against adverse post-PCI cardiac events. However, it did not have a significant effect on serum level of troponin I (TnI) or hs-CRP compared to the control groups [79].

Table 2. The effect of lycopene on signaling pathways that modulate autophagy.

Experimental Model	Dose	Signaling Mediators	Notable Results	References
Cadmium-induced Hippocampal dysfunction in mice and TH22 cell line	5 mg/kg for mice, 10 µM for cells	Reduced Akt1, MAPK1, signaling	Reduced Cd-induced autophagy (ATG expression) and cell death	[22]
Endothelial progenitor cells isolated from diabetes mellitus rats	10–50 µg/mL	Reduced mitochondrial dysfunction	Reduced apoptosis and oxidative autophagy	[22]
Hypoxia/reoxygenation- induced H9C2 myocardioblast cells	2.5 µM, 5 µM	Increased AMPK activity	Reduced apoptotic cell death through increased autophagy	[22]

Table 3. The effects of lycopene on crucial signaling pathways

Effect	Mechanisms of Action	References
Protection of grafted vessels	Lessened the expression of ROCK1, Ki-67, ICAM-1 and ROCK2, improved the expression of eNOS-implanted arteries and cGMP plasma concentration	[80]
Improvement of vascular arteriosclerosis in the case of allograft transplantation	Down-regulated the expression of Rho-related kinases	[80,81]
Protective effects on endothelial	Decreased MCP-1, IL-6, VCAM-1, NF-kB And Increased KLF2	[82]
Improvement of insulin sensitivity in mice	Prevented STAT3 signaling and inhibited Srebp-1c and downstream gene expression, resulting in inhibition of lipid accumulation, inflammation, insulin resistance and metabolic dysfunction	[83]

Table 4. Clinical Studies Investigating the Effects of Lycopene in Heart Failure

Ejection Fraction	Outcomes	References
33.9 ± 14.0	Greater intake of lycopene was associated with improvements in cardiac event-free survival (related cardiac death and time to first hospitalization for HF), independent of intake of sodium.	[84]
Confirmed diagnosis of HF, with preserved or non-preserved ejection fraction	C-reactive protein levels decreased significantly in the intervention group in women but not in men (P = .04).	[85]

Table 5. Chemoprotective potential of lycopene against cardiotoxic agents

Substances	Mechanism of damage	Effectiveness	References
Isoproterenol	Metabolic products of ISO cause cardiac toxicity by producing excessive amounts of free radicals, increased intracellular Ca ²⁺ , mitochondrial dysfunction due to insufficient blood supply, severe cardiac infarction, and necrotic damage.	Quercetin with lycopene decreased the elevation of CK-MB, LDH, TROP and MYO, controlled augmented production of MDA and GSSG, normalized the activity of SOD, CAT, GST and GPx, and normalized levels of GSH, Vit-C and Vit-E	[86]
Atrazine (water contaminated with atrazine)	Heart and serum ionic disorders which induced structural alterations and dysfunction in cardiac myocytes and inhibited the activities of Na ⁺ -K ⁺ -ATPase, Mg ²⁺ -ATPase, and Ca ²⁺ -ATPase	Modulated the ATR-induced changes in ionic levels in cardiac myocytes and ameliorated the changes in ATPase activity	[87]
Adriamycin	Oxidative damage to membrane lipids and other cellular components and increased MDA and GSH levels	Post-injection treatment with lycopene provided marked normalization in MDA and GSH concentrations, pre-injection treatment with lycopene produced no effect.	[88]
Doxorubicin	Induced oxidative stress by increasing levels of free radicals, e.g., reactive oxygen species, and decreasing levels of antioxidants, e.g., glutathione (GSH). also caused focal necrosis of cardiac myocytes, disorganization and focal fragmentation of myocardial fibers, intermuscular infiltration of inflammatory cells, cell vacuolization, and increases in plasma activities of CK and LDH	Attenuated the MDA level and remarkably elevated the GSH level, preserved the myocardial architecture, and reduced plasma CK and LDH levels	[89]
Tulathromycin	Increased the production of reactive oxygen species (ROS) and altered serum levels of coagulation factors, potassium, and ionized calcium	Reduced production of ROS, enhanced the activities of cellular antioxidant enzymes, scavenged oxygen free radicals, and inhibited the production of nitric oxide) and apoptosis (by inhibiting caspase-3 and Bax expression)	[90]
Diclofenac sodium (DFS)	Prolonged DFS intake can exert cardiotoxic effects, such as increasing the risk of myocardial infarction and initiating or worsening congestive heart failure, and increases the expression of the apoptotic enzymes caspase-3 and Bcl-2	Inhibited apoptosis (by inhibiting caspase-3 and Bax expression)	[90]

