3 Lycopene
Food Sources, Properties, and Effects on Human Health

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3.1 COMPOUND CATEGORY AND MOLECULAR CHARACTERISTICS

Dozens of studies have examined the relationship between fruit and vegetable intake and cancers, cardiovascular disease, and all-cause mortality. The Dietary Guidelines for Americans recommends that half of one’s plates should be fruits and vegetables, and to consume a variety of different types. There are numerous compounds in fruits and vegetables that could individually or synergistically contribute to improvements in human health, of which carotenoids are one. Carotenoids are a class of plant pigments that contribute to the coloring of many fruits and vegetables. For example, lycopene (Figure 3.1) imparts the red color found in tomatoes. Lycopene is one of nearly 700 carotenoids reported in nature, though only 40–50 carotenoids are commonly found in the human diet, with fewer detectable in human blood plasma. Carotenoids are derived from isoprene assembled head to tail, and often contain a series of conjugated double bonds, imparting yellow, orange, and red colors (though there are also some colorless carotenoids).

Lycopene ($C_{40}H_{56}$) is a non-provitamin A lipophilic phytochemical. The deep red crystalline pigment was first isolated from Tamus communis (black bryony) in 1873, though at the time, the chemical identity of this purified compound was not known. Subsequently, in 1875, a crude mixture containing lycopene was obtained from tomatoes and this pigment was termed “solanorubine.” In 1903, the term lycopene was coined, differentiating it from “carotenes” from carrots because of its unique absorption spectrum.
In the Western diet, lycopene is the most consumed carotenoid as well as the most abundant human plasma. It is estimated that approximately 80% of dietary lycopene comes from tomatoes. As a result, it can be readily detected in a variety of biological tissues. Continued study of carotenoids, and more specifically lycopene, has contributed to our understanding of their potential role in human health. However, it is important to note that many studies (both observational and experimental) often conflate lycopene intake with tomato consumption (given that lycopene consumed overwhelmingly comes from tomato products). The health benefits associated with tomato consumption have been assumed to be due to the presence of lycopene, though this explicit link has not yet been conclusively demonstrated.

### 3.2 Dietary Sources of Lycopene

In the U.S., it is estimated that lycopene contributes ~28% of the total carotenoid intake, and a systematic review estimated lycopene intake to be ~4.5 mg/d. Most lycopene consumed is from tomato products, though watermelon, pink grapefruit, guava, and papaya contain lycopene as well (Table 3.1). Interestingly, because a variety of food and host-dependent factors affect lycopene absorption, lycopene intake and plasma lycopene levels are often not well correlated, challenging the interpretation of both observational and interventional studies. Despite lycopene existing predominantly in plants and food in the all-trans configuration, cis configurations are equally prevalent or predominant in blood and tissues of animals and humans consuming lycopene (Figure 3.1). This has led to questions about the occurrence and effects of isomerization of lycopene in vivo.
Changes in tomato color occur as chlorophylls degrade and carotenoid production increases, as chloroplasts transform into chromoplasts. As a result, lycopene content is highly dependent on fruit ripeness. Given the phenotypic and genetic diversity that exists within tomatoes, lycopene concentration can vary from nearly absent in yellow flesh mutants, to high pigment and dark green mutants, which can increase lycopene by more than threefold from traditional elite cultivars. Orange-colored fruits with the tangerine mutation accumulate less lycopene than red fruit, though this lycopene is more bioavailable. According to the USDA Standard Reference 28, raw, ripe tomatoes contain on average 2.57 mg/100 g fruit, though reports in the literature can range considerably, from 0.72–20 mg/100 g. This challenges estimations of lycopene intake given the larger variability of lycopene content among tomato fruits. Lycopene is also commonly available in purified supplement form or as tomato extracts, though the effects of consuming these supplements on disease risk are not well understood.

