



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

Laila Rejali^{1,2}, Stephanie Ozumerzifon³, Hashem Nayeri¹, Sedigheh Asgary^{4*}

^{1, 2}Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; ³Southwest College of Naturopathic Medicine, Isfahan, Iran; ⁴Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

***Corresponding Author:** Sedigheh Asgary, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, 8174673461, Iran

Submission Date: July 26th, 2022; **Acceptance Date:** October 25th, 2022; **Publication Date:** October 31st, 2022

Please cite this article as: Rejali L., Ozumerzifon S., Nayeri H., Williams S., Asgary S. Risk Reduction and Prevention of Cardiovascular Diseases: Biological Mechanisms of Lycopene. *Bioactive Compounds in Health and Disease* 2022; 5(10): 202-221. DOI: <https://www.doi.org/10.31989/bchd.v5i10.975>

ABSTRACT

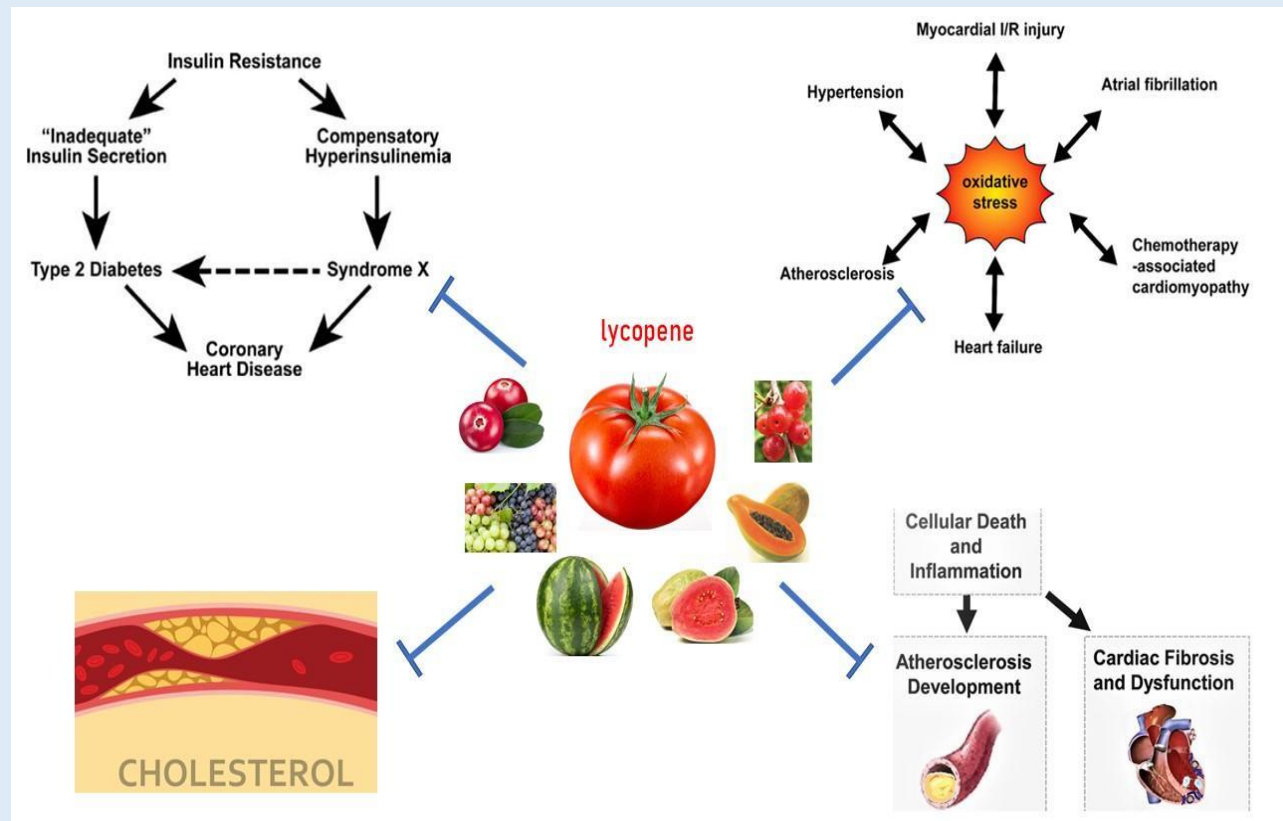
Background and aims: The conservational effects of dietary interventions as advantageous instruments in the primary and secondary prevention of cardiovascular disease (CVD) have gotten more attention in recent years. Numerous nutritional epidemiological studies have highlighted the ability of diets to 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



©FFC 2022. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0>)

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.

Competing Interests: The authors declare no conflict of interest.

Authors' Contributions: Conceptualization; S.A., L.R.; writing – initial draft preparation, L.R. writing – review and editing, S.A., S.O., L.R., H.N.; supervision, S.A.

Acknowledgments: We would like to express our gratitude and appreciation for Dr. Amirsajad Jafari whose guidance, support and encouragement has been invaluable throughout this study.

