



Lycopene: Is it Beneficial to Human Health as an Antioxidant?

Likopen: Antioksidan Olarak İnsan Sağlığına Faydalı mı?

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ABSTRACT

It is well known that free oxygen radicals play an important role in the pathogenesis of several chronic disorders. Antioxidants are known as potential scavengers of reactive oxygen species that can protect biologic membranes against oxidative damage. Recent interest in phytochemicals has increased because of their protective effects against free oxygen radicals. Lycopene, which belongs to the carotenoid family, is the most effective singlet oxygen scavenger *in vitro* of all the carotenoids. Foods that contain lycopene and related supplements have been reported to prevent chronic diseases including cancer, asthma, and cardiovascular disorders. The aim of the article was to give a brief review of the antioxidant properties and beneficial health effects of lycopene.

Key words: Lycopene, antioxidant, health effects

ÖZ

Birçok kronik hastalığın patogeneğinde serbest oksijen radikallerinin önemli rol oynadığı bilinmektedir. Antioksidanlar reaktif oksijen türevlerinin olası süpürücüleri olarak bilinir, bu nedenle biyolojik membranları oksidatif hasara karşı koruyabilirler. Serbest oksijen radikallerine karşı koruyucu etkileri nedeniyle fitokimyasallara ilgi giderek artmaktadır. Karetonoid ailesinde yer alan likopen tüm karotenoidler içerisinde *in vitro* şartlarda en etkili tekli oksijen süpürücüsüdür. Likopen içeren gıdalar ve likopen desteklerinin kanser, astım ve kardiyovasküler hastalıklar gibi kronik hastalıklara karşı koruyucu etkilerinin bulunduğu rapor edilmiştir. Bu makalede likopenin antioksidan özellikleri ve sağlığa yararlı etkilerine ilişkin bir özet verilmesi amaçlanmıştır.

Anahtar Kelimeler: Likopen, antioksidan, sağlık etkileri

INTRODUCTION

It is well known that free oxygen radicals play important roles in the pathogenesis of several chronic disorders such as cancer, diabetes, and cardiovascular and neurologic diseases.^{1,2}

Antioxidants are known as potential scavengers of reactive oxygen species (ROS) that protect biologic membranes against oxidative damage. If the balance between free radicals and antioxidant defense is destroyed by chemicals, the imbalance may lead to damage to DNA, lipids, and proteins.³ The role of oxidative stress induced by ROS and the oxidative damage of important biomolecules are the main focuses of research related to human diseases.⁴

Recent interest in phytochemicals, especially plant phenolics, has increased because of their protective effects against free oxygen radicals. Phenolic compounds are secondary metabolites that are derivatives of the pentose phosphate, shikimate, and phenylpropanoid pathways in plants.^{5,6} They contribute to the

sensory qualities of fruits and vegetables: color, astringency, bitterness, and aroma.⁷

It is estimated that approximately 50% of cancer cases and 35% of cancer deaths in the United States can be attributed to poor diet.⁸ Many studies showed that fruit and vegetable-rich diets were associated with a decreased risk of chronic diseases.⁹

Carotenoids, which produce colors ranging from yellow to red, are synthesized by plants and microorganisms.¹⁰ More than 700 carotenoids have been identified, about 40 of which are present in the human diet, and about 20 have been identified in blood and tissues.^{11,12} β -carotene, α -carotene, lycopene, α -cryptoxanthine, lutein and zeaxanthin are the main carotenoids in the human diet.^{12,13}

Lycopene (Figure 1), a noncyclic carotenoid found in tomatoes (*Solanum lycopersicum*, Solanaceae), has received considerable scientific interest in recent years. Red-colored fruits and vegetables are the main sources of lycopene in the human diet,

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although not all red-colored plants contain lycopene. Its main function is to absorb light during photosynthesis and to protect plants against photosensitization.¹⁰

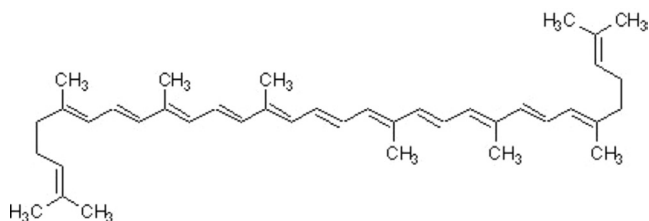


Figure 1. Lycopene

This article mainly focuses on the protective effects of lycopene against chronic diseases, and the chemistry and sources, dietary intake, mechanism of action, bioavailability, and pharmacokinetics of lycopene will also be discussed.

