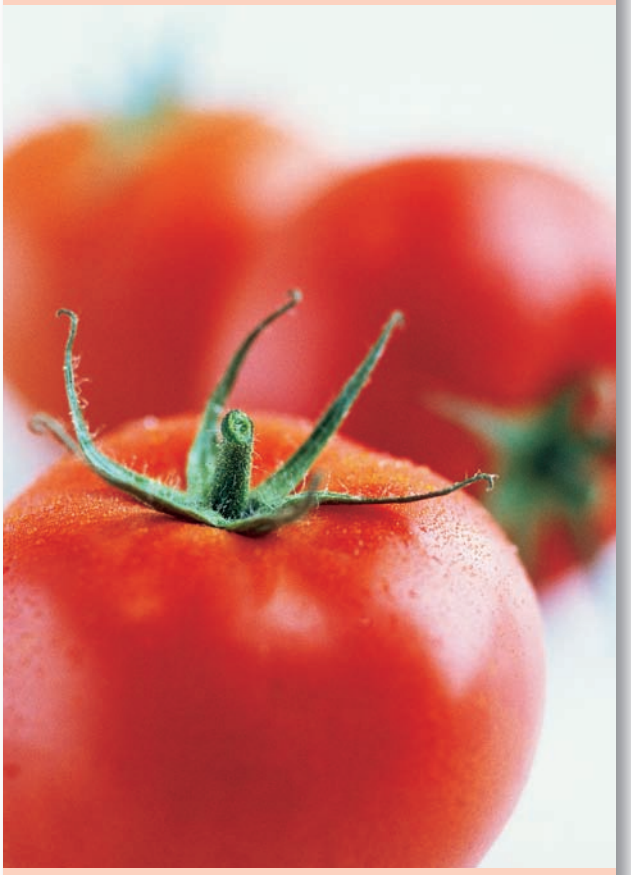
Lycopene



Lycopene provides the familiar red colour to tomatoes and tomato products and is one of the common carotenoids in the human diet and in human tissues. In concert with other dietary carotenoids it serves as an antioxidant in the human body and can help prevent tissue damage from free radical formation. High intake of lycopene and/or tomato products is associated with a reduction in risk of prostate cancer and of cardiovascular disease.

Lycopene is an acyclic carotenoid with 11 linearly arranged conjugated double bonds. It lacks the β-ionone ring structure and therefore has no provitamin A activity (Figure 1). Lycopene is a lipophillic compound and is insoluble in water. It is a red pigment and absorbs light in the visible range.

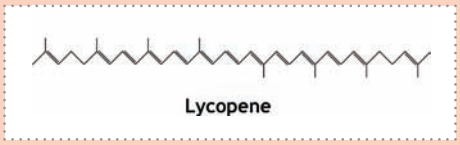


Figure 1

IMPORTANCE FOR HEALTH

Antioxidant effects

Lycopene has antioxidant functions *in vitro* and *in vivo* [1]. Studies *in vitro* show that it is an excellent singlet oxygen quencher [2]. It is about twice as effective as β-carotene in protecting lymphocytes from NO_2 radical death and membrane damage [3]. It is also a peroxyl radical scavenger. Moreover, it may have an indirect antioxidant effect by inducing endogenous antioxidant defence enzymes like glutathione peroxidase, glutathione-S-transferase, and glutathione reductase [4]. In addition, lycopene can induce gap-junctional intercellular communication and affect cell proliferation [5]. In a recent 8 week human intervention trial with healthy subjects it has been demonstrated that supplementation of 12 mg lycopene/day or a mixture of lycopene with β-carotene and lutein (4 mg/day each) can significantly decrease oxidative DNA damage of human lymphocytes [6].

Reduction of cancer risks

In recent years, studies *in vitro* and *in vivo* with tomato products and lycopene have shown promise for the prevention of certain cancer types esp. prostate cancer.

Prostate cancer

Lycopene effectively inhibits the growth of prostate cancer cells *in vitro* [7,8]. A combination of lycopene with vitamin E seems even more effective in inhibiting prostate cancer cell growth than lycopene alone [9]. This combination also effectively suppresses growth of human prostate cancer cells in mice and increases animal's survival time [10].

Human studies that have examined tomato product or lycopene intake or circulating lycopene concentrations in relation to prostate cancer risk can be broken down into those that support a statistically significant inverse association (6 studies); those that show a reduction in risk by about 30% but that were not statistically significant (3 studies); and those that are nonsupportive (7 studies) [11]. The latter studies include at least 3 studies where intake of bioavailable lycopene was most likely too low to be informative [11]. It was concluded that, in view of the potential benefit for prostate health, increased consumption of tomatoes and tomato-based products might be prudent [12].

Recently a number of intervention studies with tomato oleoresin or lycopene capsules have been carried out in prostate cancer patients. The studies (3 weeks to 2 years) carried out on patients with various types of prostate cancer all suggest that tomato oleoresin / lycopene supplementation (in the range from 4 to 30 mg/day) may decrease the growth of prostate cancer. Studies showed increased levels of lycopene in prostate tissue. Also decreased prostate tissue and leukocyte oxidative DNA damage were reported and decreased serum prostate-specific antigen (PSA) levels [11].