REFERENCES

- Guan Y, Song X, Sun W, Wang Y, Liu B. Effect of Hypoxia-Induced MicroRNA-210 Expression on Cardiovascular Disease and the Underlying Mechanism. *Oxid Med Cell Longev.* 2019 May 21;2019:1–12. DOI:[10.1155/2019/4727283](https://doi.org/10.1155/2019/4727283)
- Jensen RV, Hjortbak MV, Bøtker HE. Ischemic Heart Disease: An Update. *Semin Nucl Med.* 2020;50(3):195–207. DOI:[10.1053/j.semnuclmed.2020.02.007](https://doi.org/10.1053/j.semnuclmed.2020.02.007)
- Wong KKL, Wu J, Liu G, Huang W, Ghista DN. Coronary arteries hemodynamics: effect of arterial geometry on hemodynamic parameters causing atherosclerosis. *Med Biol Eng Comput.* 2020;58(8):1831–43. DOI:[10.1007/s11517-020-02185-x](https://doi.org/10.1007/s11517-020-02185-x)
- Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol.* 2018;17(1):1–19. DOI:[10.1186/s12933-018-0728-6](https://doi.org/10.1186/s12933-018-0728-6)
- Rodriguez-Araujo G, Nakagami H. Pathophysiology of cardiovascular disease in diabetes mellitus. *Cardiovasc Endocrinol Metab.* 2018;7(1):4. DOI:[10.1097/XCE.0000000000000141](https://doi.org/10.1097/XCE.0000000000000141)
- El-Nashar NN, Abduljawad SH. Impact effect of lycopene and tomato-based products network on cardio-protective biomarkers in vivo. *Funct Foods Heal Dis.* 2012;2(5):151–65. DOI:[10.31989/ffhd.v2i5.92](https://doi.org/10.31989/ffhd.v2i5.92)
- Grabowska M, Wawrzyniak D, Rolle K, Chomczyński P, Oziewicz S, Jurga S, Barciszewski J. Let food be your medicine: nutraceutical properties of lycopene. *Food Funct.* 2019;10(6):3090–102. DOI:[10.1039/C9FO00580C](https://doi.org/10.1039/C9FO00580C)
- Sen S. The chemistry and biology of lycopene: Antioxidant for human health. *Int J Adv Life Sci Res.* 2019;2(4):8–14.

