

Review Article

Therapeutic and medicinal uses of lycopene: a systematic review

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ABSTRACT

Lycopene is a carotenoid present in fruits and vegetables. The richest sources of lycopene are tomatoes and tomato products. The beneficial effects of lycopene in human health and disease are mainly associated with its antioxidant properties. Lycopene is a carotenoid with strongest antioxidant property because of its capability of quenching the singlet oxygen. Eleven conjugated double bonds of lycopene give it a deep red color and are responsible for its antioxidant activity which is major functional feature of lycopene. Dietary intakes of tomatoes and tomato products containing lycopene have been shown to be associated with decreased risk of chronic diseases such as cancer and cardiovascular diseases in numerous studies. Although there are evidences from many epidemiological and cell culture and animal studies explaining the inverse relationship between lycopene and cancer or cardiovascular disease risk, more clinical trial data is needed to support this hypothesis. In this article we outline the possible mechanisms of action of lycopene and review the current understanding of its role in human health and disease prevention.

Keywords: Antioxidant, Antidiabetic, Cancer, Cardiovascular disease, Lycopene

INTRODUCTION

Epidemiological research indicates that diets rich in fruits and vegetables are associated with a decreased risk of chronic diseases such as cardiovascular disease (CVD) and cancer.^{1,2} It is estimated that approximately 50% of cancer cases and 35% of cancer deaths in the United States can be attributed to poor diet. Epidemiological studies have associated tomato consumption with a decreased risk of prostate cancer and CVD.^{3,4} Despite this evidence, it is not clear whether individual compounds present in tomato, such as lycopene, impart these potential benefits or other constituents of tomatoes and tomato products produce beneficial effects. Lycopene is a natural red carotenoid pigment present in tomatoes, pink grapefruit, watermelon, papaya, guava, and other fruits.

Lycopene was named after the fruit from which it was first isolated, namely the tomato (*Lycopersicon esculentum*), by the chemist C.A. Schunck in 1903.⁵ It is responsible for the red color of many fruits and vegetables such as the tomato. It is a carotenoid, an acyclic isomer of carotene and has no vitamin A activity.⁶ Numerous studies have shown that in our diet tomato and tomato products containing lycopene is associated with decreased risk of chronic disease such as cancer and cardiovascular diseases. Among different types of tested carotenoids, lycopene has been found to be the most potent in vitro antioxidant and several leading researchers have concluded that these antioxidant properties of lycopene are responsible for disease prevention.⁷ Tomatoes and tomato-based foods account for more than 85% of all the dietary sources of lycopene. Lycopene

content in tomato ranges from 8.8 to 42 microgram/g wet weight. Tomato products have higher levels of antioxidant activity and therefore are more potent than tomatoes in reducing the risk of oxidation-related diseases.⁸ Tomatoes contain a number of different compounds such as carotenoids, vitamin C, and flavonoids that may account for its antioxidant properties. However, lycopene, as the main carotenoid in tomato products, possesses the greatest ability to quench singlet oxygen compared to the other carotenoids.⁹ This review will highlight the chemical composition of lycopene, its sources and function, as well as potential impact on human health.

SOURCES OF LYCOPENE

Animals and humans do not synthesize lycopene, and thus depend on dietary sources. Tomatoes and tomato products are the major dietary sources of lycopene. Other sources include watermelon, pink grapefruit, apricots, pink guava and papaya.¹⁰

Lycopene is the most abundant carotenoid in ripen tomatoes, comprising approximately 80-90% of the pigments present. The amount of lycopene in fresh tomatoes depends on the variety, maturity, and environmental conditions in which the fruit matures (Table 1).¹¹

Table 1: Lycopene content of tomatoes, some commonly consumed tomato products and other lycopene containing fruits and vegetables.

Source	Lycopene content (mg/100g wet basis)
Tomatoes fresh	0.72 – 20
Tomato juice	5.00 - 11.60
Tomato sauce	6.20
Tomato paste	5.40 - 15.00
Tomato soup	7.99
Pizza sauce	12.71
Watermelon	2.30 - 7.20
Pink guava	5.23 - 5.50
Pink grapefruit	0.35 - 3.36
Papaya	0.11 - 5.30
Carrot	0.65 - 0.78
Pumpkin	0.38 - 0.46
Sweet potato	0.02 - 0.11