CONCLUSION

Cardiometabolic risk factors amplify the chance of developing cardiovascular disease. Several cardiometabolic risk factors have been identified such as arterial hypertension, diabetes mellitus, dyslipidemia, and being overweight or obese. As a potent lipophilic antioxidant, lycopene may be able to mediate oxidative stress, a mechanism underlying metabolic syndrome and its risk factors [91]. Furthermore, the inappropriate production of oxidized biomolecules is a harmful phenomenon for the human body. For example, excessive generation of free radicals and oxidants can lead to pathological cardiac conditions [92].

Oxidation of LDL is considered a hallmark of early atherogenesis. Dietary antioxidants, like phenolic compounds and carotenoids, such as lycopene can strongly inhibit oxidative damage of LDL by lowering free radicals produced during oxidative metabolism, retaining vitamin E and carotenoids as endogenous antioxidants in LDL, chelating transition metal ions, and modulating the oxidative and inflammatory states of the artery wall [93].

Augmented ROS production along with oxidized proteins, lipids, and nucleic acids as a result of prolonged oxidative imbalance damages cardiomyocytes. Fruits and vegetables contain many bioactive compounds with antioxidant and anti-inflammatory properties. Therefore, consuming them may have protective effects against cardiovascular disorders. Aging results in reduced intestinal absorption of carotenoids and disruption in ROS scavenging, thereby affecting overall lycopene status. The Women's Health and Aging Study reported a remarkable depletion of circulating lycopene levels in older adults versus younger individuals with an equal ethnic and dietary history. Therefore, it appears that the elderly will more likely benefit from taking lycopene in the form of nutritional supplements [94]. Lycopene is specifically helpful in heart failure patients because of its

antioxidant effect and alleviating inflammatory reactions. Numerous pieces of evidence explicate an inverse relationship between serum lycopene levels and the risk of CVD. A positive correlation between ejection fraction and plasma levels of lycopene, lutein and vitamin A, suggests an improvement in cardiac hemodynamic function in the presence of these dietary antioxidants [95].

Hypertension is a common public health challenge of global proportions with severe health impacts; therefore, finding efficacious treatments for the control of hypertension is critical. Lowering blood pressure prevents cardiovascular accidents like strokes, myocardial infarctions, and heart failure, among others [96]. In parallel with antihypertensive drugs, a variety of non-pharmacological options can be adjunctive. The Mediterranean diet (which consists of fruits and vegetables, low consumption of red meat, and consumption of healthy fats) significantly reduces diseases associated with CVD, as shown by several epidemiological and prospective studies [96]. In this regard, dietary intake of lycopene supplementation has shown effectiveness for the prevention or treatment of hypertension and adverse vascular consequence [96]. Studies conducted on hypertensive patients reveal how a tomato-enriched diet changes the redox state, increases antioxidant enzymes, decreases lipid peroxidation, and modulates blood pressure due to higher lycopene concentrations. Interestingly, these positive effects are independent of age [96]. According to various studies, physical activity accompanied by antioxidant supplements such as lycopene can counteract the toxicity of oxygen species and free radicals and protect against many diseases, including CVD, high blood pressure, and heart failure [97]. Tomatoes and, by extension, lycopene can regulate lipid profiles in healthy and obese women by lowering triglyceride and total cholesterol levels while

increasing HDL cholesterol [98]. Tomato juice consumption reduced LDL oxidation susceptibility in type 2 diabetic patients. Furthermore, daily use of 200 g raw tomato for 8 weeks reduced both systolic and diastolic blood pressure while increasing ApoA1 plasma levels. Atheroma plaque is a major contributor to most cardiovascular events [98]. An inflammatory process is known to occur in the arterial wall at the site of a developing plaque. Many risk factors such as dyslipidemia, hyperglycemia, insulin resistance, and metabolic disorders can lead to a pro-inflammatory and pro-oxidant status, which induces early-onset atherogenesis. Considering this, experimental studies have exhibited an inverse relationship between cardiovascular events in patients with type two diabetes and plasma concentrations of lycopene [98].

