Lycopene: Antioxidant and Biological Effects and its Bioavailability in the Human

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Abstract. **Lycopene is a non-provitamin A carotenoid present in human blood and tissues. The major dietary sources of lycopene for the human are tomatoes and tomato products. Protective effects of a lycopene-rich diet on some types of cancer were suggested on the basis of epidemiological studies. There are several biochemical mechanisms potentially underlying the protective effects of lycopene. These include antioxidant activity such as the quenching of singlet oxygen and the scavenging of peroxyl radicals, induction of cell-cell communication, and growth control. *In vitro* and *in vivo* studies support this assumption. Dietary lycopene is absorbed and distributed in the human organism, but its bioavailability depends on various factors such as food processing or coingestion of fat. Little is known about the metabolism of lycopene. Potentially biologically active oxidation products of lycopene have been identified in human plasma.** [P.S.E.B.M. 1998, Vol 218]

Lycopene is the major carotenoid in the tomato and is responsible for the red color of the fruit. It is found in relatively high concentrations in all tomato products, the major source of lycopene for the human. Tomatoes contain about 30 mg lycopene/kg raw fruit; even higher amounts are found in some tomato products (e.g., up to 150 mg lycopene/l in tomato juice or about 100 mg lycopene/kg in tomato ketchup.) Other sources of lycopene are watermelon, guava, rosehips, and pink grapefruit (1).

Lycopene is an acyclic carotenoid that contains 11 conjugated double bonds arranged linearly in the *all-trans* form. It belongs to the subgroup of carotenes that consist only of hydrogen and carbon atoms. The blood level of lycopene is in the same range as that of β-carotene. But in contrast to β-carotene, lycopene exhibits no provitamin A activity. However, it has been suggested that an increased consumption of lycopene has beneficial health effects that might be related to its pronounced antioxidant properties, influences on the regulation of cell-cell communication, and cell growth or to yet other properties. Recent reviews on the biological properties of lycopene are available (2, 3).

Antioxidant Activities of Lycopene

Most carotenoids are efficient antioxidants, quenching singlet oxygen ($^1O_2$), and trapping peroxyl radicals (4). $^1O_2$ and peroxyl radicals are reactive oxygen species formed endogenously. Both species may react with biologically important macromolecules, such as DNA, proteins, or lipids, impairing their physiological functions (5, 6). Such processes are discussed as initial events in the pathogenesis of several diseases including cancer, cardiovascular diseases, or age-related macular degeneration.

Carotenoids inactivate singlet oxygen *via* physical or chemical quenching. The efficacy of physical quenching exceeds that of chemical quenching by far (>99.9%) and involves the transfer of excitation energy from $^1O_2$ to the carotenoid, resulting in ground state oxygen and excited triplet state carotenoid. The energy is dissipated between the excited carotenoid and the surrounding solvent to yield a nonreactive ground state carotenoid and thermal energy. In the process of physical quenching the carotenoid remains intact, so that it can undergo further cycles of singlet oxygen quenching. The rate constants for the reaction of carotenoids with singlet oxygen are in the range of 10^9 M^{-1} sec^{-1} (7).

The quenching activity of carotenoids is closely related to the number of conjugated double bonds. Lycopene is the most efficient singlet oxygen quencher of the natural carotenoids exhibiting higher quenching rate constants than other

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C-40 carotenoids (7). It has been suggested that the increased reactivity is related to the presence of the two additional nonconjugated double bonds.

Chemical quenching contributes less than 0.05% to the overall quenching of $^1O_2$ by carotenoids. However, this process, known as photobleaching, is responsible for the final decomposition of carotenoids. Some of the decomposition products formed in the interaction of lycopene with singlet oxygen have recently been identified (8). Irradiation of lycopene in the presence of a photosensitizer led to the formation of 2-methyl-2-hepten-6-one and apo-6′-lycopenal as the major reaction products.