### 3.3 EFFECTS OF FOOD PROCESSING ON LYCOPENE CONTENT AND PROFILE

Over 75% of tomatoes in the United States are consumed in the form of processed products, and, as a result, the effects of thermal processing on carotenoid profiles in red tomatoes have been extensively studied. Lycopene from tomato products is relatively stable to moderate heat processing, especially in the absence of fat. Extensive heat processing can cause degradation, though these conditions are not often used in traditional food processing. It has been shown that lycopene is more stable in a tomato matrix, compared to isolated, purified, or in solvents. Lycopene is stored in tomatoes as crystalline bodies in chromoplasts, relatively resistant to solubilization (a prerequisite for degradation) in the aqueous milieu of the fruit, with cell walls providing an additional barrier. When these protective factors are removed, lycopene is more prone to degradation and isomerization. This is observed in tangerine tomatoes where cis-lycopene is stored in lipid-dissolved droplets called plastoglobules and lycopene is labile to thermal degradation. The effect of fat addition to tomatoes on lycopene isomerization has yielded mixed results. The addition of 5% or 15% olive oil has been shown not to affect the lycopene isomer profile, while tomato juice heated in an oven at 180 °C with 10% safflower oil showed significant isomerization. Others have demonstrated that tomato dissolved in water underwent less isomerization compared to when dissolved in oil olive when subjected to 3 hours of heating at 75 °C.
Heating of tomato products can increase the bioavailability of lycopene.²²,²⁷ Lycopene from tomato paste has been demonstrated as more bioavailable than the same dose given from fresh tomatoes (though the isomeric profiles were not the same), with a mean area-under-the curve increase (representing bioavailability) of almost fourfold with the tomato paste treatment.²⁷ The reason for this difference is proposed to be due to mechanical disruption of cells and the extraction of lycopene into a lipid-dissolved phase that is available for absorption.²⁷ Additionally, lycopene from heat-processed tomato juice has also been shown to increase plasma lycopene more than that from unprocessed tomato juice with the same lycopene isomer distribution,²⁸ suggesting increased bioavailability of heat-treated tomatoes independent of isomer profile. Lycopene is also more bioavailable from homogenized tomatoes,²⁹ again suggesting that mechanical disruption plays a role in bioaccessibility. Lycopene can be isomerized by heat processing to a sauce enriched in cis-isomers, which also has increased bioavailability over a less processed tomato sauce.²²

### 3.4 BIOAVAILABILITY, BIOLOGICAL DISTRIBUTION, AND METABOLISM OF LYCOPENE

#### 3.4.1 Bioavailability

In order for lycopene to potential impart health benefits, it is presumed that it must be first absorbed. Given that lycopene is a fat-soluble compound existing generally in crystals within food matrices, this requires destruction of cell walls and liberation from the chloroplast/chromoplast where it can be solubilized in mixed micelles and absorbed by the enterocyte, either passively or actively via transporters.³⁰ A generalized schematic of lycopene absorption can be found in Figure 3.2.³¹

![Figure 3.2: Generalized schematic of absorption of lycopene from foods. (Adapted from Yonekura L, Nagao A. Mol Nutr Food Res. 2007;51:107–15.)](image-url)
Typically, the bioavailability of lycopene from a single dose is determined by calculating the percentage of an administered dose that reaches circulation in the blood, often in the triglyceride-rich lipoprotein fraction, mainly composed of chylomicrons. This triglyceride-rich lipoprotein fraction is often used because it includes newly absorbed lycopene while ignoring lycopene circulating in the plasma as part of LDL or HDL, which can represent a significant fraction in blood given the relatively long half-life of lycopene and its cis isomers. Lycopene varies considerably between individuals in terms of its bioavailability given its dependence on a number of factors. Recent advances in this area have recently been well reviewed by Kopec and Failla, Harrison and Kopec, Moran and others, and Bohn and colleagues.

### 3.4.2 Factors Affecting Bioavailability of Lycopene

The acronym SLAMENGHI has been coined to note the factors that affect bioavailability of carotenoids: Species of carotenoid, molecular Linkage, Amount of carotenoid in the meal, food Matrix, Effectors of absorption/bioconversion, Nutrient status of the host, Genetic factors, Host-related factors, and Interactions. Molecular linkage (often, the presence of fatty acid esters) is not relevant to lycopene, as the lack of hydroxyl groups precludes ester formation. Extensive reviews exist on this topic; thus, only a summary will be covered here. A recent and comprehensive summary of the intrinsic and extrinsic factors known to affect lycopene/carotenoid metabolism has been published by Moran et al.