- DOI:[10.31632/ijalsr.2019v02i04.002](https://doi.org/10.31632/ijalsr.2019v02i04.002)
9. Böhm V, Lietz G, Olmedilla-Alonso B, Phelan D, Reboul E, Bánati D, Borel P, Corte-Real J, de Lera AR, Desmarchelier C, Dulinska-Litewka J, Landrier JF, Milisav I, Nolan J, Porrini M, Riso P, Roob JM, Valanou E, Wawrzyniak A, Winklhofer-Roob BM, Rühl R, Bohn T. From carotenoid intake to carotenoid blood and tissue concentrations – implications for dietary intake recommendations. *Nutr Rev*. 2021 May 1;79(5):544–73. DOI:[10.1093/nutrit/nuaa008](https://doi.org/10.1093/nutrit/nuaa008)
 10. Arballo J, Amengual J, Erdman Jr JW. Lycopene: A critical review of digestion, absorption, metabolism, and excretion. *Antioxidants*. 2021;10(3):342. DOI:[10.3390/antiox10030342](https://doi.org/10.3390/antiox10030342)
 11. Dima C, Assadpour E, Dima S, Jafari SM. Bioavailability of nutraceuticals: Role of the food matrix, processing conditions, the gastrointestinal tract, and nanodelivery systems. *Compr Rev food Sci food Saf*. 2020;19(3):954–94. DOI:[10.1111/1541-4337.1254](https://doi.org/10.1111/1541-4337.1254)
 12. Bakar B, Çakmak M, Ibrahim MS, Özer D, Saydam S, Karatas F. Investigation of amounts of vitamins, lycopene, and elements in the fruits of *Opuntia ficus-indica* subjected to different pretreatments. *Biol Trace Elem Res*. 2020;198(1):315–23. DOI:[10.1007/s12011-020-02050-w](https://doi.org/10.1007/s12011-020-02050-w)
 13. Fan C, Pacier C, Martirosyan DM. Rose hip (*Rosa canina* L): A functional food perspective. *Funct Foods Heal Dis*. 2014;4(12):493–509. DOI:[10.31989/ffhd.v4i12.159](https://doi.org/10.31989/ffhd.v4i12.159)
 14. Riccioni G, Mancini B, Di Ilio E, Bucciarelli T, D’Orazio N. Protective effect of lycopene in cardiovascular disease [Internet]. *European Review for Medical and Pharmacological Sciences*. 2008. Available from: <https://pubmed.ncbi.nlm.nih.gov/18700690/>
 15. PA Silva Y, Borba BC, Pereira VA, Reis MG, Caliarì M, Brooks MSL, Ferreira TAPC. Characterization of tomato processing by-product for use as a potential functional food ingredient: nutritional composition, antioxidant activity and bioactive compounds. *Int J Food Sci Nutr*. 2019;70(2):150–60. DOI:[10.1080/09637486.2018.1489530](https://doi.org/10.1080/09637486.2018.1489530)
 16. Nagal S, Kaur C, Choudhary H, Singh J, Bhushan Singh B, Singh KN. Lycopene content, antioxidant capacity and colour attributes of selected watermelon (*Citrullus lanatus* (Thunb.) Mansfeld) cultivars grown in India. *Int J Food Sci Nutr*. 2012;63(8):996–1000. DOI:[10.3109/09637486.2012.694848](https://doi.org/10.3109/09637486.2012.694848)
 17. 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):1150–6. DOI:[10.1039/c5fo00004a](https://doi.org/10.1039/c5fo00004a)
 18. Zheng S, Deng Z, Chen F, Zheng L, Pan Y, Xing Q, Tsao R, Li H. Synergistic antioxidant effects of petunidin and lycopene in H9c2 cells submitted to hydrogen peroxide: Role of Akt/Nrf2 pathway. *J Food Sci*. 2020;85(6):1752–63. DOI:[10.1111/1750-3841.15153](https://doi.org/10.1111/1750-3841.15153)
 19. Li X, Jia P, Huang Z, Liu S, Miao J, Guo Y, Wu N, Jia D. Lycopene protects against myocardial ischemia-reperfusion injury by inhibiting mitochondrial permeability transition pore opening. *Drug Des Devel Ther*. 2019;13:2331. DOI:[10.2147/DDDT.S194753](https://doi.org/10.2147/DDDT.S194753)
 20. Pan Y, Deng ZY, Chen X, Zhang B, Fan Y, Li H. Synergistic antioxidant effects of phenolic acids and carotenes on H₂O₂-induced H9c2 cells: Role of cell membrane transporters. *Food Chem*. 2021;341:128000. DOI:[10.1016/j.foodchem.2020.128000](https://doi.org/10.1016/j.foodchem.2020.128000)
 21. Bazyel B, Dede S, Cetin S, Yuksek V, Taşpınar M. In vitro evaluation of the effects of lycopene on caspase system and oxidative DNA damage in high-glucose condition. *Pharmacogn Mag*. 2019;15(62):30. DOI:[10.4103/pm.pm.488.18](https://doi.org/10.4103/pm.pm.488.18)
 22. Choi S, Kim H. The remedial potential of lycopene in pancreatitis through regulation of autophagy. *Int J Mol Sci*. 2020;21(16):5775. DOI:[10.3390/ijms21165775](https://doi.org/10.3390/ijms21165775)
 23. Kwatra B. A review on potential properties and therapeutic applications of lycopene. *Int J Med Biomed Stud*. 2020;4:33–44. DOI:[10.32553/ijmbs.v4i4.1081](https://doi.org/10.32553/ijmbs.v4i4.1081)
 24. Kawata A, Murakami Y, Suzuki S, Fujisawa S. Anti-inflammatory activity of β-carotene, lycopene and tri-n-butylborane, a scavenger of reactive oxygen species. *In Vivo* (Brooklyn). 2018;32(2):255–64. DOI:[10.21873/invivo.11232](https://doi.org/10.21873/invivo.11232)
 25. Shafi S, Ansari HR, Bahitham W, Aouabdi S. The impact of natural antioxidants on the regenerative potential of vascular cells. *Front Cardiovasc Med*. 2019;6:28. DOI:[10.3389/fcvm.2019.00028](https://doi.org/10.3389/fcvm.2019.00028)
 26. Chang X, Zhao Z, Zhang W, Liu D, Ma C, Zhang T, Meng Q, Yan P, Zou L, Zhang M. Natural antioxidants improve the vulnerability of cardiomyocytes and vascular endothelial cells under stress conditions: a focus on mitochondrial quality control. *Oxid Med Cell Longev*. 2021; DOI:[10.1155/2021/6620677](https://doi.org/10.1155/2021/6620677)
 27. Ferreira-Santos P, Aparicio R, Carrón R, Montero MJ, Sevilla MÁ. Lycopene-supplemented diet ameliorates metabolic syndrome induced by fructose in rats. *J Funct Foods*. 2020; 73:104098. DOI:[10.1016/j.jff.2020.104098](https://doi.org/10.1016/j.jff.2020.104098)
 28. Przybylska S. Lycopene—a bioactive carotenoid offering

