

# Tomato lycopene and its role in human health and chronic diseases

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## Abstract

LYCOPENE IS A CAROTENOID THAT IS PRESENT IN TOMATOES, processed tomato products and other fruits. It is one of the most potent antioxidants among dietary carotenoids. Dietary intake of tomatoes and tomato products containing lycopene has been shown to be associated with a decreased risk of chronic diseases, such as cancer and cardiovascular disease. Serum and tissue lycopene levels have been found to be inversely related to the incidence of several types of cancer, including breast cancer and prostate cancer. Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial effects, evidence is accumulating to suggest that other mechanisms may also be involved. 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.

**C**hronic diseases, including cancer and cardiovascular disease, are the main causes of death in the Western world. Along with genetic factors and age, lifestyle and diet are also considered important risk factors.<sup>1,2</sup> About 50% of all cancers have been attributed to diet.<sup>3</sup>

Oxidative stress induced by reactive oxygen species is one of the main foci of recent research related to cancer and cardiovascular disease. Reactive oxygen species are highly reactive oxidant molecules that are generated endogenously through regular metabolic activity, lifestyle activity and diet. They react with cellular components, causing oxidative damage to such critical cellular biomolecules as lipids, proteins and DNA. There is strong evidence that this damage may play a significant role in the causation of several chronic diseases.<sup>4-7</sup>

Antioxidants are protective agents that inactivate reactive oxygen species and therefore significantly delay or prevent oxidative damage. Antioxidants such as superoxide dismutase, catalase and glutathione peroxidase are naturally present within human cells. In addition, antioxidants such as vitamin E, vitamin C, polyphenols and carotenoids are available from food. Current dietary guidelines to combat chronic diseases, including cancer and coronary artery disease, recommend increased intake of plant foods, including fruits and vegetables, which are rich sources of antioxidants.<sup>8,9</sup> The role of dietary antioxidants, including vitamin C, vitamin E, carotenoids and polyphenols, in disease prevention has received much attention in recent years.<sup>10-12</sup> These antioxidants appear to have a wide range of anticancer and antiatherogenic properties.<sup>10-14</sup> These observations may explain the epidemiological data indicating that diets rich in fruits and vegetables are associated with a reduced risk of numerous chronic diseases.<sup>1,15-17</sup>

Another dietary antioxidant thought to be important in the defence against oxidation is lycopene, of which tomatoes are an important dietary source.<sup>18,19</sup> Lycopene is a natural pigment synthesized by plants and microorganisms but not by animals. It is a carotenoid, an acyclic isomer of  $\beta$ -carotene. Lycopene is a highly unsaturated hydrocarbon containing 11 conjugated and 2 unconjugated double bonds. As a polyene it undergoes *cis-trans* isomerization induced by light, thermal energy and chemical reactions (Fig. 1).<sup>20,21</sup> Lycopene from natural plant sources exists predominantly in an all-*trans* configuration, the most thermodynamically stable form.<sup>20,21</sup> In human plasma, lycopene is present as an isomeric mixture, with 50% as *cis* isomers.<sup>22</sup>

Lycopene is one of the most potent antioxidants,<sup>23-26</sup> with a singlet-oxygen-

## Review

## Synthèse

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quenching ability twice as high as that of  $\beta$ -carotene and 10 times higher than that of  $\alpha$ -tocopherol.<sup>26</sup> It is the most predominant carotenoid in human plasma. Its level is affected by several biological and lifestyle factors.<sup>18,27</sup> Owing to their lipophilic nature, lycopene and other carotenoids are found to concentrate in low-density and very-low-density lipoprotein fractions of the serum.<sup>19</sup> Lycopene is also found to concentrate in the adrenal gland, testes, liver and prostate gland, where it is the most prominent carotenoid.<sup>28-31</sup> Table 1 shows the lycopene levels in various human and rat tissues.<sup>28-32</sup> Tissue-specific lycopene distribution may be important in the role of this antioxidant. However, unlike other carotenoids, lycopene levels in serum or tissues do not correlate well with overall intake of fruits and vegetables.<sup>33,34</sup>