CHEMISTRY AND PROPERTIES OF LYCOPENE

Lycopene is a lipophilic, 40-carbon atom highly unsaturated, straight chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds. The all-trans isomer of lycopene is the most predominant isomer in fresh tomatoes and is the most thermodynamically stable form. The many conjugated double bonds of lycopene make it a potentially powerful antioxidant, a characteristic believed to be responsible for its beneficial

effects.¹² The antioxidant activity of lycopene is high light by its singlet oxygen-quenching property and its ability to trap peroxy radicals. This singlet quenching ability of lycopene is twice as high as that of β - carotene and 10 times higher than that of α -tocopherol and butylated hydroxytoluene.¹³

All - trans, 5 - cis, 9 - cis, 13 - cis, and 15 - cis are the most commonly identified isomeric forms of lycopene with the stability sequence being 5 - cis > all - trans > 9 - cis > 13 - cis > 15 - cis > 7 - cis > 11 - cis, so that the 5 - cis - form is thermodynamically more stable than the all-trans-isomer.¹³

Whereas a large number of geometrical isomers are theoretically possible for all-trans lycopene, according to only certain ethylenic groups of a lycopene molecule can participate in cis-trans isomerization because of steric hindrance. In fact, only about 72 lycopene cis isomers are structurally favorable.¹⁴ Molecular structure and physical properties of lycopene are shown in Figure 1 and Table 2 respectively.

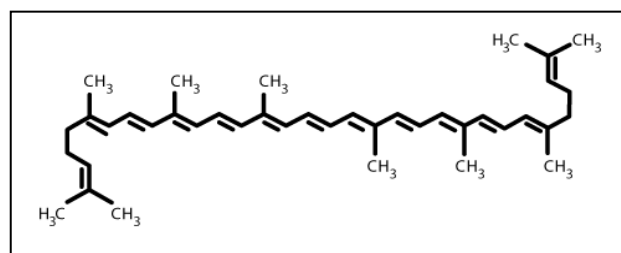


Figure 1: Molecular structure of lycopene.

Table 2: Physical properties of lycopene source.¹⁵

Molecular formula	C ₄₀ H ₅₆
Melting point	172–175 °C
Molecular weight	536.85 Da
Crystal form	Long red needles separate from a mixture of carbon disulfide and Ethanol
Powder form	Dark reddish-brown
Solubility	Soluble in chloroform, hexane, benzene, carbon disulfide, acetone, petroleum ether and oil; Insoluble in water, ethanol and methanol
Stability	Sensitive to light, oxygen, high temperature, acids, catalyst and metal ions

ABSORPTION, TRANSPORTATION AND DISTRIBUTION OF LYCOPENE IN HUMAN

Absorption

As a fat soluble compound, lycopene has a similar absorption as dietary fat. In the stomach and duodenum,

lycopene will separate from the food matrix and subsequently dissolve in the lipid phase.¹⁶ Prior to absorption, the lipid phase will form droplets, resulting from the reaction with bile salts and pancreatic lipases. Then, it enters the duodenum and appears as the multi-lamellar lipid vesicles (Figure 2).¹⁷ Finally, the lipid vesicles will absorb into small intestine via passive or diffusion process. Additionally, there is in-vitro studies suggested that the intestinal absorption of lycopene was aided by the participation of a specific epithelial transporter.¹⁷ However, there are many factors that might affect the absorption of lycopene. The degree of lycopene release from the food matrix into the digestive tract will be lowered when the indigestible fraction increases. High fibers diets will reduce the uptake of lycopene and decrease lycopene adsorption whereby lycopene supplemented together with different dietary fibers has resulted in the reduction of plasma lycopene for more than 40%.¹⁸

Transportation

After the uptake by intestinal mucosa, lycopene will be parceled into triacylglycerol-rich chylomicrons and will be secreted into lymph transport system, and lastly transferred to the liver (Figure 2).¹⁹ Lycopene is prone to accumulate in the lipophilic compartments of membrane or lipoprotein. It is transported by plasma lipoproteins and the distribution depends on its chemical structure. As a hydrophobic compound, lycopene is found at the lipophilic part of lipoproteins which is the core of the lipoprotein, while other polar carotenoids can be found at the surface of lipoproteins. Therefore, lycopene is mostly transported by low density lipoproteins, while other oxygenated carotenoids are transported by both low density and high density lipoprotein.¹⁹ In addition, cis-isomers of lycopene were reported to have higher ability to be incorporated in lipoprotein and other protein compared to all-trans isomer due to the shorter chain length.²⁰

Distribution

The distribution of lycopene in human organs and plasma has been reported by Erdman where higher concentrations of lycopene are found in the liver, adrenal and reproductive tissues (ten times higher than other tissues).²¹ The concentrations were within the range of 0.2 - 21.4 nmol/g tissue.²⁶ Goralczk and Siler reported that lycopene concentration was the highest in human testes, followed by adrenal gland > liver > prostate > breast > pancreas > skin > colon > ovary > lung > stomach > kidney > fat tissue > cervix.²² A review by Rao and Agarwal quoted that lycopene concentrations in human tissues are around 0.15 - 21.36 nmol/g tissue, but not detectable in brainstem tissue.²³ On the other hand, a study on rats carried out by Zaripheh et al. showed that lycopene was highly distributed in the liver.²⁴ Besides, high lycopene content was found in adipose tissue, the spleen and adrenal tissue (Figure 2).