Lycopene cis isomers have been shown to be more bioavailable than all-trans in a number of studies. This has been hypothesized to be because cis isomers are less likely to crystallize, and, as a result, are more bioaccessible (and thus more bioavailable) and easily incorporated into mixed micelles.

Generally, lycopene (and carotenoid) bioavailability as a fraction of dose decreases as dose increases. When providing lycopene in the form of tomato beverages, only marginally more lycopene is absorbed in a 30-mg dose as compared to a 10-mg dose, and there is almost no significant increase in the amount absorbed from 30 to 120 mg. There is also considerable interindividual variation in lycopene absorption.

In general, carotenoids found in foods are tightly bound within the food matrix, which may result in absorption difficulties and reduced bioavailability. Destruction of cellular structure (often via thermal processing or homogenization) has been demonstrated to increase the bioavailability of lycopene from tomatoes. Lycopene absorption is also affected by how lycopene is stored within the plant, with storage in lipid-dissolved droplets leading to higher bioaccessibility than when stored as crystals. The effects of carotenoid storage in plastids and the resulting impact on bioavailability have been thoroughly reviewed by Schweiggert and Carle.

Because lycopene is lipophilic, its absorption is dependent upon the same processes that enable fat digestion and absorption. This includes solubilization by bile acids and digestive enzymes and incorporation into micelles. The simultaneous presence of dietary fat in the small intestine is recognized as an important factor for the absorption of lycopene. A number of studies have shown that fat is essential for the absorption of carotenoids. Lycopene circulates in blood primarily on LDL, unlike xanthophylls, which are roughly equally distributed on LDL and HDL. Dietary fiber has shown to be a negative effector of carotenoids. The effects of both dietary fat and fiber on lycopene (and carotenoid) absorption have been recently reviewed.

Lycopene is handled by the body in a similar way as dietary lipid. Thus, any disorder, drug, or dietary compound that contributes to lipid malabsorption or that disrupts the micelle-mediated process could potentially reduce the bioavailability of lycopene as well as other carotenoids. Optimal carotenoid absorption occurs if these compounds can be effectively extracted from the food matrix and subsequently incorporated into the lipid phase of the chyme present in the gut. Consequently, patients with cholestasis, who are known to have difficulties with fat absorption, have lower plasma concentrations of lipophilic compounds, including lycopene, as compared to healthy control patients.
There are a number of genetic factors that have been associated with carotenoid and lycopene concentrations in blood. Single nucleotide polymorphisms (SNPs) in a number of genes involved (or hypothesized to be involved) in lycopene uptake and lipid metabolism have been thought to partially explain the large interindividual variation observed in lycopene bioavailability. A list of SNPs known or thought to affect carotenoid absorption or metabolism has recently been compiled, as well as a review on genetic factors involved in bioavailability of tomato carotenoids specifically.

Host-related factors can also affect the absorption of lycopene, and have been recently reviewed. There has been no consistent association between plasma lycopene and age, though often, lower plasma lycopene has been associated with cigarette smoking. Many of these host-related factors are thought to contribute to the large interindividual variation in plasma lycopene levels noted. The interaction of all of these factors together is almost impossible to assess but cannot be ruled out as an effecter of lycopene bioavailability.

### 3.4.3 Biological Distribution of Lycopene

It is often thought that a prerequisite to the action of lycopene in target tissues is the presence of lycopene in those target tissues. It is common to measure lycopene in blood plasma/serum, and the analysis of lycopene in other human tissues is much less common, given the difficulty or impossibility of conducting biopsies. Weighted averages have been calculated by Moran et al. for concentrations of lycopene in serum/plasma and a variety of tissues, including testes, adrenals, liver, adipose, prostate, lung, kidney, colon, heart, skin, thyroid, breast adipose, spleen, and brain when concentrations of lycopene were available in plasma/serum and at least one other tissue. Some additional studies have reported concentrations of lycopene in plasma/serum as related to tissues, including prostate, since 2013. Data correlating carotenoids (including lycopene) in human milk, neonatal plasma, and material plasma has also been collected. By using 13C labeled lycopene, isolated from tomato callus culture grown with 13C-glucose, compartmental modeling has been used to estimate flow rates of lycopene to different tissues and fractional transfer coefficients.