Methylene blue was used as a sensitizer to study the consumption of carotenoids during photooxidation of human plasma and LDL (9). Lycopene and β-carotene were more resistant to photooxidation in blood plasma than lutein and zeaxanthin. Upon exposure of blood plasma to a water-soluble $^1O_2$ generator, the levels of the lipophilic antioxidants lycopene, β-carotene, and α-tocopherol remained unchanged (10). The data suggest that carotenoids contribute to the prevention of lipid peroxidation *via* singlet oxygen quenching.

Carotenoids are efficient scavengers of peroxyl radicals, especially at low oxygen tension (11, 12). The interaction of carotenoids with free radicals has been studied using 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid-diammonium salt (ABTS) as a radical source (13). Lycopene was the most efficient scavenger of the ABTS-radical followed by cryptoxanthin, lutein, zeaxanthin, and β-carotene. Astaxanthin and canthaxanthin showed only minor effects. The radical scavenging effect of lycopene exceeded that of trolox, a water-soluble analog of vitamin E, by a factor of three.

Protective effects of lycopene toward oxidative stress–mediated damage of the skin were suggested following a study on carotenoid levels in human skin upon irradiation with UV light (14). When skin was subjected to UV light stress, more skin lycopene was destroyed than β-carotene. Because carotenoids are consumed in the process of radical quenching, a preferential protective role of lycopene has been suggested.

Biological Effects of Lycopene

Lycopene was shown to exhibit moderate curative effects by increasing the survival rate of X-irradiated mice, and it also increased the resistance of mice toward bacterial infections and the development of ascites tumors (15, 16). Lycopene was found to be superior to β-carotene in suppressing cell proliferation as determined by the thymidine incorporation assay (17). The proliferation of human cancer cells from endometrium (Ishikawa), mammary gland (MCF-7) and lung (NCI-H226) was strongly inhibited by lycopene at μM concentrations of 1–2 μM. In contrast, human fibroblasts were less sensitive.

In vivo studies have shown a tumor-suppressive activity of lycopene. The development of spontaneous mammary tumors in a high-tumor strain of SHN virgin mice was significantly diminished in the group of mice on a diet enriched in lycopene (18). The suppression of tumor incidence was associated with a decrease in mammary gland activity of thymidylate synthetase and diminished serum levels of free fatty acids and prolactin. In a dimethyl benzanthracene (DMBA)–induced mammary tumor model in mice, intraperitoneal injections of lycopene-enriched tomato extracts led to a significantly lower number of tumors and smaller tumor areas in comparison to controls (19). β-Carotene showed no protective effect. The mechanisms underlying these effects of lycopene are not yet known.

Carotenoids are capable of inducing intercellular communication *via* gap junctions, which have been associated with inhibiting proliferation of transformed cells (20, 21). Non-provitamin A carotenoids such as canthaxanthin were also shown to be active (22). The ability of lycopene to increase gap junctional communication is less pronounced (23).

The intake of carotenoids and retinol in relation to the risk of prostate cancer was evaluated based on a food-frequency questionnaire obtained from participants of the Health Professionals Follow-up Study (24). Analyses of the data from 773 prostate cancer cases revealed that an increased lycopene intake was associated with a diminished risk. α- and β-Carotene intake as well as the consumption of food rich in lutein and cryptoxanthin were not associated with a lower prostate cancer risk. The number of servings of lycopene-rich food, such as tomatoes, tomato sauce, and pizza significantly correlated with a lower risk for prostate cancer. However, no correlation was found for tomato juice, potentially due to the lower bioavailability of lycopene from juice.

Bioavailability of Lycopene

Carotenoid intake is usually evaluated on the basis of food frequency questionnaires. In Great Britain the daily consumption of lycopene-rich food was equivalent to a lycopene intake of about 1.1 mg/d (25). In a study from the United States a daily intake of lycopene of about 3.7 mg/d was seen which is in about the same range as β-carotene intake, with each of these contributing about 30% of total carotenoids in the diet (26).