## Mechanisms of action

The biological activities of carotenoids such as  $\beta$ -carotene are related in general to their ability to form vitamin A within the body.<sup>19</sup> Since lycopene lacks the  $\beta$ -ionone ring structure, it cannot form vitamin A.<sup>35</sup> Its biological effects in humans have therefore been attributed to mechanisms other than vitamin A. Two major hypotheses have been proposed to explain the anticarcinogenic and an-

tiatherogenic activities of lycopene: nonoxidative and oxidative mechanisms. The proposed mechanisms for the role of lycopene in the prevention of chronic diseases are summarized in Fig. 2.

Among the nonoxidative mechanisms, the anticarcinogenic effects of lycopene have been suggested to be due to regulation of gap-junction communication in mouse embryo fibroblast cells.<sup>36,37</sup> Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb antioncogenes and stop cell division at the  $G_0$ - $G_1$  cell cycle phase.<sup>38</sup> Astorg and colleagues<sup>39</sup> proposed that lycopene-induced modulation of the liver metabolizing enzyme, cytochrome P450 2E1, was the underlying mechanism of protection against carcinogen-induced preneoplastic lesions in the rat liver. Preliminary in vitro evidence also indicates that lycopene reduces cellular proliferation induced by insulin-like growth factors, which are potent mitogens, in various cancer cell lines.<sup>40</sup> Regulation of intrathymic T-cell differentiation (immunomodulation) was suggested to be the mechanism for suppression of mammary tumour growth by lycopene treatments in SHN retired mice.<sup>41,42</sup> Lycopene also has been shown to act as a hypocholesterolemic agent by inhibiting HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase.<sup>43</sup>

Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins and DNA.<sup>44-46</sup> In healthy human subjects, lycopene- or tomato-free diets resulted in loss of lycopene and increased lipid oxidation,<sup>47</sup> whereas dietary supplementation with lycopene

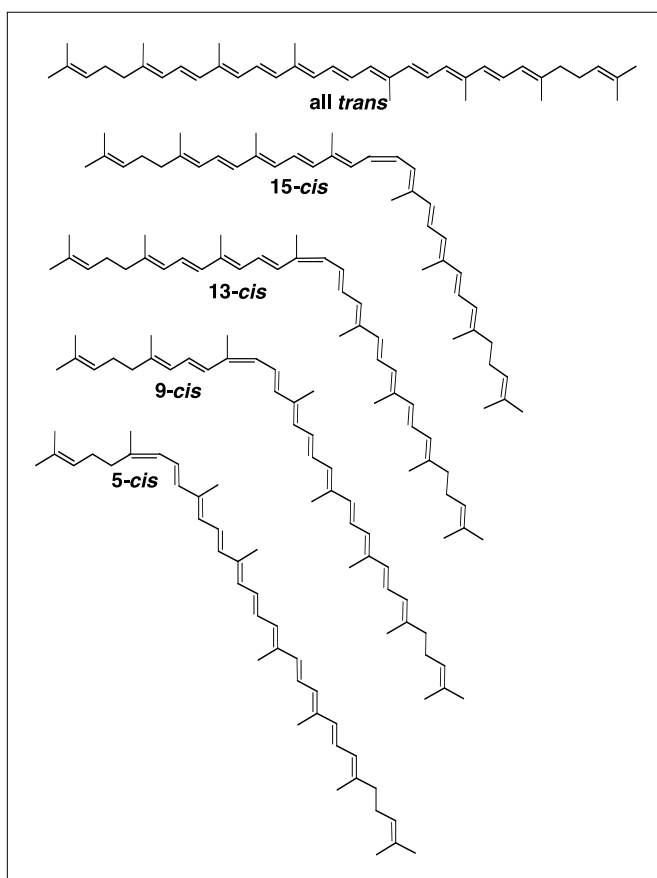


Fig. 1: Structures of *trans* and *cis* isomers of lycopene.