DATA COLLECTION

Information about lycopene was obtained from a literature search of electronic databases such as Google Scholar, PubMed, and Scopus for publications on health beneficial effects of lycopene. *Lycopene*, *antioxidant*, *tomato lycopene*, and *lycopene and health* were used as key terms.

Chemistry and sources of lycopene

Lycopene is found in processed tomato products, watermelon, pink grapefruits, papaya, and apricot.¹⁹ Its chemical structure is an open chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds arranged in a linear array. During chemical reactions, light or thermoenergy, these bonds can undergo isomerization from trans to mono or poly *cis*-isomers. It lacks a β -ionene ring structure and has no provitamin A activity, but exhibits a physical quenching rate constant with singlet oxygen (¹O₂) almost twice as high as that of β -carotene. Its molecular formula is C₄₀H₅₆ and it has all-*trans*, 5-*cis*, 9-*cis*, 13-*cis* and 15-*cis* isoforms.¹⁹ The *trans* isoform is commonly found in the human diet and the *cis* isoform is found in human blood, plasma, breast milk, and human tissues.²²⁻²⁵ The color of lycopene is related to its isomeric form.²² Antioxidant potential of lycopene isomers are 5-*cis*>9-*cis*>7-*cis*>13-*cis*>15-*cis*>11-*cis*>all-*trans*, respectively.²⁶

Dietary intake levels of lycopene

The United States Food and Drug Administration in America granted Generally Recognized as Safe status to lycopene as a nutritional supplement.¹⁰ Dietary intake of lycopene varies due to populations. Lycopene intake in Italy with an average intake of 7.4 mg/day is greater than in other countries.¹⁴ The average intake of lycopene is 6.6-10.5 mg/day for men and 5.7-10.4 mg/day for women in the United States, 1.1 mg/day in the United Kingdom, 1.6 mg/day in Spain, 3.8 mg/day in Austria, 4.8 mg/day in France, and 4.9 mg/day in the Netherlands.^{15,16}

For many years, lycopene containing foods and lycopene supplements have been used without any safety problems. Rao and Agarwal¹⁷ (1998) demonstrated that lycopene intake levels varied from 5 to 75 mg/day in tomato juice, tomato sauce, and nutritional supplements in healthy humans. No adverse effects due to lycopene consumption were observed. Similarly, no evidence of toxic effects of lycopene were seen with two synthetic crystalline lycopene (BASF lycopene 10 CWD and Lyco Vit 10%, each containing approximately 10% lycopene)¹⁸ and lycopene derived from a fungal biomass of *Blakeslea trispos*, suspended in sunflower oil in rats.¹⁹ No teratogenic effects were also observed in a two-generation rat study.²⁰

Bioavailability and kinetics of lycopene

Lycopene bioavailability can be affected by many factors such as food processing and dietary composition.²¹ Food processing in particular and thermal processing may improve lycopene bioavailability by breaking down cell walls, which weakens the bonding forces between lycopene and the tissue matrix, thus making lycopene more accessible and enhancing the *cis*-isomerization. The bioavailability of *cis*-isomers in food is higher than that of all-*trans* isomers.

The amount of lycopene present in processed tomato products is often much higher in fresh tomatoes given that processing often involves concentrations via water loss. Multiple studies have shown that lycopene from thermally processed tomato products was more bioavailable than lycopene from fresh tomatoes.²² Ketchup contains 9.9-13.44 mg lycopene/100 g, whereas fresh tomatoes contain 0.88-7.44 mg lycopene/100 g wet weight.^{23,24}

Lycopene bioavailability is also greatly affected by dietary composition. Consuming lycopene with fat increases its bioavailability because lycopene is a lipid-soluble compound. For example, consuming salads with full-fat dressing results in higher blood carotenoid levels than eating salads with reduced fat dressing. When salads were consumed without fat in the same study, no measurable lycopene uptake occurred.²⁵ The consumption of tomato salsa with avocado (as lipid source) led to a 4.4-fold increase in lycopene absorption as compared with salsa without avocado.²⁶