The excretion of lycopene through feces and urine was also reported.²⁴

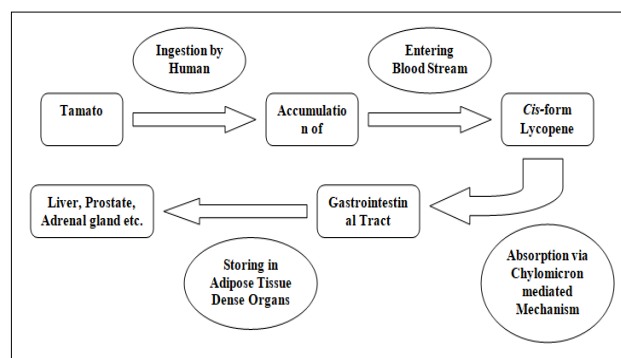


Figure 2: Schematic illustration of absorption, transportation, and distribution of lycopene.

HEALTH BENEFICIAL EFFECTS OF LYCOPENE

Tomato and tomato-based products are important sources of many established nutrients and are predominant sources of some phytochemicals that may have health benefits. Tomatoes are relatively rich sources of folate, vitamin C, vitamin A, and potassium.

Overall, tomatoes are an important source of several nutrients and a predominant source of several carotenoids, particularly lycopene. Very few items other than tomato products contribute to dietary lycopene; these include watermelon, pink grapefruit, and apricots.²⁵ The numerous biological functions of lycopene on human health are as follows (Figure 3).

Anticancer activities

Cancer is the second leading cause of death in the United States, with approximately 1.5 million new cases of cancer diagnosed in 2008.²⁶ This health issue has raised the awareness of people to go for natural products and their therapeutic or preventive value. The beneficial effect of lycopene is associated to decrease cancer incidence worldwide especially in prostate. Lycopene (1- 4 μ M) was also reported to reduce the risk of lung, leukemic and digestive tract cancers. Besides, research was done on chemopreventive effects of lycopene (10 - 50 μ M) in liver and ovary cells.²⁷

The most impressive results come from the US Health Professionals follow-up study, which evaluated the intake of various carotenoids and retinol, from a food frequency questionnaire, in relation to risk of prostate cancer.²⁸ The estimated intake of lycopene from various tomato products was inversely related to the risk of prostate cancer. This result was not observed with any other carotenoid. A reduction in risk of almost 35% was observed for a consumption frequency of 10 or more servings of tomato products per week, and the protective

effects were even stronger with more advanced or aggressive prostate cancer.²⁹

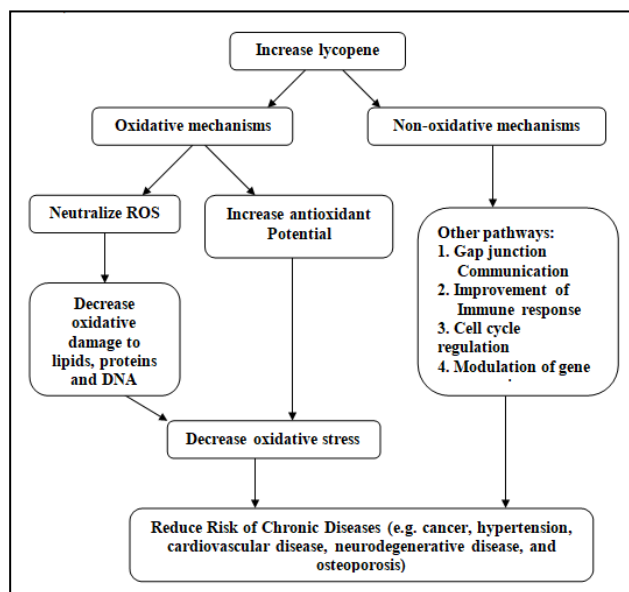


Figure 3: General mechanisms of action of lycopene.

