The Functions of Tomato Lycopene and Its Role in Human Health

by Joseph Levy, PhD and Yoav Sharoni, PhD

Introduction

Carotenoids, compounds found in fruits and vegetables, benefit human health by playing an important role in cell function. The dietary necessity of the carotenoid beta-carotene, the precursor of vitamin A, has been recognized for many decades. More recently, lycopene has attracted substantial interest among carotenoid and medical researchers. Lycopene is the red carotenoid found predominantly in tomatoes and in a few other fruits and vegetables. Claims have been made that lycopene may be beneficial in diseases such as cancer and coronary heart disease as well as other chronic conditions. These claims have been studied extensively, through epidemiological studies, biochemical investigations of lycopene's properties, and thorough examination of lycopene's bioavailability from tomato-based diets. This article summarizes the current state of knowledge of the properties of lycopene, its possible role in human health, and areas for future lycopene research.
Lycopene's function in the human body

Although not considered an essential nutrient, research has shown that lycopene may have various benefits for human health. As a major carotenoid in human blood, lycopene protects against oxidative damage to lipids, proteins, and DNA. Lycopene is a potent quencher of singlet oxygen (a reactive form of oxygen), which suggests that it may have comparatively stronger antioxidant properties than other major plasma carotenoids. Lycopene has been found to be a potent and specific inhibitor of cancer cell proliferation, which is regulated by an elaborated cellular process called "cell cycle." Rapid and uncontrolled cell division is a hallmark of cancer cell metabolism; lycopene's activity in retarding cell cycle progression may explain its demonstrated activity in retarding the spread of certain types of cancer. Lycopene may prevent malignant transformation (the cellular process which describes the transformation of a normal cell into a cancer cell). Contact inhibition is one of the mechanisms that controls excessive cell division. By this mechanism, a cell, in crowded surroundings, will stop multiplying. Special structures in the cell membrane, termed a "gap-junction," function as communication channels between cells. Normal cells are both contact-inhibited and have a functional gap-junction whereas most tumor cells exhibit fewer of these structures. Lycopene was found to induce the formation of the protein connexin 43, one of the major building blocks of these channels, and thereby to restore gap junctions. Lycopene induces Phase II enzymes which help to eliminate carcinogens and toxins from the body. The change of the levels of so many regulatory proteins is related to lycopene's ability to modulate various transcription factors which are key players in the process of new cellular protein synthesis.

Structure, intake absorption, and transport

Lycopene is defined chemically as an acyclic carotene with 11 conjugated double bonds, normally in the all-trans configuration (Fig. 1). The double bonds are subject to isomerization, and various cis isomers (mainly 5, 9, 13, or 15) are found in plants and also in blood plasma. Since the human body is unable to synthesize carotenoids from endogenously produced biochemicals, the body is totally dependent on dietary sourced (exogenous) carotenoids. In general, tomato fruit and tomato-based food products provide at least 85% of dietary lycopene in humans. The remaining 15% are usually obtained from watermelon, pink grapefruit, guava, and papaya—all fruits that are dietary sources of lycopene, although at much lower levels than tomatoes (Table 1).