It is believed that lycopene was absorbed by passive diffusion as lipids. Many studies suggested that lycopene absorption may be facilitated by other transporters, but this has not yet been confirmed.^{27,28} Competition by other carotenoids or cholesterol may also influence lycopene absorption.¹⁶ Age, sex, hormonal status, body mass and composition, blood lipid levels, smoking and alcohol may influence the absorption of lycopene.²⁹ Lycopene is found in the highest concentrations in the liver, testes, adrenal glands, and adipose tissues. It is found in lower concentrations in the kidney, ovary, lung, and prostate.³⁰

Very little is known about the *in vivo* metabolism of lycopene. Only a few metabolites, such as 5,6-dihydroxy-5,6-dihydro lycopene, have been detected in human plasma. It is suggested that lycopene may undergo *in vivo* oxidation to form epoxides, which then may be converted to the polar 5,6-dihydroxy-5,6-dihydrolycopene through metabolic reduction.³¹ In humans,

lycopene absorption is in the range of 10-30%, with the remainder being excreted.^{17,29}

Health protective effects of lycopene

The biologic activities of carotenoids depend on their provitamin A activity, but lycopene does not have provitamin activity due to the lack of a β -ionic ring structure.³² The main biologic activity of lycopene is thought to be its antioxidant properties. It is the most effective $^1\text{O}_2$ scavenger *in vitro* of all the carotenoids.³³

Increasing clinical evidence supports the role of lycopene as a micronutrient with important health benefits because it is suggested to play a role in disorders related to oxidative stress and cancer. It is a highly efficient antioxidant with a $^1\text{O}_2$ and has free radical scavenging capacity. Lycopene can scavenge oxygen radicals, reduce oxidative stress, and prevent ROS generation. It may protect against the *in vivo* oxidation of lipids, proteins, and DNA.^{34,35}

Inhibition of insulin-like growth factor-I and androgen signaling, interleukin-6 expression, improving immune responses and gap junction communication (GJC), induction of phase II drug metabolizing enzymes and oxidative defense genes are the important suggested non-oxidative mechanisms of action of lycopene.³⁶

Human tumors are generally deficient in GJC and its upregulation is associated with the decreased proliferation of tumor cells. Thereby, improving GJC is a suggested mechanism in the prevention of cancers. With this effect, lycopene could be an anticarcinogenic compound.^{10,37} Suppression of the carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb antioncogenes by lycopene may also play an important role in the suppression of cell division at the G-G1 cell cycle phase.³⁸

Lycopene acts as a hypocholesterolemic agent by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase. This mechanism may be associated with the reduction of risk of cardiovascular diseases.³⁹ In experimental animals, lycopene induced immunoenhancement.⁴⁰ The increase in the phenotypic and functional maturation of dendritic cells by lycopene was also reported.⁴¹

Cancer

The consumption of tomatoes and tomato products has been associated with a reduced risk of a number of different types of cancers.⁴² A study of older Americans indicated that a high intake of tomatoes was associated with a significant reduction in mortality from cancers of all sites.^{43,44} In the Mediterranean, the incidence of cancer is lower due to the rich diet in tomatoes and tomato products.⁴⁵

It has been shown that lycopene reduced the oxidative injury by stimulating the levels and activities of antioxidant enzymes including glutathione (GSH), glutathione-S-transferases, and glutathione peroxidase in animals with gastric cancer.⁴⁶ Lycopene prevents the oxidative damage of DNA, lipids, and proteins.⁴⁷ It modulates immune function, and induces apoptotic cell death.¹⁰ It is also suggested to inhibit ROS production and decrease the phosphorylation of extracellular signal-regulated kinase (ERK), which results in the inhibition of cancer cell

growth.^{34,48,49} Lycopene inhibited phosphorylation of ERK, which is a major regulator of cell proliferation, apoptosis, and differentiation in gastric cells, as well as hepatocarcinoma cells.