Table 1: Reported mean lycopene levels in human<sup>28-31</sup> and rat<sup>32</sup> tissues\*

Tissue	Mean lycopene level (and SD), nmol/g wet weight	
	Humans	Rats
Testes	4.34-21.36	NA
Spleen	NA	21.21 (2.22)
Adrenal gland	1.90-21.60	NA
Liver	1.28-5.72	20.30 (1.90)
Prostate gland	0.80	0.32 (0.06)
Breast	0.78	NA
Pancreas	0.70	NA
Lung	0.22-0.57	0.115 (0.015)
Heart	NA	0.08 (0.03)
Kidney	0.15-0.62	NA
Colon	0.31	0.046 (0.006)
Skin	0.42	NA
Ovary	0.30	NA
Stomach	0.20	NA
Brain	ND	0.017 (0.006)

Note: SD = standard deviation, NA = not available, ND = not detectable.

\*Fischer 344 male rats were fed the AIN-93M diet supplemented with 10 ppm of lycopene for 2 months (AIN = American Institute of Nutrition).

for 1 week increased serum lycopene levels and reduced endogenous levels of oxidation of lipids, proteins, lipoproteins and DNA.<sup>44,45</sup> Patients with prostate cancer were found to have low levels of lycopene and high levels of oxidation of serum lipids and proteins.<sup>48</sup>