- multiple health benefits: a review. *Int J Food Sci Technol*. 2020;55(1):11–32. DOI:[10.1111/ijfs.14260](https://doi.org/10.1111/ijfs.14260)
29. Yanai H. Anti-atherosclerotic effects of tomatoes. *Funct Foods Heal Dis*. 2017;7(6):411–28. DOI:[10.31989/ffhd.v7i6.351](https://doi.org/10.31989/ffhd.v7i6.351)
 30. Mozos I, Stoian D, Caraba A, Malainer C, Horbańczyk JO, Atanasov AG. Lycopene and vascular health. *Front Pharmacol*. 2018;9:521. DOI:[10.3389/fphar.2018.00521](https://doi.org/10.3389/fphar.2018.00521)
 31. Hachem A, Hariri E, Saoud P, Lteif C, Lteif L, Welty F. The role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in cardiovascular homeostasis: a non-systematic literature review. *Curr Cardiol Rev*. 2017;13(4):274–82. DOI:[10.2174/1573403X13666170804150954](https://doi.org/10.2174/1573403X13666170804150954)
 32. Kilany OE, Abdelrazek HMA, Aldayel TS, Abdo S, Mahmoud MMA. Anti-obesity potential of Moringa olifera seed extract and lycopene on high fat diet induced obesity in male Sprague Dawley rats. *Saudi J Biol Sci*. 2020;27(10):2733–46. DOI:[10.1016/j.sjbs.2020.06.026](https://doi.org/10.1016/j.sjbs.2020.06.026)
 33. Wang J, Geng T, Zou Q, Yang N, Zhao W, Li Y, Tan X, Yuan T, Liu X, Liu Z. Lycopene prevents lipid accumulation in hepatocytes by stimulating PPAR α and improving mitochondrial function. *J Funct Foods*. 2020;67:103857. DOI:[10.1016/j.jff.2020.103857](https://doi.org/10.1016/j.jff.2020.103857)
 34. Yin Y, Zheng Z, Jiang Z. Effects of lycopene on metabolism of glycolipid in type 2 diabetic rats. *Biomed Pharmacother*. 2019;109:2070–7. DOI:[10.1016/j.biopha.2018.07.100](https://doi.org/10.1016/j.biopha.2018.07.100)
 35. Alvi SS, Ansari IA, Khan I, Iqbal J, Khan MS. Potential role of lycopene in targeting proprotein convertase subtilisin/kexin type-9 to combat hypercholesterolemia. *Free Radic Biol Med*. 2017;108:394–403. DOI:[10.1016/j.freeradbiomed.2017.04.012](https://doi.org/10.1016/j.freeradbiomed.2017.04.012)
 36. Wang W, Yang W, Shen Z, Wen S, Hu M. The Dose–Response Effect of Lycopene on Cerebral Vessel and Neuron Impairment Induced by Hyperlipidemia. *J Agric Food Chem*. 2018;66(50):13173–82. DOI:[10.1021/acs.jafc.8b05232](https://doi.org/10.1021/acs.jafc.8b05232)
 37. Lorenz M, Fechner M, Kalkowski J, Fröhlich K, Trautmann A, Böhm V, Liebisch G, Lehneis S, Schmitz G, Ludwig A. Effects of lycopene on the initial state of atherosclerosis in New Zealand White (NZW) rabbits. *PLoS One*. 2012;7(1):e30808. DOI:[10.1371/journal.pone.0030808](https://doi.org/10.1371/journal.pone.0030808)
 38. Li X, Xu J. Lycopene supplement and blood pressure: an updated meta-analysis of intervention trials. *Nutrients*. 2013;5(9):3696–712. DOI:[10.3390/nu5093696](https://doi.org/10.3390/nu5093696)
 39. Wolak T, Sharoni Y, Levy J, Linnewiel-Hermoni K, Stepensky D, Paran E. Effect of tomato nutrient complex on blood pressure: A double blind, randomized dose–response study. *Nutrients*. 2019;11(5):950. DOI:[10.3390/nu11050950](https://doi.org/10.3390/nu11050950)
 40. Frosini M, Marcolongo P, Gamberucci A, Tamasi G, Pardini A, Giunti R, Fiorenzani P, Aloisi AM, Rossi C, Pessina F. Effects of Aqueous Extract of *Lycopersicon esculentum* L. var. “Camone” Tomato on Blood Pressure, Behavior and Brain Susceptibility to Oxidative Stress in Spontaneously Hypertensive Rats. *Pathophysiology*. 2021;28(1):189–201. DOI:[10.3390/pathophysiology28010012](https://doi.org/10.3390/pathophysiology28010012)
 41. Ferreira-Santos P, Aparicio R, Carrón R, Sevilla MÁ, Monroy-Ruiz J, Montero MJ. Lycopene-supplemented diet ameliorates cardiovascular remodeling and oxidative stress in rats with hypertension induced by Angiotensin II. *J Funct Foods*. 2018;47:279–87. DOI:[10.1016/j.jff.2018.06.002](https://doi.org/10.1016/j.jff.2018.06.002)
 42. Sharifi-Rad J, Rodrigues CF, Sharopov F, Docea AO, Can Karaca A, Sharifi-Rad M, Kahveci Karıncaoglu D, Gülsersen G, Şenol E, Demircan E. Diet, lifestyle and cardiovascular diseases: linking pathophysiology to cardioprotective effects of natural bioactive compounds. *Int J Environ Res Public Health*. 2020;17(7):2326. DOI:doi.org/10.3390/ijerph17072326
 43. Martirosyan D, Lampert T, Ekblad M. Classification and regulation of functional food proposed by the Functional Food Center. *Funct Food Sci*. 2022;2(2):25–46. DOI:[10.31989/ffs.v2i2.890](https://doi.org/10.31989/ffs.v2i2.890)
 44. Dalbeni A, Treggiari D, Tagetti A, Bevilacqua M, Bonafini S, Montagnana M, Scaturro G, Minuz P, Fava C. Positive effects of tomato paste on vascular function after a fat meal in male healthy subjects. *Nutrients*. 2018;10(9):1310. DOI:[10.3390/nu10091310](https://doi.org/10.3390/nu10091310)
 45. Gajendragadkar PR, Hubsch A, Mäki-Petäjä KM, Serg M, Wilkinson IB, Cheriyan J. Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: a randomised controlled trial. *PLoS One*. 2014;9(6):e99070. DOI:[10.1371/journal.pone.0099070](https://doi.org/10.1371/journal.pone.0099070)
 46. Han GM, Liu P. Higher serum lycopene is associated with reduced prevalence of hypertension in overweight or obese adults. *Eur J Integr Med*. 2017;13:34–40. DOI:[10.1016/j.eujim.2017.07.002](https://doi.org/10.1016/j.eujim.2017.07.002)
 47. Alam P, Raka MA, Khan S, Sarker J, Ahmed N, Nath PD, Hasan N, Mohib MM, Tisha A, Sagor MAT. A clinical review of the effectiveness of tomato (*Solanum lycopersicum*) against cardiovascular dysfunction and related metabolic syndrome. *J Herb Med*.