Lycopene also decreased Bcl-2 and increased levels of Bax, which induce the release of cytochrome C and other pro-apoptotic factors from mitochondria, leading to apoptosis. Bcl-2 is an important anti-apoptotic protein that regulates cell death. Bcl-2 inhibits apoptosis by reducing caspase activation such as caspase 3 and 8. Bax protein, a member of the Bcl-2 family of proteins, is a regulator of apoptosis and promotes apoptosis.^{50,51} Lycopene treatment inhibited cancer cell proliferation by increasing cell cycle arrest in the G0-G1 phase.⁵²

Lycopene supplementation prevented changes in p53 expression in gastric mucosa of ferrets and it was suggested that lycopene may protect against the development of gastric cancer by inhibiting p53 dependent apoptosis and providing the balance of apoptosis and cell proliferation. Lycopene also prevented changes in p53 overexpression in gastric mucosa exposed to cigarette smoke.⁵³ The main evidence in support of the role of lycopene in the prevention of these cancers comes from cell culture, animal, and epidemiologic studies.¹⁰

Of all cancers, the role of lycopene in the prevention of prostate cancer has been studied the most.¹⁰ Hall⁵⁴ (1996) and Kotake-Nara et al.⁵⁵ (2001) demonstrated that lycopene inhibited the growth of DU145 prostate cancer cells. Similar to these studies, Kim et al.⁵⁶ (2002) showed the protective effects of lycopene as an antioxidant on LNCaP prostate cancer cells growth. The effect of whole tomato powder (13 mg lycopene per kg diet), lycopene beadlets (161 mg lycopene per kg diet), and control beadlets (0 mg lycopene per kg diet) were evaluated for their effect on prostate cancer in a rat model. The study showed that the consumption of tomato powder, but not lycopene, inhibited prostate carcinogenesis.⁵⁷ In a cohort study, Seventh-Day Adventist men who consumed high levels of tomato products more than five times per week had significantly decreased risk of prostate cancer compared with men who consumed lower amounts of tomato products less than once per week.⁵⁸ In another study, lycopene induced the apoptosis of pancreatic cancer cells by suppressing the expression of survivin, cIAP1, and cIAP2. Lycopene may be a promising therapeutic agent for human pancreatic cancer.⁵⁹

Gastric (stomach) cancer remains as one of the major causes of cancer death in the world.^{60,61} Dietary factors are believed to play an important role in the prevention of gastric cancer, among which dietary carotenoids have received considerable interest.⁶²⁻⁶⁴ Inverse associations between tomato or lycopene consumption (intake) and gastric cancer risk were observed in a variety of populations.^{44,65-76} A suggestive, but not statistically significant, inverse association was observed in a study conducted in Belgium with 449 subjects even though the study population had a low consumption of tomatoes.⁷⁴ In an ecologic study, plasma levels of various nutrients in samples of Japanese populations in various regions were evaluated and the lowest gastric cancer rates were found in regions higher

in plasma lycopene, whereas regions low in lycopene had the highest rates.⁷⁷ Ito et al.⁷⁸ (2005) examined cancer mortality and serum levels of carotenoids, retinol and tocopherol, in the inhabitants of a rural area of Japan and found that serum levels of lycopene were associated with a reduced risk of death from stomach cancer. They suggested that lycopene may be a promising biomarker to predict mortality related with stomach cancer.

It has been concluded that consumption of lycopene-containing foods may decrease for risk of breast cancers. Cui et al.⁷⁹ (2008) found that lycopene consumption was inversely associated with estrogen and progesterone receptor positive breast cancer risk in postmenopausal women. Lung cancer is the leading cause of cancer death for both men and women. Epidemiological studies suggest that higher intake of lycopene is associated with either a reduced risk of lung cancer⁸⁰, or no change in lung cancer risk, as compared with lower intake levels.⁸¹ The protective effects against ovarian cancer, colorectal cancer, and pancreatic cancer were demonstrated in different epidemiologic studies.¹⁶

Cardiovascular diseases

Cardiovascular disease is a leading cause of death in America and the Western world.⁸² Oxidation of low-density lipoprotein (LDL) is the main mechanism of cardiovascular diseases. Thus, antioxidants may have an effect in reducing LDL oxidation. Due to this effect, lycopene may be beneficial in cardiovascular diseases as an antioxidant.⁸³