Uptake and distribution of carotenoids in the human organism have been examined (27, 28). In the small intestine, ingested carotenoids including lycopene are incorporated into micelles formed from dietary lipids and bile acids, which facilitate absorption into the intestinal mucosa cell, a process suggested to occur *via* passive transport. The intact carotenoids are incorporated into chylomicrons, which are released into the lymphatic system. In blood plasma, carotenoids appear initially in the chylomicron and VLDL fraction, whereas the levels in other lipoproteins such as LDL and HDL rise at later time points with peak levels at 24–48 hr. The major vehicle of hydrocarbon carotenoids such as lycopene and β-carotene is the LDL fraction.

Regarding absorption of lycopene from dietary sources, surprisingly no increase in lycopene serum levels are observed after the single intake of large amounts of tomato juice (29). After ingestion of 180 g or even 700 g of tomato juice corresponding to a single dose of 12 or 80 mg of lycopene, respectively, no change in serum lycopene levels was observed. However, in subjects ingesting 2–3 cans of tomato juice daily over a period of 4 weeks, the lycopene serum levels increased 3-fold; a doubling of β-carotene serum levels was also detected, although the β-carotene content in the juice was only about 3% that of lycopene (30).

In contrast to unprocessed tomato juice, lycopene levels increased significantly in human serum when processed juice was consumed. Boiling for 1 hr in the presence of 1% corn oil increased the bioavailability of lycopene from tomato juice significantly (29).

Differences in lycopene bioavailability are also observed when raw tomatoes (versus tomato paste) are used as a source (31). After ingestion of fresh tomatoes or tomato paste, both containing 23 mg of lycopene, the lycopene levels in chylomicrons and responses measured as area under the curve (AUC) were compared. Consumption of tomato paste led to 2.5-fold higher lycopene peak levels in chylomicrons as compared to the fresh tomatoes; AUC values were 3.8-fold higher. Possible factors improving lycopene availability from processed tomato products might be the release of the carotenoid by thermally induced rupture of the cell walls or heat-improved extraction of lycopene into the oily phase of the mixture, using corn oil as a vehicle.

Lycopene in Blood and Tissues

The mean plasma levels of lycopene range from 0.22–1.06 nmol/ml (2). Lycopene contributes between 21% and 43% of total carotenoids. In some studies lycopene exceeded the levels of all the other carotenoids. In a Japanese study, including 923 subjects, significantly higher lycopene, β- and α-carotene serum levels were detected for females than for males (32). However, very similar lycopene serum levels for men and women were described in other studies; significantly lower carotenoid levels associated with male gender were only detected for α-carotene (−31%), β-carotene (−35%), and cryptoxanthin (−31%). Lower lycopene levels were found with older age.

Hydroxylated derivatives of lycopene have been detected in human serum (33). Tomatoes and tomato-based products are the major source of these compounds. They contain lycopene 5,6-epoxide, which might be enzymatically or chemically modified in the organism.

Lycopene in human plasma consists of an isomer mixture with the *cis*-isomers contributing about 50% to total lycopene. The most prominent geometrical isomers are *all-trans* and 5-*cis* lycopene (34).

Rather high levels of lycopene and β-carotene were found in liver, adrenals, and testes, whereas other tissues such as lung and kidney contained less (35–37). In the studies from the United States, the lycopene levels exceeded that of β-carotene in almost every tissue except the ovary (35, 36). Higher β-carotene values than lycopene were reported in liver, adrenals, and kidney in a study from Germany; but the lycopene levels in testes exceeded that of β-carotene (37). The lycopene level in skin also was somewhat higher than that of β-carotene, 0.25 and 0.13 nmol/g, respectively (38). Higher values have been reported with lycopene and β-carotene levels of 1.6 and 1.4 nmol/g skin tissue (14). Carotenoid levels were also measured in the prostate gland. Lycopene and β-carotene are the major carotenoids in this tissue with mean levels of about 0.8 and 0.54 nmol/g, respectively (39).