- 2019;16:100235. DOI:[10.1016/j.hermed.2018.09.006](https://doi.org/10.1016/j.hermed.2018.09.006)
48. Zielińska MA, Wesołowska A, Pawlus B, Hamułka J. Health effects of carotenoids during pregnancy and lactation. *Nutrients*. 2017;9(8):838. DOI:[10.3390/nu9080838](https://doi.org/10.3390/nu9080838)
 49. Zhu R, Chen B, Bai Y, Miao T, Rui L, Zhang H, Xia B, Li Y, Gao S, Wang XD. Lycopene in protection against obesity and diabetes: A mechanistic review. *Pharmacol Res*. 2020;159:104966. DOI:[10.1016/j.phrs.2020.104966](https://doi.org/10.1016/j.phrs.2020.104966)
 50. 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(09):610–7. DOI:[10.1055/s-0043-101919](https://doi.org/10.1055/s-0043-101919)
 51. Petyaev IM, Dovgalevsky PY, Klochkov VA, Chalyk NE, Pristensky D V, Chernyshova MP, Udumyan R, Kocharyan T, Kyle NH, Lozbiakova M V. Effect of lycopene supplementation on cardiovascular parameters and markers of inflammation and oxidation in patients with coronary vascular disease. *Food Sci Nutr*. 2018;6(6):1770–7. DOI:[10.1002/fsn3.734](https://doi.org/10.1002/fsn3.734)
 52. 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. DOI:[10.2147/DMSO.S265944](https://doi.org/10.2147/DMSO.S265944)
 53. Wang J, Suo Y, Zhang J, Zou Q, Tan X, Yuan T, Liu Z, Liu X. Lycopene supplementation attenuates western diet-induced body weight gain through increasing the expressions of thermogenic/mitochondrial functional genes and improving insulin resistance in the adipose tissue of obese mice. *J Nutr Biochem*. 2019; 69:63–72. DOI:[10.1016/j.jnutbio.2019.03.008](https://doi.org/10.1016/j.jnutbio.2019.03.008)
 54. 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):805. DOI:[10.1186/s13104-019-4841-8](https://doi.org/10.1186/s13104-019-4841-8)
 55. Assis RP, Arcaro CA, Gutierrez 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. DOI:[10.3390/ijms18040332](https://doi.org/10.3390/ijms18040332)
 56. Lagisetty U, Habibuddin M, Sivakumar R. Effect of Lycopene on Pharmacokinetic and Pharmacodynamics of Gliclazide in Diabetic Animal Model. *J Complement Med*. 2018;8(1). DOI:[10.9790/3008-1305021119](https://doi.org/10.9790/3008-1305021119)
 57. Saeed NM, Mansour AM, Allam S. Lycopene induces insulin signaling and alleviates fibrosis in experimental model of non-alcoholic fatty liver disease in rats. *PharmaNutrition*. 2020;14:100225. DOI:[10.1016/j.phanu.2020.100225](https://doi.org/10.1016/j.phanu.2020.100225)
 58. 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):1194–200. DOI:[10.1111/1750-3841.14505](https://doi.org/10.1111/1750-3841.14505)
 59. van Steenwijk HP, Bast A, de Boer A. The role of circulating lycopene in low-grade chronic inflammation: a systematic review of the literature. *Molecules*. 2020;25(19):4378. DOI:[10.3390/molecules25194378](https://doi.org/10.3390/molecules25194378)
 60. Petyaev IM. Lycopene deficiency in ageing and cardiovascular disease. *Oxid Med Cell Longev*. 2016;1. DOI:[10.1155/2016/3218605](https://doi.org/10.1155/2016/3218605)
 61. H. A H, G. M. E. Therapeutic effect of lycopene-rich tomato juice on cardiac disorder in rats fed on fried food in oxidized frying oil. *Egypt J Hosp Med*. 2004;14(1):115–26. DOI:[10.21608/eihm.2004.18226](https://doi.org/10.21608/eihm.2004.18226)
 62. Böhm V. Lycopene and heart health. *Mol Nutr Food Res*. 2012;56(2):296–303. DOI:[10.1002/mnfr.201100281](https://doi.org/10.1002/mnfr.201100281)
 63. Chen D, Huang C, Chen Z. A review for the pharmacological effect of lycopene in central nervous system disorders. *Biomed Pharmacother*. 2019; 111:791–801. DOI:[10.1016/j.biopha.2018.12.151](https://doi.org/10.1016/j.biopha.2018.12.151)
 64. Thies F, Mills LM, Moir S, Masson LF. Cardiovascular benefits of lycopene: fantasy or reality? *Proc Nutr Soc*. 2017;76(2):122–9. DOI:[10.1017/S0029665116000744](https://doi.org/10.1017/S0029665116000744)
 65. Kumar PVN, Elango P, Asmathulla S, Kavimani S. A systematic review on lycopene and its beneficial effects. *Biomedical and Pharmacology Journal*. 2017. DOI:[10.13005/bpj/1335](https://doi.org/10.13005/bpj/1335)
 66. Ellis AC, Dudenbostel T, Locher JL, Crowe-White K. Modulating oxidative stress and inflammation in elders: the MOXIE study. *J Nutr Gerontol Geriatr*. 2016;35(4):219–42. DOI:[10.1080/21551197.2016.1250693](https://doi.org/10.1080/21551197.2016.1250693)
 67. Montesano D, Blasi F, Cossignani L. Lycopene and cardiovascular disease: An overview. *Ann Short Rep [Internet]*. 2019; 2:1033. Available from: <http://www.remedypublications.com/annals-of-short-reports-abstract.php?aid=677>
 68. Casas R, Estruch R, Sacanella E. Influence of bioactive nutrients on the atherosclerotic process: A review. *Nutrients*. 2018;10(11):1630. DOI:[10.3390/nu10111630](https://doi.org/10.3390/nu10111630)
 69. Lapuente M, Estruch R, Shahbaz M, Casas R. Relation of