Low plasma lycopene levels were reported by many researchers in hypertension, myocardial infarction, stroke, and atherosclerosis.⁸⁴ Lycopene was decreased in carotid artery intima-media thickness.⁸⁵ Some clinical trials have also supported a relationship between cardiovascular disease and lycopene intake. In a study, 19 healthy subjects consumed placebo (0 mg lycopene), tomato juice (50.4 mg lycopene), spaghetti sauce (39.2 mg lycopene), and tomato oleoresin (75 mg lycopene) treatment daily for one week and went through a one-week washout period between each treatment week. The serum lycopene concentration doubled in subjects on lycopene-containing treatments and also a significant decrease in serum lipid peroxidation and LDL oxidation was observed after subjects consumed any one of the three lycopene-containing treatments.⁸⁶ In another study, healthy individuals received one of three tomato treatments for 15 days (condensed tomato soup, ready-to-serve tomato soup, or V8[®] vegetable juice). Blood samples were taken at baseline and after treatment. A measure of protection against oxidative stress was significantly increased in all three treatment groups.⁸⁷ Shen et al.⁸⁸ (2007) treated 24 subjects with either fresh tomato, tomato juice, or a lycopene drink (all delivering 40 mg lycopene/day) for six weeks. It was found that triglyceride levels and LDL were decreased, and high-density lipoprotein (HDL) increased in subjects who consumed fresh tomato and tomato juice.⁸⁹ Bohn et al.⁸⁹ (2009) demonstrated that soy tomato beverage consumption significantly reduced LDL+VLDL levels and increased HDL levels in 18 healthy men and women.

Neurodegenerative diseases

The high lipid content of the nervous system, low antioxidant capacity, and the presence of iron, coupled with its high aerobic metabolic activity, make it particularly susceptible to oxidative damage.⁹⁰ Most studies have shown the effects of antioxidants on nervous system disorders including Alzheimer's disease, Huntington's disease, and Parkinson disease.⁹¹ In an animal study, a beneficial effect of lycopene supplementation in rotenone-induced Parkinson's disease was demonstrated.⁹² Lycopene showed protective effects against myeloid β -induced neurotoxicity in cultured rat cortical neurons⁹³, 3-nitropropionic acid-induced mitochondrial oxidative stress, and dysfunctions in nervous system⁹⁴, and trimethyltin-induced neurotoxicity in primary cultured rat hippocampal neurons.⁹⁵

Gastrointestinal diseases

A significant increase has been seen in peptic ulcer incidence worldwide. The generation of ROS is the major cause of stress-induced ulcers.⁹⁶ Therefore, it is suggested that powerful antioxidants may be useful in the treatment of ulcers.⁹⁷ Accordingly, to overcome the adverse effects of drugs and provide efficacious and safe therapy, herbal antioxidants may be useful due to their antioxidant effects.⁹⁸ The anti-ulcer activity of lycopene can be attributed to different mechanisms, including inhibition of gastric acid secretion, reinforcement of the gastric mucosal barrier, and its free radical scavenging activity.⁹⁹ It has been shown that lycopene (2 mg/kg) and hesperidin (100 mg/kg) decreased gastric secretions and total acidity as well as increased gastric pH due to the restoration of normal gastric conditions in ulcer-induced rats.⁹⁸ Similarly, Boyacioglu et al.¹³ (2016) demonstrated that lycopene treatment exhibited protection against indomethacin-induced gastric ulcer in rats in a dose-dependent manner. In the same study, it was demonstrated that superoxide dismutase (SOD) activity and GSH levels were higher in the lycopene-treated group, and catalase (CAT) activity and malondialdehyde (MDA) levels were lower in the lycopene-treated group when compared with controls. These results suggest that lycopene had antioxidant effects on the treatment of ulcers.¹³

Helicobacter pylori is an important risk factor for chronic gastritis, peptic ulcer, and gastric carcinoma. In *H. pylori*-induced gastric injury, ROS is the major toxic factor.¹⁰⁰ Lycopene is reported to have a significant inhibitory effect on gastric acid secretion followed by efficacy against *H. pylori* infections.¹⁰¹⁻¹⁰³ Jang et al.¹⁰⁰ (2012) showed that lycopene rescued the *H. pylori*-infected cells from DNA damage and apoptosis in gastric epithelial cells. It also inhibited *H. pylori*-induced increases in ROS production and alterations in the cell cycle.¹⁰⁰