1. Mangels AR, Holden JM, Beecher GR, Forman MR, Lanza E. Carotenoid content of fruits and vegetables: An evaluation of analytical data. J Am Diet Assoc **93:**284–296, 1993.
2. Stahl W, Sies H. Lycopene: A biologically important carotenoid for humans? Arch Biochem Biophys **336:**1–9, 1996.
3. Gerster H. The potential role of lycopene for human health. J Am Coll Nutr **16:**109–126, 1997.
4. Sies H, Stahl W. Vitamins E and C, β-carotene, and other carotenoids as antioxidants. Am J Clin Nutr **62:**1315S–1321S, 1995.
5. Sies H. Biochemistry of oxidative stress. Angewandte Chemie International Edition **25:**1058–1071, 1986.
6. Halliwell B. Cellular stress and protection mechanisms. Biochem Soc Trans **24:**1023–1027, 1996.
7. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch Biochem Biophys **274:**532–538, 1989.
8. Ukai N, Lu Y, Etoh H, Yagi A, Ina K, Oshima S, Ojima F, Sakamoto H, Ishiguro Y. Photosensitized oxygenation of lycopene. Biosci Biotech Biochem **58:**1718–1719, 1994.
9. Ojima F, Sakamoto H, Ishiguro Y, Terao J. Consumption of carotenoids in photosensitized oxidation of human plasma and plasma low-density lipoprotein. Free Radic Biol Med **15:**377–384, 1993.
10. Wagner JR, Motchnik PA, Stocker R, Sies H, Ames BN. The oxidation of blood plasma and low-density lipoprotein components by chemically generated singlet oxygen. J Biol Chem **268:**18502–18506, 1993.
11. Burton GW, Ingold KU. β-Carotene: An unusual type of lipid antioxidant. Science **224:**569–573, 1984.
12. Kennedy TA, Liebler DC. Peroxyl radical scavenging by β-carotene in lipid bilayers. J Biol Chem **267:**4658–4663, 1992.
13. Miller NJ, Sampson J, Candeias LP, Bramley PM, Rice-Evans CA. Antioxidant activities of carotenes and xanthophylls. FEBS Lett **384:**240–242, 1996.
14. Ribaya-Mercado JD, Garmyn M, Gilchrest BA, Russell RM. Skin lycopene is destroyed preferentially over β-carotene during ultraviolet irradiation in humans. J Nutr **125:**1854–1859, 1995.
15. Forssberg A, Lingen C, Ernster L, Lindberg O. Modification of the X-irradiation syndrome by lycopene. Exp Cell Res **16:**7–14, 1959.
16. Lingen C, Ernster L, Lindberg O. The promoting effect of lycopene on the nonspecific resistance of animals. Exp Cell Res **16:**384–393, 1959.
17. Levy J, Bosin E, Feldman B, Giat Y, Miinster A, Danilenko M, Sharoni Y. Lycopene is a more potent inhibitor of human cancer cell proliferation than either α-carotene or β-carotene. Nutr Cancer **24:**257–266, 1995.
18. Nagasawa H, Mitamura T, Sakamoto S, Yamamoto K. Effects of lycopene on spontaneous mammary tumor development in SHN virgin mice. Anticancer Res **15:**1173–1178, 1995.
19. Sharoni Y, Levi J. Anticarcinogenic properties of lycopene. In: Kumpulainen JT, Salonen J, Eds. Natural antioxidants and food quality in atherosclerosis and cancer prevention. Cambridge: The Royal Society of Chemistry, pp 378–385, 1996.