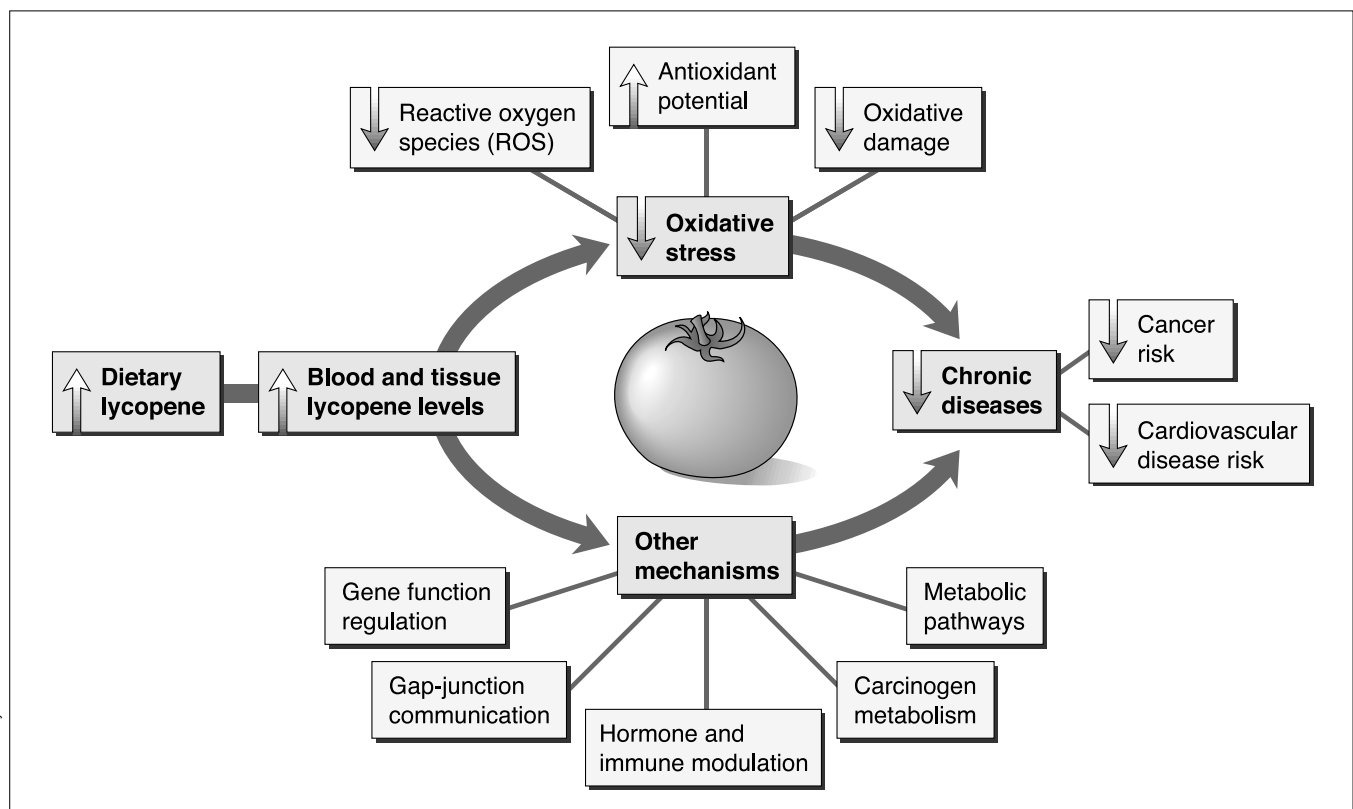
## Epidemiological evidence

### Risk of cancer

The Mediterranean diet, which is rich in vegetables and fruits, including tomatoes, has been suggested to be responsible for the lower cancer rates in that region.<sup>49</sup> Dietary intake of tomatoes and tomato products has been found to be associated with a lower risk of a variety of cancers in several epidemiological studies.<sup>50</sup> A high intake of tomatoes was linked to protective effects against digestive tract cancers in a case-control study<sup>51</sup> and a 50% reduction in rates of death from cancers at all sites in an elderly US population.<sup>52</sup> 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-fre-

quency questionnaire, in relation to risk of prostate cancer.<sup>53</sup> 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. In recent studies serum and tissue levels of lycopene were shown to be inversely associated with the risk of breast cancer<sup>54</sup> and prostate cancer;<sup>48,55</sup> no significant association with other important carotenoids, including  $\beta$ -carotene, was observed.<sup>48,55</sup> Giovannucci<sup>50</sup> recently reviewed 72 epidemiological studies, including ecological, case-control, dietary and blood-specimen-based investigations of tomatoes, tomato-based products, lycopene and cancer. 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. None of the studies showed adverse effects of high tomato intake or high lycopene levels.

Although the epidemiological evidence of the role of



**Fig. 2: Proposed mechanisms for the role of lycopene in preventing chronic diseases.** Dietary lycopene may increase the lycopene status in the body and, acting as an antioxidant, may trap reactive oxygen species, increase the overall antioxidant potential or reduce the oxidative damage to lipid (lipoproteins, membrane lipids), proteins (important enzymes) and DNA (genetic material), thereby lowering oxidative stress. This reduced oxidative stress may lead to reduced risk for cancer and cardiovascular disease. Alternatively, the increased lycopene status in the body may regulate gene functions, improve intercell communication, modulate hormone and immune response, or regulate metabolism, thus lowering the risk for chronic disease. These mechanisms may also be interrelated and may operate simultaneously to provide health benefits.

lycopene in cancer prevention is persuasive, this role remains to be proven. There are few human intervention trials investigating the effectiveness of lycopene in lowering cancer risk. Most of the workers have investigated the effects of tomato or tomato product (lycopene) supplementation on oxidative damage to lipids, proteins and DNA.<sup>44-46</sup> A preliminary report has indicated that tomato extract supplementation in the form of oleoresin capsules lowers the levels of prostate-specific antigen in patients with prostate cancer.<sup>56</sup>

### Risk of cardiovascular disease

Oxidation of low-density lipoproteins, which carry cholesterol into the blood stream, may play an important role in the causation of atherosclerosis.<sup>6,57,58</sup> Antioxidant nutrients are believed to slow the progression of atherosclerosis because of their ability to inhibit damaging oxidative processes.<sup>14,58-60</sup> Several controlled clinical trials and epidemiological studies have provided evidence for the protective effect of vitamin E, which has been ascribed to its antioxidant properties.<sup>14,61,62</sup> However, in the recently completed Heart Outcomes Prevention Evaluation (HOPE) Study, supplementation with 400 IU/d of vitamin E for 4.5 years did not result in any beneficial effects on cardiovascular events in patients at high risk.<sup>63</sup> In contrast, other studies indicated that consuming tomatoes and tomato products containing lycopene reduced the risk of cardiovascular disease.<sup>43,44,64</sup>