Tomato juice, tomato soup, ketchup, pizza, and spaghetti sauce are the major contributing tomato products in the diet. Uptake of carotenoids from the diet has been studied for many years. The bioavailability of dietary lycopene appears to be dependent upon several factors. It is absorbed better from lipid-rich diets and from cooked, rather than raw foods. Once ingested, lycopene appears in plasma, initially in the chylomicrons (microscopic emulsified fat particles found in the blood serum and lymph that result from fat digestion) and VLDL (very low-density lipoprotein) fractions and later in LDL (low-density lipoproteins, the so-called "bad" cholesterol) and HDL (high-density lipoproteins, often called "good" cholesterol). The highest levels are found in LDL. Serum concentrations vary markedly from about 20 to 500 mcg/liter of serum with large interpersonal variations. Several lines of evidence suggest that oxidatively modified LDL is damaging to the arterial wall, and that atherosclerosis can be attenuated by natural antioxidants. As reported by Fuhman et al., tomato lycopene, alone or in combination with other natural antioxidants, inhibits LDL oxidation. Moreover, the same group reported that dietary supplementation of tomato's lycopene (60 mg/day) when administered to 6 males for a 3-month period resulted in a significant reduction in their plasma LDL cholesterol. This was in agreement with their in vitro results showing that lycopene suppresses cholesterol synthesis and augments LDL receptor activity in macrophages.
Lycopene is found in most human tissues but is not accumulated uniformly. There is preferential accumulation of lycopene, particularly in the adrenals and testes. The confirmed ability to increase lycopene levels in tissues is one prerequisite for using it as a dietary supplement to improve health. Indeed, it has recently been reported that supplementation of tomato lycopene oleoresin in volunteers undergoing elective surgery produced a significant increase in carotenoids in plasma, skin, and adipose tissues. Little is known about the metabolism or degradation of lycopene in mammals. A number of oxygenated metabolites have been found in plasma and tissues, but more studies are needed in order to estimate their physiological roles, if any.

Clinical research demonstrates that lycopene is absorbed more readily from heat processed tomato products than from uncooked sources and absorption is improved by the presence of oil.

**Lycopene benefits from synergistic relationship with other micronutrients**

When reviewing data related to the chemoprevention of various diseases, it becomes evident that the use of a single carotenoid, or any other micronutrient which has been successful in in vitro and animal models, does not prove as favorable in human intervention studies. That is, there is no magic bullet. In fact, accumulating evidence suggests that a concerted, synergistic action of various micronutrients is more likely to be the basis of the disease-prevention activity of a diet rich in vegetables and fruit. Indeed, the sources of lycopene used in most of the human studies reviewed here were either prepared tomato products or tomato extracts containing lycopene and other tomato micronutrients and carotenoids in various proportions. Pure lycopene has not been tested as a single agent in human prevention studies. On the other hand, many studies showing the beneficial effect of lycopene in alleviating chronic conditions have been conducted in which the subjects were provided with tomato-based foods, or tomato extracts, but not with the pure compound. For example, the oleoresin preparation used in many of these studies also contained other tomato carotenoids such as phytoene, phytofluene, and beta-carotene (Fig 1). A critical view of these studies might question whether compounds other than lycopene in tomato may be responsible for the benefit; however, in vitro studies support synergistic action of the tomato carotenoids and other antioxidants present in tomato.

This approach was tested in a recent study that compared the potency of freeze-dried whole tomatoes (tomato powder) or pure lycopene in a rat model of prostate cancer. Rats were treated with the carcinogen NMU (N-methyl-N-nitrosourea) combined with androgens to stimulate prostate carcinogenesis, and the ability of these two preparations containing lycopene to enhance survival was compared. Mortality with prostate cancer was lower by 25% (P = 0.09) for rats fed the tomato powder diet than for rats fed control feed. Prostate cancer mortality of rats fed pure lycopene was similar to that of the control group. The authors concluded that consumption of tomato powder but not pure lycopene inhibited prostate carcinogenesis, suggesting that tomato products contain other compounds, besides lycopene, that modify prostate carcinogenesis. In an accompanying editorial, Gann et al. note that this study contributes to the debate about whether cancer prevention is best

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**Table 1: Lycopene content of common foods**

<table>
<thead>
<tr>
<th>Food Type</th>
<th>Amount mg per 100 gr.</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guava Fresh, pink</td>
<td>5.4</td>
<td>7</td>
</tr>
<tr>
<td>Tomatoes Fresh, red</td>
<td>3.1-7.7</td>
<td>8</td>
</tr>
<tr>
<td>Tomato Juice</td>
<td>7.83</td>
<td>8</td>
</tr>
<tr>
<td>Tomato Paste</td>
<td>30.07</td>
<td>8</td>
</tr>
<tr>
<td>Grapefruit Fresh, pink</td>
<td>3.36</td>
<td>8</td>
</tr>
<tr>
<td>Watermelon Fresh, red</td>
<td>4.1</td>
<td>7</td>
</tr>
<tr>
<td>Ketchup</td>
<td>16.6</td>
<td>7</td>
</tr>
<tr>
<td>Pizza sauce</td>
<td>32.9</td>
<td>8</td>
</tr>
<tr>
<td>Spaghetti sauce</td>
<td>17.5</td>
<td>9</td>
</tr>
<tr>
<td>Papaya Fresh, red</td>
<td>2.0-5.3</td>
<td>10</td>
</tr>
</tbody>
</table>
achieved with whole foods or with single compounds. They point out that carotenoids and other secondary plant compounds have evolved as sets of interacting compounds, a complexity that limits the usefulness of reductionist approaches seeking to identify single protective compounds. Unfortunately, the ensuing coverage of the results of this study in the media included headlines declaring that lycopene was found to be ineffective in treating prostate cancer, while ignoring the beneficial results from the tomato powder.