- fruits and vegetables with major cardiometabolic risk factors, markers of oxidation, and inflammation. *Nutrients*. 2019;11(10):2381. DOI:[10.3390/nu11102381](https://doi.org/10.3390/nu11102381)
70. Chen Y, Wang L, Huang S, Ke J, Wang Q, Zhou Z, Chang W. Lutein attenuates angiotensin II-induced cardiac remodeling by inhibiting AP-1/IL-11 signaling. *Redox Biol*. 2021;44:102020. DOI:[10.1016/j.redox.2021.102020](https://doi.org/10.1016/j.redox.2021.102020)
 71. Ruiz-León AM, Lapuente M, Estruch R, Casas R. Clinical advances in immunonutrition and atherosclerosis: a review. *Front Immunol*. 2019;10:837. DOI:[10.3389/fimmu.2019.00837](https://doi.org/10.3389/fimmu.2019.00837)
 72. He Q, Zhou W, Xiong C, Tan G, Chen M. Lycopene attenuates inflammation and apoptosis in post-myocardial infarction remodeling by inhibiting the nuclear factor- κ B signaling pathway. *Mol Med Rep*. 2015; DOI:[10.3892/mmr.2014.2676](https://doi.org/10.3892/mmr.2014.2676)
 73. Pereira BLB, Reis PP, Severino FE, Felix TF, Braz MG, Nogueira FR, Silva RAC, Cardoso AC, Lourenço MAM, Figueiredo AM, Chiuso-Minicucci F, Azevedo PS, Polegato BF, Okoshi K, Fernandes AAH, Paiva SAR, Zornoff LAM, Minicucci MF. Tomato (*Lycopersicon esculentum*) or lycopene supplementation attenuates ventricular remodeling after myocardial infarction through different mechanistic pathways. *J Nutr Biochem*. 2017; DOI:[10.1016/j.jnutbio.2017.05.010](https://doi.org/10.1016/j.jnutbio.2017.05.010)
 74. Ferron AJT, Francisqueti-Ferron FV, de Almeida Silva CCV, Bazan SGZ, De Campos DHS, Garcia JL, Ghiraldeli L, Minatel IO, Correa CR, Moreto F. Tomato-oleoresin anti-inflammatory effect recovers obesity-induced cardiac dysfunction by modulating myocardial calcium handling. *Cell Physiol Biochem*. 2020;54(5):1013–25. DOI:[10.33594/000000284](https://doi.org/10.33594/000000284)
 75. Saini RK, Rengasamy KRR, Mahomoodally FM, Keum YS. Protective effects of lycopene in cancer, cardiovascular, and neurodegenerative diseases: An update on epidemiological and mechanistic perspectives. *Pharmacol Res*. 2020;155:104730. DOI:[10.1016/j.phrs.2020.104730](https://doi.org/10.1016/j.phrs.2020.104730)
 76. Bergman M, Djaldetti M, Salman H, Bessler H. On the combined effect of statins and lycopene on cytokine production by human peripheral blood cells. *Heart Vessels*. 2010;25(5):426–31. DOI:[10.1007/s00380-009-1204-8](https://doi.org/10.1007/s00380-009-1204-8)
 77. Alidadi M, Jamialahmadi T, Cicero AFG, Bianconi V, Pirro M, Banach M, Sahebkar A. The potential role of plant-derived natural products in improving arterial stiffness: A review of dietary intervention studies. *Trends Food Sci Technol*. 2020;99:426–40. DOI:[10.1016/j.tifs.2020.03.026](https://doi.org/10.1016/j.tifs.2020.03.026)