20. Pung A, Rundhaug JE, Yoshizawa CN, Bertram JS. β-Carotene and canthaxanthin inhibit chemically- and physically-induced neoplastic transformation in 10T1/2 cells. Carcinogenesis **9:**1533–1539, 1988.
21. Stahl W, Nicolai S, Briviba K, Hanusch M, Broszeit G, Peters M, Martin H-D, Sies H. Biological activities of natural and synthetic carotenoids: Induction of gap junctional communication and singlet oxygen quenching. Carcinogenesis **18:**89–92, 1997.
22. Hanusch M, Stahl W, Schulz WA, Sies H. Induction of gap junctional communication by 4-oxoretinoic acid generated from its precursor canthaxanthin. Arch Biochem Biophys **317:**423–428, 1995.
23. Zhang L-X, Cooney RV, Bertram JS. Carotenoids enhance gap junctional communication and inhibit lipid peroxidation in C3H/10T1/2 cells: Relationship to their cancer chemopreventive action. Carcinogenesis **12:**2109–2114, 1991.
24. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst **87:**1767–1776, 1995.
25. Scott J, Thurnham DI, Hart DJ, Bingham SH, Day K. The correlation between the intake of lutein, lycopene, and beta-carotene from vegetables and fruits, and plasma concentrations in a group of women aged 50–65 years in the UK. Br J Nutr **75:**409–418, 1996.
26. Forman MR, Lanza E, Yong L-C, Holden JM, Graubard BI, Beecher GR, Melitz M, Brown ED, Smith JC. The correlation between two dietary assessments of carotenoid intake and plasma carotenoid concentrations: Application of a carotenoid food-composition database. Am J Clin Nutr **58:**519–524, 1993.
27. Parker RS. Absorption, metabolism, and transport of carotenoids. FASEB J **10:**542–551, 1996.
28. Erdman JW, Bierer TL, Gugger ET. Absorption and transport of carotenoids. Ann NY Acad Sci **691:**76–85, 1993.
29. Stahl W, Sies H. Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. J Nutr **122:**2161–2166, 1992.
30. Sakamoto H, Mori H, Ojima F, Ishiguro Y, Arimoto S, Imae Y, Nanba T, Ogawa M, Fukuba H. Elevation of serum carotenoids after continual ingestion of tomato juice. J Jpn Soc Nutr Food Sci **47:**93–99, 1994.
31. Gärtner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. Am J Clin Nutr **66:**116–122, 1997.
32. Ito Y, Sasaki R, Minohara M, Otani M, Aoki K. Quantitation of serum carotenoid concentrations in healthy inhabitants by high-performance liquid chromatography. Clin Chim Acta **169:**197–208, 1987.
33. Khachik F, Spangler CJ, Smith JC, Canfield LM, Steck A, Pfander HP. Identification, quantification and relative concentrations of carotenoids and their metabolites in human milk and serum. Anal Chem **69:**1873–1881, 1997.
34. Schierle J, Bretzel W, Bühler I, Faccin N, Hess D, Steiner K, Schüep W. Content and isomeric ratio of lycopene in food and human blood plasma. Food Chemistry **59:**459–465, 1997.
35. Schmitz HH, Poor CL, Wellman RB, Erdman JW. Concentrations of selected carotenoids and vitamin A in human liver, kidney, and lung tissue. J Nutr **121:**1613–1621, 1991.
36. Kaplan LA, Lau JM, Stein EA. Carotenoid composition, concentrations, and relationship in various human organs. Clin Physiol Biochem **8:**1–10, 1990.
37. Stahl W, Schwarz W, Sundquist AR, Sies H. *cis-trans* Isomers of lycopene and β-carotene in human serum and tissues. Arch Biochem Biophys **294:**173–177, 1992.
38. Peng YM, Peng Y-S, Lin Y. A nonsaponification method for the determination of carotenoids, retinoids, and tocopherols in solid human tissues. Cancer Epidemiol Biomarkers Prev **2:**139–144, 1993.
39. Clinton SK, Emenhiser C, Schwartz SJ, Bostwick DG, Williams AW, Moore BJ, Erdman JW. *cis-trans* Lycopene isomers, carotenoids, and retinol in the human prostate. Cancer Epidemiol Biomarkers Prev **5:**823–833, 1996.