Gastroesophageal reflux disease (GERD) commences due to reflux of gastric content into the esophagus, which results in mucosal devastation.¹⁰⁴ ROS play an important role in the pathogenesis of GERD.¹⁰⁵ In rats, lycopene (50 and 100 mg/kg) showed significant protection against experimental esophagitis. The gastric content is a major factor in the pathogenesis of GERD and it is claimed that lycopene decreased the acidity (total and free) and gastric volume, and thereby subsequently

increased the pH. Modulation in pH and acidity of gastric content after lycopene treatment was also reflected through a decrease in esophagitis indices. In the same study, a positive modulation in GERD by lycopene was seen in physiologic changes. Similar to other studies, it was shown that SOD and CAT enzyme activities and GSH levels were higher in the lycopene group and MDA levels were lower when compared with controls.¹⁰⁶

Bone health

Oxidative stress, which has been shown to control the function of both osteoclasts and osteoblasts, may contribute to the pathogenesis of the skeletal system including the most prevalent metabolic disease, osteoporosis. A number of studies revealed that ROS increase bone resorption. Others suggested that ROS may be involved in the regulation of osteoclast formation and osteoclast motility. Limited studies demonstrated that lycopene had beneficial effects on bone health.¹⁰⁷

Kim et al.¹⁰⁸ (2002) showed that lycopene stimulated the proliferation of osteoblast-like SaOS-2 cells. On the other hand, Park et al.¹⁰⁹ (1997) reported that lycopene had an inhibitory effect on the cell proliferation of MC3T3 cells, which are osteoblastic cells of lower species. However, both studies reported a stimulation of alkaline phosphatase activity. Rao et al.¹¹⁰ (2003) cultured cells from bone marrow prepared from rat femurs in 16-well calcium phosphate-coated Osteologic™ multi-test slides (Millenium Biologix Inc.). Varying concentrations of lycopene in the absence or presence of the resorbing agent PTH-(1-34) were added at the start of culture and at each medium change every 48 hours. Lycopene inhibited TRAP+ multinucleated cell formation in both vehicle- and PTH-treated cultures. The number of cells stained with the NBT reduction product formazan was decreased by treatment with 10⁻⁵ M lycopene, indicating that lycopene inhibited the formation of ROS-secreting osteoclasts.¹¹⁰ Ishimi et al.¹¹¹ (1999) in murine osteoclasts formed in coculture with calvarial osteoblasts. Furthermore, they could not demonstrate any effect of lycopene on bone resorption.¹¹¹

Other diseases

Oxidative stress has been suggested as an important contributory factor in male infertility.¹¹² Antioxidants for male infertility could potentially have a great impact on the management of couples with infertility. To date, a small number of studies have evaluated the role of vitamins and antioxidants (mostly as single agents) in male infertility, but additional studies are needed.¹⁰ Dawson et al.¹¹³ (1993) demonstrated the activity of vitamin C on semen quality, and Geva et al.¹¹⁴ (1996) and Suleiman et al.¹¹⁵ (1996) showed the activity of vitamin E on semen quality. Men with antibody-mediated infertility were found to have lower semen lycopene levels than fertile controls.¹¹⁶

Low serum levels of lycopene have also been associated with increased risk of psychiatric disorders.¹¹⁷

A study with 17 adults with asthma treated with placebo, tomato extract (Lyc-o-Mato®, 45 mg/day lycopene), and tomato juice (45 mg/day of lycopene) for 7 days showed reduced airway neutrophil influx and reduced sputum neutrophil elastase

activity after the tomato extract and tomato juice treatment. During placebo treatment, plasma lycopene concentrations decreased, the percentage of neutrophils increased, and neutrophil elastase levels increased.¹¹⁸

CONCLUSION

Diets rich in fruits and vegetables are associated with a lower risk of numerous diseases including cancers. Intake of fruits and vegetables that contain high levels of vitamins C and A, phenolics, and carotenoids for reducing cancer risk have been made by several researchers.

Lycopene is one of the major carotenoids in Western diets, accounting for more than 50% of carotenoids in humans. A brief summary of the literature relating to lycopene and its role in health is presented in this article. Promising data from epidemiologic as well as cell culture and animal studies suggest that lycopene and the consumption of lycopene-containing foods may affect several chronic disorders. Nevertheless, more clinical data are needed to support this hypothesis. In addition, further detailed research is required to understand other beneficial health effects of lycopene and its mechanisms.

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