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Cancers of the digestive tract

Reviews on the available data indicated that the majority of the studies on gastric cancer (all case-control studies) showed an inverse association between tomato consumption and risk of gastric cancer, but not all were significant and still a number of studies showed no effect [14]. Also for colon and rectal cancer or other forms of cancer of the digestive tract there is emerging evidence on an inverse relationship between intake of tomato products and reduced risk of colon and rectal cancer, but this is still not conclusive.

Heart health

In a multi-centre study in 10 European countries, lycopene concentration in adipose tissue was associated with a lower risk of coronary heart disease indicating a possible protective effect from lycopene containing foods [15]. Furthermore beneficial effects on resistance of LDL to oxidation after supplementation with tomato products or lycopene [16,17] and LDL-cholesterol lowering properties by high doses of lycopene (60 mg/day) have been demonstrated [18].

Skin protection

Exposure of the skin to UV light results in skin injury. Reactive oxygen species and other free radicals that can seriously damage membranes, proteins, and DNA and RNA seem to play an important role in this adverse event [19]. Carotenoids are suitable photoprotectants, and ß-carotene supplements are used for protection against UV light-induced erythema. Combinations of ß-carotene with lycopene and lutein but also lycopene alone (from tomato sources or synthetic) showed protective effects on UV-induced erythema in humans [19,20,21]. Carotenoids such as lycopene cannot replace a sunscreen, but may confer some basal protection and thus may contribute to defence against UV-dependent skin damage.

DIETARY SOURCES AND INTAKE OF LYCOPENE

Sources

The main sources of lycopene are tomatoes and tomato products followed by watermelon, papaya, pink guavas, pink grapefruit, apricots, and rosehip *(Table 1)*. Tomato products are by far the most relevant sources of lycopene in the daily diet. The lycopene content is lowest in raw tomatoes and higher in processed products such as tomato sauce or tomato paste.

In unprocessed tomato products, about 95% of lycopene is present in the all-trans form. Processing of tomatoes such as cooking, freezing or canning does not significantly change the total lycopene content but results in conversion of all-trans lycopene to various cis-isomers, mainly 5-*cis*, 9-*cis* and 13-*cis* lycopene [22,23]. The extent of isomerisation depends on the duration and temperature of processing, the presence of oxygen, antioxidants, moisture, and the dehydration technique applied. In commercial tomato products *cis*-isomers account for up to 10% of total lycopene with occasional percentages as high as 33% [22]. During storage of processed tomato products in the absence of oxygen, lycopene is stable [22].

In addition to tomato lycopene there are also sources of synthetic lycopene and lycopene from microorganisms available as dietary ingredients or food colourant that can be added to foods or food supplements.

Table 1. Lycopene content of various foods [3,24] (means and ranges of means)

Food	Lycopene (mg/100 g wet weight)
Tomatoes, fresh	0.9 - 4.2
Tomatoes, cooked	3.7
Tomato paste	5.4 - 150
Tomato sauce	6.2
Tomato soup, condensed	8
Tomato powder, drum or spray dried	112 - 126
Tomato juice	5 –11.6
Sun-dried tomato in oil	46.5
Pizza sauce, canned	12.7
Ketchup	9.9 – 13.4
Apricot	<0.01
Apricot, canned	0.06
Apricot, dried	0.9
Grapefruit, raw pink	3.4
Guava, fresh	5.4
Guava, juice	3.3
Watermelon, fresh	2.3 – 7.2
Papaya, fresh	2.0 – 5.3
Rosehip [24]	12.9 – 35.2

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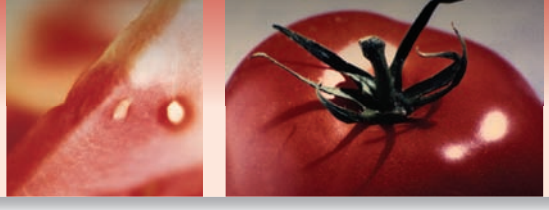

Intake from foods

In Europe, mean intake of lycopene ranges from about 0.5 to 5 mg/day, with high mean intakes up to 7.5 mg/day *(Table 2)*. Intake varies with food habits and also with the method of assessment (e.g. food frequency questionnaires, diet history questionnaires, 24-h recall or household purchases) employed. Food frequency questionnaires for example are thought to overestimate food and vegetable consumption. Note that in individuals consuming large amounts of tomato products, lycopene intake can be several fold the mean intake (e.g. 20 mg/day and more) [25]. Mean intake in North America does not materially differ from that in Europe.