### 3.4.4 Mammalian Lycopene Metabolism

Very little is known regarding the metabolism of lycopene in humans. Humans absorb a portion of lycopene intact; the extent of this absorption is dependent on a number of factors, as has been discussed. Given that lycopene is a non-provitamin A carotenoid, it cannot be cleaved by mammalian enzymes to yield vitamin A. However, it is known that lycopene predominates in foods as the all-trans isomer, while blood plasma and tissues are enriched in various cis-lycopene isomers. This has often been explained as an increase in bioavailability of cis isomers, though it has more recently been shown that in vivo isomerization from trans to cis also occurs. These cis isomers of lycopene could be considered in vivo lycopene metabolites. It has been hypothesized that isomerization is the first step toward degradation of lycopene in mammals.

It has been hypothesized that lycopene could be cleaved oxidatively, in a way similar to vitamin A, to produce a series of products called lycopenoids. There are two mammalian enzymes that cleave carotenoids, β-carotene 15,15'-oxygenase 1 (BCO1) and β-carotene 9,10'-oxygenase 2 (BCO2). BCO1 is known to cleave provitamin A carotenoids to produce retinal, though more recently human recombinant BCO1 expressed in Escherichia coli was shown to cleave lycopene with a similar catalytic efficiency to β-carotene. The products of lycopene cleavage by BCO1 (i.e., acyleretinal, acyleretinyl esters), however, have not been reported in mammalian systems. BCO2 has been demonstrated to eccentrically cleave β-carotene to produce apo-10-carotenal, while not acting on lycopene. Apolycopenoids, however, have been detected in tomato products, as well as in human plasma and mouse tissues, though it is unclear if these products are in fact bona fide metabolites or simply absorbed from the diet. Apolycopenals (aldehyde cleavage products smaller
than lycopene) were not observed\textsuperscript{94} after the feeding of a \textsuperscript{13}C-labelled dose of lycopene.\textsuperscript{14} However, a \textsuperscript{13}C-labelled lycopene 1,2-epoxide was observed at about 2\% of the levels of \textsuperscript{13}C-lycopene,\textsuperscript{94} though this epoxide was also present in the administered dose, so it is unclear whether it is an \textit{in vivo} metabolite or absorbed from the dose.

A recent study aimed to understand the relationship between plasma carotenoids and apocarotenoids after continued consumption of tomato juice.\textsuperscript{95} Apolycopenoids existed in tomato juices at 0.28\% of the levels of lycopene, and despite feeding over 42 mg lycopene per day, lycopenoids were generally absent from blood plasma.\textsuperscript{95} This lends credibility to the idea that aldehyde cleavage products of lycopene are not primary carotenoid metabolites. Since many of the lycopenoids in tomato juice are not known to be produced from mammalian enzymes, it is hypothesized many of these lycopenoids are non-enzymatic, oxidative degradation products of lycopene.

A \sim 6-\mu g dose of 6,6′,7,7′,\textsuperscript{14}C-lycopene was fed to two healthy volunteers and radioactivity tracked over 42 days.\textsuperscript{96} It was found that radiolabeled lycopene reached maximum concentration in plasma at 6 hours and had a half-life of 5 days. Lycopene was isomerized from 92\% \textit{trans} at dosing to 50\% \textit{trans} at 24 hours, demonstrating extensive isomerization. An average of 18\% of radioactivity was detected in urine with 3\% in exhaled breath, suggesting that lycopene is broken down or metabolized to become sufficiently polar/small to be excreted via these pathways.\textsuperscript{96} Together, this leaves a chasm-sized gap in our understanding of what happens \textit{in vivo} to lycopene after consumption that is still left to be filled.

### 3.5 Lycopene and Chronic Diseases

There is widespread interest in lycopene and the role it may play in the health of humans. For this reason, a PubMed or Scopus search of lycopene yields thousands of articles, spanning associations with many different disease states or health measures. In this review, those studies that represent the consensus of the literature are presented, with a focus on meta-analyses of epidemiological studies and controlled intervention trials in humans. The intent is not to dismiss the importance of other pre-clinical data, which is invaluable to understanding the relationship between lycopene and health outcomes, but to summarize the consensus in the field as it relates to human health.