In a multicentre case-control study, the relation between antioxidant status and acute myocardial infarction was evaluated.<sup>64</sup> Subjects were recruited from 10 European countries to maximize the variability in exposure within the study. Adipose tissue antioxidant levels, which are better indicators of long-term exposure than blood antioxidant levels, were

**Table 2: Estimates of daily intake of lycopene from tomatoes and tomato products, as determined from a food-frequency questionnaire<sup>67</sup>**

Product	Serving size	Lycopene intake, mg/d per subject	% of total daily lycopene intake
Tomatoes	200 g	12.70	50.5
Tomato purée	60 mL	1.02	4.1
Tomato paste	30 mL	2.29	9.1
Tomato sauce	227 mL	1.52	6.0
Spaghetti sauce	125 mL	2.44	9.7
Pizza sauce	60 mL	0.66	2.6
Chili sauce	30 mL	0.30	1.2
Tomato ketchup	15 mL	0.53	2.1
Barbecue sauce	30 mL	0.06	0.2
Tomato juice	250 mL	2.20	8.7
Tomato soup	227 mL	0.79	3.1
Clam cocktail	250 mL	0.50	2.0
Bloody Mary mix	156 mL	0.15	0.6
Total		25.16	

used as markers of antioxidant status. Biopsy specimens of adipose tissue were taken directly after the infarction and were analysed for various carotenoids. After adjustment for a range of dietary variables, only lycopene levels, and not  $\beta$ -carotene levels, were found to be protective.

A study from Johns Hopkins University, Baltimore, showed that smokers with low levels of circulating carotenoids were at increased risk for subsequent myocardial infarction.<sup>65</sup> Lower blood lycopene levels were also found to be associated with increased risk for and death from coronary artery disease in a population study comparing Lithuanian and Swedish cohorts with different rates of death from coronary artery disease.<sup>66</sup>

### Food sources and bioavailability

Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots and pink guavas, contain lycopene.<sup>20</sup> Processed tomato products, such as juice, ketchup, paste, sauce and soup, all are good dietary sources of lycopene. In a recent study in our laboratory, the average daily dietary intake of lycopene, assessed by means of a food-frequency questionnaire, was estimated to be 25 mg/d with processed tomato products, accounting for 50% of the total daily intake<sup>67</sup> (Table 2).

Although comparative bioavailability values for lycopene from different tomato products are unknown, lycopene from processed tomato products appears to be more bioavailable than that from raw tomatoes.<sup>68,69</sup> The release of lycopene from the food matrix due to processing, the presence of dietary lipids and heat-induced isomerization from an all-*trans* to a *cis* conformation enhance lycopene bioavailability.<sup>18</sup> The bioavailability of lycopene is also affected by the dosage and the presence of other carotenoids, such as  $\beta$ -carotene: Johnson and associates<sup>70</sup> found that the bioavailability of lycopene was significantly higher when it was ingested along with  $\beta$ -carotene than when ingested alone.

### Future directions

The current dietary recommendation to increase the consumption of fruits and vegetables rich in antioxidants has generated interest in the role of lycopene in disease prevention. However, the evidence thus far is mainly suggestive, and the underlying mechanisms are not clearly understood. Further research is critical to elucidate the role of lycopene and to formulate guidelines for healthy eating and disease prevention. Areas for further study include epidemiological investigations based on serum lycopene levels, bioavailability and effects of dietary factors, long-term dietary intervention studies, metabolism and isomerization of lycopene and their biological significance, interaction with other carotenoids and antioxidants, and mechanism of disease prevention.

Competing interests: None declared.

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