**The protective role of lycopene in preventing degenerative diseases**

A comprehensive review of the epidemiological literature on the relation of tomato consumption and cancer was published by Giovannucci. He found that among 72 studies, 57 reported inverse associations between tomato intake or blood lycopene level and the risk of cancer at a defined anatomic site. Thirty-five out of 57 of these inverse associations were statistically significant. None of the cited studies indicated that higher tomato consumption or blood lycopene level significantly increased the risk of cancer at any of the investigated sites. The evidence for a benefit was strongest for cancers of the prostate, lung, and stomach. Data were also suggestive of a benefit for cancers of the pancreas, colon and rectum, esophagus, oral cavity, breast, and cervix. Giovannucci suggests that lycopene may contribute to these beneficial effects of tomato containing foods, but this has not been conclusively proven. In addition, as discussed above, the anticancer properties can also be explained by interactions among multiple components found in tomatoes. Cancer of the prostate continues to be the focus of lycopene research and, following Giovannucci’s comprehensive review, several new studies have appeared in the literature.

In a recently published meta-analysis, Emtian et al. tested the assumption that intake of tomato products reduces the risk of prostate cancer. Researchers reviewed 21 studies involving the daily intake of one serving or more of tomatoes, tomato products, or lycopene supplements. The results show that tomato products may play a role in the prevention of prostate cancer. However, this effect is modest (11% reduction in cancer risk) and restricted to high amounts of tomato intake. Moreover, the preventive effect was slightly stronger for high intakes of cooked tomato products than for high intakes of raw tomatoes, probably due to the bioavailability of lycopene, which is increased with processing, heat, and presence of fat. It was previously reported that there is low correlation between dietary lycopene intake and serum level, probably due to the saturation of absorption at higher lycopene intake levels. Thus, stronger protective effect was observed in studies that directly measured plasma lycopene as compared to those that estimated lycopene intake. The authors concluded that further research is needed to determine the type and quantity of tomato products and their role in preventing prostate cancer.

An ecologic (multi-country statistical) approach has also found that tomatoes reduce the risk of prostate cancer, most likely due to the action of lycopene. High lycopene intake was associated with lower risk for gastric cancer. In an integrated series of studies in Italy, tomato consumption showed a consistent inverse relationship to the risk of digestive tract neoplasm (abnormal new tissue growth, tumor). Two small-scale, preliminary intervention studies on prostate cancer patients were carried out with natural tomato preparations. In one, Chen et al. showed that after dietary intervention, serum and prostate lycopene concentrations were increased and oxidative DNA damage both in leukocytes and in prostate tissue was significantly lower. Furthermore, serum levels of prostate-specific antigen (PSA) decreased after the intervention. In the other study, Kucuk et al. reported that supplement with tomato extract in men with prostate cancer modulates the grade and volume of prostate intraepithelial neoplasia and tumor, the level of serum PSA, and the level of biomarkers of cell growth and differentiation. High lycopene intake was associated with lower risk for breast cancer in women.