#### 3.5.1 Cancer

Epidemiological studies have correlated higher plasma lycopene levels with decreased risk of development of cancer at various sites. Given the multifactorial nature of cancer as a disease, as well as the long period in which the disease develops, it is challenging to demonstrate experimentally that consumption of a single compound (e.g., lycopene) can decrease risk of disease. However, below, meta-analyses of epidemiological studies, as well as human clinical trial interventions investigating the effect of lycopene (or, more often, tomato) on cancer outcomes are presented.

Interest in the association between lycopene intake and prostate cancer increased with data published from the Health Professionals Follow-Up study suggesting an inverse relationship between tomato/lycopene consumption and prostate cancer risk.\textsuperscript{97,98} Since these initial reports, a number of meta-analyses and systematic reviews have been published investigating the relationship between tomato/lycopene and prostate cancer, and the strength of this relationship.\textsuperscript{99–104} These meta-analyses find a consistent association with increased tomato/lycopene intake and a decreased prevalence of prostate cancer, though the magnitude of this association ranges. There are a handful of intervention human clinical trials designed to glean additional information about the relationship between tomato/lycopene and prostate cancer.\textsuperscript{83,105–109} Many studies report administering a lycopene supplement, when most often this lycopene supplement is a commercially available oleoresin of tomato called Lyc-o-Mato\textsuperscript{®}. This should be kept in mind, as there are many additional phytochemicals in a tomato oleoresin aside from lycopene, which places tomato extracts somewhere between tomato foods and lycopene supplements. Some of these studies have found modulation of markers of growth and differentiation, or prostate-specific antigen, with tomato extracts,\textsuperscript{70,105–107,110–112} while others found
no effect of treatment (though well tolerated).\textsuperscript{108,109,113–115} These results are still promising given the challenges of assessing what a nutritional intervention might do past middle age on a disease that takes years to progress. Investigating a preventative agent in a population where the seeds of disease are likely already planted challenges the interpretation of the current literature.

The impact of lycopene in the context of other cancers is less studied. A few studies suggest that tomato/lycopene supplements can alter markers for colorectal cancer\textsuperscript{16,117} though recent meta-analyses of epidemiological studies have found a lack of an association.\textsuperscript{118} Relationships have been noted between increased lycopene and decreased risk for breast\textsuperscript{119,120} (with some reporting no effect)\textsuperscript{121,122} and gastric cancers,\textsuperscript{123} though a lack of intervention trials limits our understanding of the causal relationship between lycopene and cancers at these sites.

### 3.5.2 Heart Disease

Cardiovascular disease (CVD) is a major cause of death in the Western world. Often, a diet rich in fruits and vegetables is recommended as a prevention measure for development of CVD.\textsuperscript{124–127} There are a number of published reviews on the topic of lycopene and heart health.\textsuperscript{128,129} Additionally, there are meta-analyses of both epidemiological and intervention trials.\textsuperscript{130–133} A comprehensive review on the effect of whole food (tomato) and supplement (lycopene) administration on risk factors associated with cardiovascular disease has been published recently, highlighting intervention trials that assess oxidation of LDLS, oxidative stress and damage, markers of inflammation, endothelial function, blood pressure, and blood lipids,\textsuperscript{130} which is summarized below. A recent systematic review of intervention trials investigating tomato products and lycopene on cardiovascular function evaluates studies that assess the effect of tomatoes/lycopene on blood lipids, blood pressure, and endothelial function.\textsuperscript{132}

Oxidation of LDL is often measured in the context of nutritional interventions because of its suggestive indication of atherogenic activity. A number of intervention trials have investigated the effect of tomato extract, lycopene supplement (beadlets or purified), or tomato products on oxidation of LDLS, some finding a decrease in LDL oxidation,\textsuperscript{134–142} while others found no effect.\textsuperscript{143–151} There is little data about how tomato/lycopene supplementation affects a non-healthy population.\textsuperscript{130} Many studies where lycopene was provided as a supplement provide Lyc-o-Mato\textsuperscript{®}, an oleoresin of tomato; thus, these studies do not represent true, single-compound supplementation with lycopene. Very few studies contained a true lycopene supplement arm.\textsuperscript{152}

### 3.5.3 Inflammation

Inflammation is an adaptive response triggered by noxious stimuli and conditions such as chemical or physical injury.\textsuperscript{153} In addition to activation of immune cells, inflammatory stimuli induce release of various chemical mediators, including cytokines and reactive oxygen species, that promote leukocyte recruitment to areas of injury to eliminate pathogens and/or repair damaged tissue.\textsuperscript{154} This inflammatory process is normally self limiting to prevent extensive damage to the host.\textsuperscript{155} However, in many cases, repeated exposure to harmful stimuli can trigger inappropriate regulation or failure to resolve inflammatory responses that leads to excess tissue damage and disease.