 78. Vasconcelos AG, das GN Amorim A, Dos Santos RC, Souza JMT, de Souza LKM, de SL Araújo T, Nicolau LAD, de Lima Carvalho L, de Aquino PEA, da Silva Martins C. Lycopene rich extract from red guava (*Psidium guajava* L.) displays anti-inflammatory and antioxidant profile by reducing suggestive hallmarks of acute inflammatory response in mice. *Food Res Int*. 2017;99:959–68. DOI:[10.1016/j.foodres.2017.01.017](https://doi.org/10.1016/j.foodres.2017.01.017)
 79. Asgary S, Soltani R, Daraei F, Salehizadeh L, Vaseghi G, Sarrafzadegan N. The effect of lycopene on serum level of cardiac biomarkers in patients undergoing elective percutaneous coronary intervention: A randomized controlled clinical trial. *ARYA Atheroscler*. 2021;17(1):1. DOI:[10.22122/arya.v17i0.2194](https://doi.org/10.22122/arya.v17i0.2194)
 80. Imran M, Ghorat F, Ul-Haq I, Ur-Rehman H, Aslam F, Heydari M, Shariati MA, Okuskhanova E, Yessimbekov Z, Thiruvengadam M. Lycopene as a natural antioxidant used to prevent human health disorders. *Antioxidants*. 2020;9(8):706. DOI:[10.3390/antiox9080706](https://doi.org/10.3390/antiox9080706)
 81. He Y, Xia P, Jin H, Zhang Y, Chen B, Xu Z. Lycopene ameliorates transplant arteriosclerosis in vascular allograft transplantation by regulating the NO/cGMP pathways and Rho-associated kinases expression. *Oxid Med Cell Longev*. 2016;2016. DOI:[10.1155/2016/3128280](https://doi.org/10.1155/2016/3128280)
 82. Bujor A, Miron A, Trifan A, Luca SV, Gille E, Miron SD, Aprotosoae AC. Phytochemicals and endothelial dysfunction: recent advances and perspectives. *Phytochem Rev*. 2021;20(4):653–91. DOI:[10.1007/s11101-020-09728-y](https://doi.org/10.1007/s11101-020-09728-y)
 83. Chao HH, Sung LC, Chen CH, Liu JC, Chen JJ, Cheng TH. Lycopene Inhibits Urotensin-II-Induced Cardiomyocyte Hypertrophy in Neonatal Rat Cardiomyocytes. *Kuo WW, editor. Evidence-Based Complement Altern Med [Internet]*. 2014;2014:724670. DOI:[10.1155/2014/724670](https://doi.org/10.1155/2014/724670)
 84. Allen KE, Billingsley HE, Carbone S. Nutrition, heart failure, and quality of life: Beyond dietary sodium. Vol. 8, *Heart Failure*. American College of Cardiology Foundation Washington DC; 2020. p. 765–9. DOI:[10.1016/j.jchf.2020.04.006](https://doi.org/10.1016/j.jchf.2020.04.006)
 85. Biddle MJ, Lennie TA, Bricker G V, Kopec RE, Schwartz SJ, Moser DK. Lycopene Dietary Intervention: A Pilot Study in Patients With Heart Failure. *J Cardiovasc Nurs*. 2015;30(3). DOI:[10.1097/JCN.000000000000108](https://doi.org/10.1097/JCN.000000000000108)
 86. Chen L, Wu X, Wang W, Wang XIA, Ma J. Quercetin with lycopene modulates enzymic antioxidant genes pathway in isoproterenol cardiotoxicity in rats. *Libyan J Med*. 2021;16(1). DOI:[10.1080/19932820.2021.1943924](https://doi.org/10.1080/19932820.2021.1943924)