**Coronary heart disease**

Coronary heart disease (CHD) is one of the primary causes of death in the Western world. The emphasis of research so far has been on the relationship between serum cholesterol levels and the risk of CHD. More recently, oxidative stress induced by reactive oxygen species (ROS) is also considered to play an important part in the etiology of this disease. Dietary lycopene has been shown in in vitro studies to prevent the formation of oxidized LDL, a key player in the pathogenesis of atherosclerosis and CHD. The source of lycopene used in most of these studies was either tomato food products or tomato-derived lycopene extracts. Both of these sources contain various proportions of other carotenoids in addition to lycopene; therefore, it is not possible to attribute the demonstrated effects solely to lycopene.
The evidence in support of the role of lycopene in the prevention of CHD stems primarily from the epidemiological observations of normal and at-risk populations. The most impressive population-based evidence comes from a multicenter case-control study (the EURAMIC study) in which subjects from 10 European countries were evaluated for a relationship between their antioxidant status and acute myocardial infarctions. After adjusting for a range of dietary variables, only lycopene levels, not beta-carotene levels, were found to be protective. \(^{33}\) These results were also confirmed by another study (the Rotterdam Study). \(^{34}\)

Serum lycopene concentration may play a role in the early stages of atherosclerosis. Increased thickness of intima-media (the innermost lining of a blood vessel, including the middle, muscular layer in the wall of the blood vessel) has been shown to predict coronary events. A low serum lycopene concentration, prevalent in eastern Finland, was associated with an increased thickness of the intima-media. \(^{35,36}\) In Lithuanian and Swedish populations showing diverging mortality rates from CHD, lower blood lycopene levels were found to be associated with increased risk and mortality from CHD. \(^{37}\)

Recently a prospective, nested, case-control study was conducted by Harvard University researchers on 39,876 women. The study showed that higher plasma lycopene concentrations are associated with a lower risk of cardiovascular disease in middle-aged and elderly women. \(^{38}\) Moreover, as noted previously by the same group, \(^{39}\) the possible inverse associations with cardiovascular disease for higher levels of tomato-based products (particularly tomato sauce and pizza), suggest that dietary lycopene or other phytochemicals consumed as oil-based or oil-containing tomato products confer cardiovascular benefits.

**Skin protection**

Oral sun protectants are probably more effective than topical ones, as most sun exposure is incidental to daily living and not related to vacation time when topical sunscreens are commonly used. \(^{40}\) (This hypothesis has not been adequately investigated or confirmed.) Studies are scarce, however, on the protective effect of oral carotenoid supplements against skin responses to sun exposure. The protective effects are thought to be related to the antioxidant properties of the carotenoids. During ultraviolet (UV) irradiation, skin is exposed to photooxidative damage induced by the formation of ROS. Photodamage affects cellular lipids, proteins, and DNA and is considered to be involved in the formation of erythema, premature aging of the skin, photodermatoses, and skin cancer.

Carotenoids, and especially lycopene, are efficient scavengers of ROS. \(^{40}\) Several animal studies and in vitro experiments provided evidence that carotenoids and tocopherols prevent UV light–induced skin lesions and protect against skin cancer. Plasma and skin carotenoid concentrations decrease with UV irradiation; however, it is interesting that lycopene is lost preferentially over other carotenoids. \(^{41}\) Exposure of a small area of the forearm skin to UV light resulted in a reduction in skin lycopene. The same UV dose, however, did not result in significant changes in skin beta-carotene concentration. The authors concluded that when skin is subjected to UV light stress, more skin lycopene is destroyed as compared with beta-carotene, suggesting that lycopene plays a role in mitigating oxidative damage in tissues. However, other interpretations of these results are possible.

In a recent study, \(^{42}\) the efficacy of a mixture of carotenoids containing beta-carotene, lutein, and lycopene was compared to beta-carotene alone for protection from UV induced skin erythema. Caucasian volunteers were tested in a placebo-controlled, parallel study. The intake of either beta-carotene or a mixture of carotenoids similarly increased total carotenoids in skin from week 0 to week 12. No changes in total carotenoids in skin occurred in the control group. The intensity of erythema 24 hours after irradiation was diminished in both groups that received carotenoids and was significantly lower than baseline after 12 weeks of supplementation. Long-term supplementation for 12 weeks with 24 mg/day of a carotenoid mix supplying similar amounts of beta-carotene, lutein, and lycopene ameliorates UV-induced erythema in humans. The superior protection with mixtures may be due to different absorption wavelengths of the various compounds, leading to a greater absorption potential of the broader range of...
wavelengths. In another study, the same research group demonstrated that supplementation with tomato, a natural source for lycopene and other carotenoids (see Fig. 1), protects against UV-induced skin erythema in humans.45