Consumption of a tomato-rich diet has been suggested to decrease systemic inflammation.\textsuperscript{143} A recent study found that adding tomato juice to a usual diet for 2 months could increase adiponectin and decrease MCP-1 (a pro-inflammatory cytokine), while decreasing body weight, BMI, waist circumference, and percent body fat in healthy, normal-weight women.\textsuperscript{156} Lower plasma C-reactive protein (CRP) levels were observed in healthy males who consumed eight servings of carotenoid-rich fruits and vegetables per day for 4 weeks compared to men who consumed only two servings per day.\textsuperscript{157} In healthy subjects, consumption of 500 mL tomato juice/day for 2 weeks resulted in reduced CRP, but did not affect IL-1β or TNF-α.\textsuperscript{158} In a post-prandial feeding study of tomato paste, the rise in LDL oxidation and IL-6 as a result of a high-fat meal were attenuated in the tomato-containing meal compared to the control, but there was no effect on pro-inflammatory cytokines.\textsuperscript{140} Additionally, consumption of a beverage
containing a tomato extract of 5.7 mg lycopene, 3.7 mg phytoene, and 2.7 mg phytofluene for 26 days resulted in 34% lower TNF-α compared to the placebo group, suggesting that even with low levels of inflammation, a dietary intervention with tomatoes can affect cytokine levels.\textsuperscript{160} A summary of studies investigating the effects of tomato/lycopene on markers of inflammation has been compiled by Burton-Freeman and Sesso.\textsuperscript{130} Often, studies measured multiple biomarkers of inflammation and observed effects on some but not all of these indices.\textsuperscript{139,140,143,145,156,158,160–164} Others found no effect of intervention.\textsuperscript{137,152,165–167}

### 3.5.4 Skin and UV-Induced Sun Sensitivity

Carotenoids function as accessory pigments in plants, helping quench free radicals\textsuperscript{168} and dissipate excess energy produced during the energy-intensive process of photosynthesis. Because of this function \textit{in planta}, it has been postulated that carotenoids and lycopene may function via a similar mechanism in humans (although this has not been explicitly demonstrated).

β-carotene was studied in the 1970s for its ability to reduce the photosensitivity response in patients that had erythropoietic protoporphyria (EPP). Those with this debilitating disease accumulate photosensitizing porphyrins in blood after exposure to the sun of as little to 10–20 minutes, causing burning and extreme redness and swelling.\textsuperscript{169} It has been shown that megadoses of β-carotene, up to 300 mg/day, can lessen this response.\textsuperscript{170–172} This ability of β-carotene to reduce this photosensitivity response made researchers question whether this idea could be exploited to reduce sunburn\textsuperscript{173} or prevent development of skin cancer\textsuperscript{174} (using animal models), and has been investigated using lycopene/tomato products, as lycopene accumulates in human skin.\textsuperscript{68,72,77,80,81,175}

Feeding lycopene-rich foods prior to exposure to UV light has resulted in a dampened erythema response, suggesting that something about tomato consumption is altering the skin’s response to this damaging stimulus.\textsuperscript{176–181} This subject has been thoroughly reviewed elsewhere.\textsuperscript{10,159,176}

### 3.6 CONCLUSIONS

Lycopene, the predominant carotenoid in tomatoes; a Western diet; and blood plasma have been the subject of over a century of scientific research. Lycopene is absorbed and distributed among various tissues in humans, where it can exist for some time. There is a body of evidence suggesting that tomato consumption is beneficial for health. However, the exact function that lycopene plays is still an active area of research. Additional research is needed to further understand the specific role that lycopene may play in imparting health benefits to humans.

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### REFERENCES