87. Lin J, Li HX, Xia J, Li XN, Jiang XQ, Zhu SY, Ge J, Li JL. The chemopreventive potential of lycopene against atrazine-induced cardiotoxicity: modulation of ionic homeostasis. *Sci Rep.* 2016;6(1):1–12. DOI:[10.1038/srep24855](https://doi.org/10.1038/srep24855)
88. Yilmaz S, Atessahin A, Sahna E, Karahan I, Ozer S. Protective effect of lycopene on adriamycin-induced cardiotoxicity and nephrotoxicity. *Toxicology.* 2006;218(2–3):164–71. DOI:[10.1016/j.tox.2005.10.015](https://doi.org/10.1016/j.tox.2005.10.015)
89. Zhu J, Hu Q, Shen S. Enhanced antitumor efficacy and attenuated cardiotoxicity of doxorubicin in combination with lycopene liposomes. *J Liposome Res.* 2020;30(1):37–44. DOI:[10.1080/08982104.2019.1580720](https://doi.org/10.1080/08982104.2019.1580720)
90. Abdel-Daim MM, Eltaysh R, Hassan A, Mousa SA. Lycopene attenuates tulathromycin and diclofenac sodium-induced cardiotoxicity in mice. *Int J Mol Sci.* 2018;19(2):344. DOI:[10.3390/ijms19020344](https://doi.org/10.3390/ijms19020344)
91. Senkus KE, Tan L, Crowe-White KM. Lycopene and metabolic syndrome: a systematic review of the literature. *Adv Nutr.* 2019;10(1):19–29. DOI:[10.1093/advances/nmy069](https://doi.org/10.1093/advances/nmy069)
92. Elgawish RA, El-Beltagy MA, El-Sayed RM, Gaber AA, Abdelrazek H. Protective role of lycopene against metabolic disorders induced by chronic bisphenol A exposure in rats. *Environ Sci Pollut Res.* 2020;27(9):9192–201. DOI:[10.3390/foods10092219](https://doi.org/10.3390/foods10092219)
93. Benchagra L, Berrougui H, Islam MO, Ramchoun M, Boulbaroud S, Hajjaji A, Fulop T, Ferretti G, Khalil A. Antioxidant effect of moroccan pomegranate (*Punica granatum L. sefri* variety) extracts rich in punicalagin against the oxidative stress process. *Foods.* 2021;10(9):2219. DOI:[10.3390/foods10092219](https://doi.org/10.3390/foods10092219)
94. Crowe-White KM, Phillips TA, Ellis AC. Lycopene and cognitive function. *J Nutr Sci.* 2019;8. DOI:[10.1017/jns.2019.16](https://doi.org/10.1017/jns.2019.16)
95. Biddle M, Moser D, Song EK, Heo S, Payne-Emerson H, Dunbar SB, Pressler S, Lennie T. Higher dietary lycopene intake is associated with longer cardiac event-free survival in patients with heart failure. *Eur J Cardiovasc Nurs.* 2013;12(4):377–84. DOI:[10.1177/1474515112459601](https://doi.org/10.1177/1474515112459601)
96. Ferreira-Santos P, Carrón R, Montero MJ, Sevilla MÁ. The antihypertensive and antihypertrophic effect of lycopene is not affected by and is independent of age. *J Funct Foods.* 2021; DOI:[10.1016/j.jff.2021.104656](https://doi.org/10.1016/j.jff.2021.104656)
97. Valaei K, Taherkhani S, Arazi H, Suzuki K. Cardiac Oxidative Stress and the Therapeutic approaches to the intake of antioxidant supplements and physical activity. *Nutrients.* 2021;13(10):3483. DOI:[10.3390/nu13103483](https://doi.org/10.3390/nu13103483)
98. Chiva-Blanch G, Jiménez C, Pinyol M, Herreras Z, Catalán M, Martínez-Huélamo M, Lamuela-Raventos RM, Sala-Vila A, Cofán M, Gilibert R. 5-CIS-, trans-and total lycopene plasma concentrations inversely relate to atherosclerotic plaque burden in newly diagnosed type 2 diabetes subjects. *Nutrients.* 2020;12(6):1696. DOI:[10.3390/nu12061696](https://doi.org/10.3390/nu12061696)
99. Inoue T, Yoshida K, Sasaki E, Aizawa K, Kamioka H. Effects of lycopene intake on HDL-cholesterol and triglyceride levels: A systematic review with meta-analysis. *J Food Sci.* 2021;86(8):3285–302. DOI:[10.1111/1750-3841.15833](https://doi.org/10.1111/1750-3841.15833)
100. Foster H, Wilson C, Philippou H, Foster R. Progress toward a glycoprotein VI modulator for the treatment of thrombosis. *J Med Chem.* 2020;63(21):12213–42. DOI:[10.1021/acs.jmedchem.0c00262](https://doi.org/10.1021/acs.jmedchem.0c00262)
101. Olas B, Urbańska K, Bryś M. Selected food colourants with antiplatelet activity as promising compounds for the prophylaxis and treatment of thrombosis. *Food Chem Toxicol.* 2020;141:111437. DOI:[10.1016/j.fct.2020.111437](https://doi.org/10.1016/j.fct.2020.111437)
102. Kim L, Lim Y, Park S yeon, Kim YJ, Kwon O, Lee JH, Shin JH, Yang YK, Kim JY. A comparative study of the antithrombotic effect through activated endothelium of garlic powder and tomato extracts using a rodent model of collagen and epinephrine induced thrombosis. *Food Sci Biotechnol.* 2018;27(5):1513–8. DOI:[10.1007/s10068-018-0469-z](https://doi.org/10.1007/s10068-018-0469-z)
103. Cámara M, Fernández-Ruiz V, Sánchez-Mata MC, Domínguez Díaz L, Kardinaal A, van Lieshout M. Evidence of antiplatelet aggregation effects from the consumption of tomato products, according to EFSA health claim requirements. *Crit Rev Food Sci Nutr.* 2020;60(9):1515–22. DOI:[10.1080/10408398.2019.1577215](https://doi.org/10.1080/10408398.2019.1577215)
104. O’Kennedy N, Crosbie L, Song HJ, Zhang X, Horgan G, Duttaroy AK. A randomised controlled trial comparing a dietary antiplatelet, the water-soluble tomato extract Fruitflow, with 75 mg aspirin in healthy subjects. *Eur J Clin Nutr.* 2017;71(6):723–30. DOI:<https://doi.org/10.1038/ejcn.2016.222>