**Mechanism of action**

**a. Antioxidant Activity**

Oxidative stress is recognized as one of the major contributors to the increased risk of cardiovascular disease and cancer. Among the common carotenoids lycopene stands as the most potent antioxidant as demonstrated by in vitro experimental systems. Based on this study the antioxidant potency of carotenoids can be ranked as follows: lycopene > [is greater than] alpha-tocopherol > alpha-carotene > beta-cryptoxanthin > zeaxanthin > beta-carotene > lutein. Mixtures of carotenoids were more effective than the single compounds. This synergistic effect was most pronounced when lycopene or lutein was present. The superior protection of mixtures may be related to the specific positioning of different carotenoids in cell membranes.

Several studies of tomato consumption demonstrate the antioxidant properties in humans. For example, recently it was found that daily consumption of a tomato product containing 15 mg lycopene plus other tomato phytonutrients significantly enhanced the protection of lipoproteins from ex vivo oxidative stress. These results indicate that lycopene absorbed from tomato products may act as an in vivo antioxidant.

**b. Inhibition of cancer cell proliferation (cell cycle)**

Lycopene has been found to inhibit proliferation of several types of cancer cells, including those of breast, prostate, lung, and endometrium. The inhibitory effects of lycopene on mammary and prostate cancer cell growth were not accompanied by apoptotic (programmed) or necrotic (resulting from injury or disease) cell death, a mechanism related to the action of some drugs but not to micronutrients frequently consumed in the human diet. This effect was accompanied by inhibition of cell cycle progression from the G0/G1 to the S phase as measured by flow cytometry. The inhibition of cell proliferation correlated with a decrease in cyclin D1 protein levels which is a key regulator of this process. It is well documented that growth factors affect the cell cycle apparatus (primarily during G1 phase) and that the main components acting as growth factor sensors are the D-type cyclins. Moreover, cyclin D1 is known to act as an oncogene (a gene whose dysregulation causes normal cells to become cancerous) and is found to be over-expressed in many breast cancer cell lines as well as in primary tumors. Thus, the decrease in cellular cyclin D1 level by lycopene provides a mechanistic explanation for the anticancer activity of the carotenoid.

**c. Interference with growth factors stimulation of cancer cell proliferation**

The growth stimulation of mammary cancer cells by insulin-like growth factor 1 (IGF-1) was markedly reduced by physiological concentrations of lycopene in experimental in vitro studies. The significance of this finding for cancer prevention is related to independent epidemiological findings that elevated IGF-1 levels increase lifetime risks of breast and prostate cancer. If lycopene interference with IGF-1 stimulation of tumor cell growth is confirmed in clinical studies, this would provide a strong rationale for recommending increased intake of lycopene, particularly via tomato-based food products, for cancer prevention.

**d. Cancer prevention by inducing phase II enzymes**

Induction of phase II enzymes, which conjugate reactive electrophiles (chemicals that are attracted to electrons or tend to accept electrons from other chemicals) and act as indirect antioxidants, appears to be an effective means for achieving protection against a variety of carcinogens in animals and humans. Bhuwaneswari et al. associated the chemopreventive (cancer-preventive) effect of lycopene on the incidence of DMBA-induced hamster buccal (cheek, mouth) pouch tumors with a simultaneous rise in the level of reduced glutathione, enzymes of the glutathione redox cycle, and glutathione S-transferase (GST) in the buccal pouch mucosa. (Note: DMBA is a 9,10-dimethylbenz-a-anthracene, a potent tumor-initiating compound.) These results suggest that the lycopene-induced increase in the levels of GSH and the phase II enzyme GST inactivates carcinogens by forming conjugates (chemicals formed by two or more compounds), products that are less toxic and readily excreted.