A meta-analysis carried out in September 2020 that included 11 studies with a total of 854 participants demonstrated that taking lycopene should have a similar effect to statins in improving blood HDL-c levels. Although the impact of lycopene on blood triglycerides in various studies is controversial, this meta-analysis found no significant change in triglycerides in the lycopene group compared to the control group [99]. There are other remarkable features of lycopene, such as its antiplatelet and antithrombotic effects [100]. Interestingly, lycopene and γ -aminobutyric acid can reduce blood clots *in vivo*, but safety considerations, such as increased bleeding events were not reported [100]. Various mechanisms are involved in the antiplatelet activity of lycopene: (1) enhancement of cyclic GMP/nitrate formation followed by inhibition of phosphoinositide breakdown and suppression of the phosphorylation of p47 inhibition of relative intracellular Ca^{2+} mobilization; and (2) downregulation of phospholipase C following inhibition of phosphoinositide breakdown of thromboxane A2 production [101].

Investigators have shown that tomato extract and garlic powder have increased activated partial thromboplastin time (APTT), which is an intrinsic coagulation pathway, and downregulated the expression of adhesion molecule ICAM-1 in the aorta [102]. This signified that these supplements might help to improve blood circulation and endothelial function by delaying coagulation time, adjusting vascular tone, and suppressing the expression of ICAM-1. In consideration of these mechanisms, these treatments prevent dysfunctional endothelial cells and vascular inflammation [102]. The literature covered in this article discusses that tomato products and lycopene can be considered dietary supplements for the primary prevention of CVD due to their antioxidant, anti-inflammatory, antidiabetic, cardiovascular protectivity, antiplatelet, and anticoagulant activity [103]. Antiplatelet activity is attributed to (1) affecting adenosine diphosphate (ADP), collagen, thrombin, and thromboxane A2-mediated signaling, (2) impressing integrin activation, fibrinogen binding, and (3) suppressing platelet protein disulfide isomerase (PDI). The mechanism is multidirectional in (1) deactivating the receptors for ADP, collagen, and von Willebrand factor; (2) inhibiting the activation of the $\alpha IIb\beta 3$ integrin and GPIIb/IIIa glycoprotein, and (3) inhibiting the expression of P-selectin on the platelet surface [103].

One randomized-controlled trial displayed that consuming tomato extract resulted in suppression of platelet function and thromboxane A2 generation approximately equal to the efficacy of a single dose of 75 mg aspirin (ASA); however, daily administration revealed ASA to be 3 times as effective over one week compared to the tomato extract. That said, because the effect of the tomato extract is reversible compared to the irreversible nature of ASA, it comparatively reduces the possibility of excessively increased primary hemostatic clot formation

time compared to ASA, which is an important safety factor for primary prevention [104].

Many epidemiological studies have advocated that a daily intake of 2–20 mg of lycopene has significant benefits in the prevention and treatment of CVD. Many risk factors for CVD, such as hypertension, hyperlipidemia, LDL oxidation, diabetes, obesity, inflammation and oxidative stress are best managed by lycopene supplementation. Despite lycopene supplement, further research should be done to determine the CVD preventive and management potential of lycopene and other active tomato ingredients.

Abbreviations: ALT: Alanine transaminase; AST: Aspartate aminotransferase; APTT: Activated partial thromboplastin time; ARE: Antioxidant response element; BCO1: β -carotene oxygenase 1; CAT: Catalase; CHOP: C/EBP-homologous protein; CK: Creatine Kinase; COX2: cyclooxygenase-2; CVD: Cardiovascular disease; EPC: Endothelial progenitor cells; ERK: Extracellular regulated kinases; FF: Functional Food; FFC: Functional Food Center; GSH-Px: Glutathione peroxidase; HFD: High-fat diet; HFFD: High-fat, high-fructose diet; HMGCoA: 3-hydroxy-3-methylglutaryl coenzyme A; ICAM-1: Intercellular Adhesion Molecule-1; iNOS: inducible nitric oxide synthase; IRI: Ischemia-Reperfusion injury; LDL: Low-density lipoprotein; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; MCP-1: Monocyte chemoattractant protein-1; MAPK: Mitogen-activated protein kinase; PCI: Percutaneous coronary intervention; PCSK9: Proprotein convertase subtilisin/Kexin type 9; T2DM: Type 2 diabetes mellitus; TNF- α : Tumor necrosis factor- α , (Tnl); Troponin I; ROS: Reactive oxygen species; SOD: Superoxide dismutase.

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