In recent studies serum and tissue levels of lycopene were shown to be inversely associated with the risk of breast cancer 54 and prostate cancer, no significant association with other important carotenoids, including β-carotene, was observed.²⁹ Giovannucci recently reviewed 72 epidemiological studies, including ecological, case-control, dietary and blood-specimen-based investigations of tomatoes, tomato based products, lycopene and cancer.³⁰ In 57 studies there was an inverse association between tomato intake or circulating lycopene levels and risk of several types of cancer; in 35 cases the association was statistically significant.³⁰

Antioxidative activities

Oxidative stress is recognized as one of the major contributors of increased risk of cancer, and in chemical assays, lycopene is the most potent antioxidant among various common carotenoids.³¹ The antioxidant activity of carotenoids in multilamellar liposomes has been assayed by inhibition of formation of thiobarbituric acid reactive substances. In this assay, lycopene has been demonstrated to be the most potent antioxidant with the ranking: lycopene > - tocopherol > - carotene > - cryptoxanthin > zeaxanthin - carotene > lutein. Mixtures of carotenoids were more effective than the single compounds. This synergistic effect was most pronounced when lycopene or lutein was present. Biologically, lycopene tends to act as singlet oxygen (¹O₂) and peroxy radical scavenger (LOO•).³² Lycopene degradation may result in color loss when exposed to free radicals or oxidizing agents. This is due to the reaction with free radicals and causes interruption of the polyene chain, in which the conjugated double bond system may either be affected by cleavage or addition to one of the double

bonds.¹⁶ The highly conjugated double bonds of lycopene play the most important role in energy transfer reactions.³³ Lycopene has quenching ability towards singlet oxygen (¹O₂), based on the excited energy state, and is greatly related to the length of the conjugated double bond system. Among the carotenoids, lycopene is the most efficient singlet oxygen quencher.³³ The mechanism of action for lycopene towards the reactive species can be predicted through three possible mechanisms:

- Adduct formation,
- Electron transfer to the radical and
- Allylic hydrogen abstraction, and is also shown in Figure 4.³³

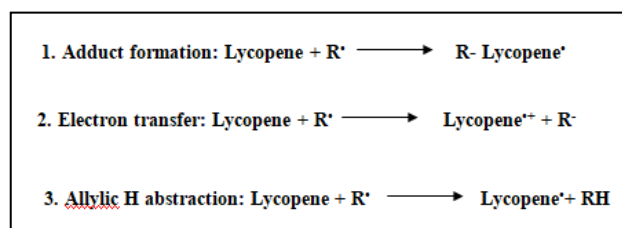


Figure 4: Three possible reactions of lycopene with radical species (R•).

Hypocholesterolemic effects

Maintenance of cholesterol homeostasis is vital for healthy status and is achieved through a regulatory network consisting of genes involved in cholesterol synthesis, absorption, metabolism and elimination. Imbalance of cholesterol level leads to hypercholesterolemia, a predominant risk factor for atherosclerosis and associated coronary and cerebrovascular diseases.³⁴ The American Heart Association's recommendations are (no higher than) 200 mg/dl for total cholesterol levels while classifying 'high cholesterol' as at least 240 mg/dl. 'Optimal' high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels are at least 60 mg/dl and no higher than 100mg/dl, respectively. The potential antiatherogenic role of lycopene has been ascribed mainly to its antioxidant capacity, which is related to the prevention of LDL oxidation.³⁵ Recently, a new mechanism involving a regulation of cholesterol metabolism by carotenoids has been evoked.^{34, 36} This seems to be sustained by the observation that lycopene shares similar initial synthetic pathways with cholesterol, which is synthesized in animal but not in plant cells. Moreover, increasing evidence from clinical trials show that lycopene supplementation is effective in reducing LDL cholesterol. The reduction of intracellular cholesterol by lycopene and tomato derivatives has been associated with a decrease in cholesterol synthesis through an inhibition of enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and expression, a modulation of LDL receptor

and enzyme acyl-coenzyme A: cholesterol acyltransferase (ACAT) activity (Figure 5).³⁶

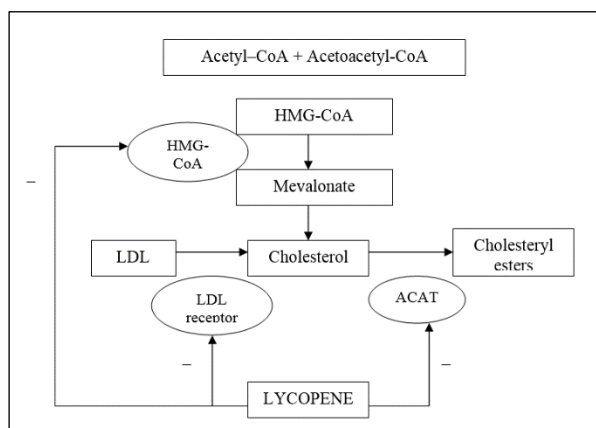


Figure 5: Possible mechanisms implicated in the reduction of intracellular cholesterol by lycopene: decrease in cholesterol synthesis through inhibition of HMG CoA reductase activity and expression, modulation of LDL receptor and inhibition of ACAT activity.