**e. Regulation of transcription**

Transcription is the process whereby genetic information is carried from the DNA molecule via the RNA molecule acting as a messenger. This biochemical route leads to the formation of new proteins by the process called translation. As discussed above, lycopene modulates the basic mechanisms of cell proliferation, growth factor signaling, and gap junctional intercellular communication. Additionally, lycopene produces changes in the expression of many proteins participating in these processes, e.g., connexins, cyclins, and phase II enzymes. Therefore, the question that arises is “By what mechanisms does lycopene affect so many diverse cellular pathways?” The changes in the expression of multiple proteins suggest that the initial effect of lycopene involves modulation of transcription; this process is reviewed by Sharoni et al. in a recent publication. This may be due to either direct interaction of the carotenoid molecules or their derivatives with transcription factors (e.g., with ligand-activated nuclear receptors) or indirect modification of transcriptional activity (e.g., via changes in status of cellular redox, which affects redox-sensitive transcription systems).

**Safety of lycopene**

The safety issue for carotenoids attracted much attention after the publication of the beta-carotene supplementation trials, which yielded negative results. It is interesting that in those studies an increased risk for lung cancer was related to a 12- and 16-fold increase in beta-carotene plasma levels due to supplementation (the CARET and ATBC studies, respectively). In these studies beta-carotene plasma levels increased from 0.32 μM before supplementation up to 3.9 and 5.9 μM, respectively. (Note: One microMolar [μM] denotes a concentration of 1 x 10^6 gram-molecular weight of solute per liter of solution.) In a third study, which showed no effect for beta-carotene supplementation (the Physicians’ Health Study), only a 5-fold increase in the carotenoid serum level was achieved. Interestingly, the only study with positive results after supplementation with beta-carotene was achieved in Linxian, a Chinese community with very low carotenoid levels (0.11 μM) before the intervention. Although supplementation caused an 11-fold increase in beta-carotene level, the final
concentration of beta-carotene reached was a relatively low 1.5 μM. All these studies used synthetic beta-carotene. Thus, keeping plasma levels of carotenoids in the upper range of physiological level, but not higher, may be a good safety guide. Interestingly, reviewing many studies which measured serum levels of beta-carotene and lycopene after supplementation suggests that beta-carotene serum levels are significantly higher than those found for lycopene. Serum levels reached for beta-carotene are around 3 μM and may exceed 5 μM after supplementation; on the other hand lycopene levels above 1.2 μM are rarely seen even after long-term application. Moreover, the serum level achieved for lycopene was not directly correlated to the amount of the supplemented carotenoid. For example, supplementation as high as 75 mg/day did not increase lycopene serum levels more than 1 μM. In conclusion, by some unknown mechanism, lycopene plasma levels after supplementation remain relatively low, which may provide a safety valve.

Several safety studies on formulated synthetic lycopene preparation were performed in rats and rabbits. The results of these studies demonstrated the absence of any significant toxicological effects of the tested materials in animals. However, the Scientific Committee on Food of the European Commission found these synthetic preparations to be unacceptable for use as food because of their high sensitivity to oxygen and light, which form degradation products with mutagenic activity. A thorough safety review by an independent panel of toxicologists has resulted in a GRAS (generally recognized as safe) self-affirmation for Lyc-O-Mato® (LycORed, Beer-Sheva, Israel), a branded tomato extract that has been the subject for several of the studies evaluating the effects of tomato products in dietary supplement form on a variety of disease parameters.

Concluding remarks

The scientific research to date has demonstrated an array of health benefits clearly associated with tomato products in the diet. A look at the synergy between carotenoids has demonstrated that neither synthetic lycopene nor tomato lycopene alone will act as a magic bullet. Effectiveness and safety are married together in the whole tomato. Health benefits are derived from the addition of tomato products to the diet, particularly cooked tomato products containing oil, or from supplements of tomato extract suspended in oil. The natural tomato oil increases the bioavailability of the tomato phytonutrients. For maximum benefit, dietary supplement customers who have opted for a nutritional approach should consider products containing a standardized tomato extract that supplies many of the active phytonutrients in tomato.

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