On cardiovascular system

Cardiovascular disease (CVD) is the leading cause of death in the United States and was responsible for more than 652,000 deaths in 2005.³⁷ Increased plasma lycopene levels have been associated with reductions in CVD risk and have also been reported to improve biomarkers associated with CVD.

In the Kuopio Ischemic heart disease risk factor study, lower levels of plasma lycopene were seen in men who had a coronary event compared with men who did not. In addition, a higher concentration of serum lycopene was inversely correlated with a decrease in the mean and maximal intima-mediated thickness of the common carotid artery (CCA-IMT) with low lycopene, resulting in an 18% increase in CCA-IMT.³⁸ The European Multicenter case - control study on antioxidants, myocardial infarction and breast cancer study (EURAMIC Study) reported that a higher lycopene concentration was independently protective against cardiovascular diseases.³⁹ A study by Sesson et al. of 38,445 women found that higher levels of tomato based product intake were associated with a reduced risk of cardiovascular disease and myocardial infarction between the highest and lowest quintiles of intake.⁴⁰ A separate study in Finnish men (n = 1028) found an inverse association between serum lycopene concentrations and common carotid artery intima-media thickness, a measure of early atherosclerosis.⁴¹

Antidiabetic activity

Lycopene is closely related to various metabolic complications, especially diabetes. Serum lycopene is

inversely associated with type - 2 diabetes and impaired glucose metabolism. Oxidative stress has been found responsible for pathogenesis of diabetes mellitus and in the development of its complications.⁴² Increase in oxidative stress due to free radicals cause pancreatic beta cell dysfunction and disturb the action of insulin at the peripheral tissue.⁴³ In addition, diabetic patient's present increased polyunsaturated fatty acid peroxidation, which leads to the generation of chain reactions, which contributes to, increased cardiovascular risk. The intake of natural antioxidants from fruits and vegetables like tomato decreases the morbidity and mortality of these patients.⁴⁴

Anti-aging activity

Lycopene level in blood is found to be decreased during aging process. Older individuals show statistically lower lycopene concentration values in blood as compared to younger matching individuals with similar ethnic and dietary background.⁴⁵ During aging process gastrointestinal absorption of carotenoids is decreased due to age related gastric disorders like acute and chronic gastritis, abnormal gastric acid secretion as well as deviations in intestinal enzyme spectrum.⁴⁶ In addition to that an age-related change in the intestinal microbiota, which regulates bioavailability of carotenoids and polyphenols in the large intestine, is responsible for depleted level of lycopene level in old age.⁴⁷ Lycopene has inherent ability to reduce free radicals which is beneficial in several diseased conditions in old age. The impairment in memory in old age can be minimized by regular use of lycopene containing product. The treatment of lycopene using 3-nitropropionic acid-induced rats has significantly improved the memory and restored glutathione system functioning.⁴⁸

CONCLUSION

Lycopene is a pigment responsible for red color of tomato and some fruits like watermelon, pink grape fruit, papaya and guava. Lycopene is one of the most potent antioxidant and now it is established that this property is responsible for disease prevention. The beneficial effects of fruits and vegetables rich in antioxidant in health are now clear and this has generated interest in lycopene which has high antioxidant property. Several epidemiological researches have shown the beneficial effects of lycopene in prevention of cardiovascular disease and prostate cancer and many other chronic degenerative diseases. Still the role of lycopene in human beings is questionable. Though many studies support the role of lycopene in animals but the strong evidences supporting in vivo response in humans are still lacking. So, extensive studies are required which can explain the effects of lycopene in human health. On the other hand however, many researches advocate the role of lycopene rich foods in preventing degenerative diseases, it is not clear whether lycopene alone or complex interactions among multiple components are responsible for these

actions. Some biological effects may due to the lycopene isomers, its metabolites or numerous other potentially beneficial compounds present in tomatoes but there is lack of information. More research is clearly needed to identify and characterize additional lycopene metabolites and their biological activities, which will potentially provide invaluable insights into the mechanisms underlying the effects of lycopene in humans.

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