Table 2. Intake of lycopene in Europe and North America

* mean

**mean ± standard deviation

*** interquartile range

**** range of means ± standard deviations reported for epidemiologic studies

Country	Daily intake, mg	Reference
Netherlands	1.05 ± 1.56 (men)**	
	1.33 ± 1.88 (women)**	26
Netherlands	4.85 (2.79-7.53)***	27
Britain	1.03*	24
United Kingdom	5.01 (3.2-7.28)***	27
Spain	1.54 (0.50-2.64)***	27
Italy	7.5 (± 3.5)**	28
Ireland	4.43 (2.73-7.13)***	27
France	5.01 (3.2-7.28)***	27
France	2.8*	29
Finland	0.70* (women)	30
	0.85* (men)	
Germany	0.55*	31
Canada	6.3±11.8**	32
	1.3 (median)	
Canada	25.2*	33
United States	1.1 ± 7.2 to 9.4 ± 0.28 ****	32

Intake from foods containing lycopene as colouring agents and from food supplements

Tomato lycopene obtained by solvent extraction is permitted as a colouring agent for several food products including non-alcoholic beverages, bakery products, ice cream, desserts, fish products, meal replacements and food supplements in the EU (E 160d, Directive 94/36/EC).

Lycopene can also be used as dietary ingredient in food supplements. Products in the market (esp. in the USA) contain between 5 and 20 mg lycopene per recommended daily dose. Multiple-component supplements targeted at prostate health contain 3 to 5 mg lycopene per daily dose. Some multi-vitamin supplements also contain lycopene at doses ranging from 0.3 to 1 mg per day.

Recommended intake

No Dietary Reference Intake for lycopene has been established. However several human intervention trials indicate that lycopene may play an important role in protection of cellular functions against oxidative damages.

ABSORPTION AND METABOLISM

The main factors affecting bioavailability of lycopene are the source, food processing, dietary fat, and factors interfering with absorption. In raw tomatoes, lycopene is present in crystalline form in the chromoplast [22] and the crystalline nature may account for the apparently low absorption efficiency [34]. Heating of tomato juice in oil results in a two to threefold higher bioavailability compared with untreated juice [35]. Hence, tomato products like tomato and spaghetti sauce, tomato soup, ketchup, and tomato paste are better sources of bioavailable lycopene than are fresh tomatoes [36]. About 5 g fat is essential for an efficient absorption. Thus, lycopene from tomato juice consumed in between meals is not absorbed at all. Bioavailability of synthetic lycopene has been shown to be comparable with lycopene enriched tomato oleoresin [37]. A variety of dietary factors and drugs interfere with lycopene absorption, e.g. dietary fibre, fat substitutes, plant sterols and cholesterol lowering drugs.

Pure crystalline lycopene obtained by chemical synthesis is highly sensitive to oxygen and light. Therefore, for use as a food colour, dietary ingredient or supplement it has to be stabilised by formulating with suitable carriers, antioxidants and encapsulation materials. Customary formulations containing 10% lycopene are usually stable over several

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months under appropriate storage conditions [38].

Digestion and absorption of lycopene proceed in several consecutive steps. The initial step is the release from the food matrix. Being a fat-soluble compound lycopene is then solubilized in the aqueous environment of the intestinal chyme with the help of bile salts and incorporated into mixed micelles. These mediate transfer across the unstirred water layer and uptake into the enterocyte by passive diffusion [3]. The presence of fat is essential for lycopene absorption, because fat stimulates the secretion of bile acids from the gall bladder and is required for the formation of stable micelles. In the intestinal mucosa lycopene is incorporated into chylomicrons and released into the lymphatic system and subsequently into the blood stream. In the liver lycopene is incorporated into nascent lipoproteins, which are secreted into the blood stream and act as a transport vehicle for lycopene to other tissues. Lycopene is predominantly found in the testes, adrenals, liver, adipose tissue, prostate gland, kidneys and ovaries [3,39].

Lycopene concentrations in blood vary widely. Mean concentrations in different populations range from about 50 to 900 nmol/L and generally reflect the consumption of tomato products [3]. Typical plasma concentration levels of lycopene in men in different European regions are listed in *Table 3*.

While about 95% of lycopene in the diet is present in the all-trans form, cis-lycopene isomers contribute one to two thirds of total lycopene in plasma and in most tissues [40,41]. Between 10 and 20 different cis isomers are typically observed in human blood [31,42]. Little is known about the metabolism of lycopene in humans.

Few oxidative metabolites have been identified in human blood and tissues [43,44]. Lycopene metabolism and degradation in rats is stimulated by testosterone [43,45].

Most dietary lycopene is excreted via the stool. Due to its lipophilic nature lycopene is not found in urine. It is assumed that bile and urine are the main excretion routes for lycopene metabolites [3].

Table 3: Lycopene plasma levels in men in Europe (µmol/l, mean and standard deviation) [46]

European Region	Lycopene
Varese/Turin, IT (n=99)	1.03 ± 0.43
Florence, IT (n=97)	1.01 ± 0.37
Ragusa/Naples, IT (n=92)	1.29 ± 0.46
Athens, GR (n=95)	0.90 ± 0.38
Granada, ES (n=97)	0.69 ± 0.40
Murcia, ES (n=99)	0.66 ± 0.30
Nothern Spain, ES (n=97)	0.53 ± 0.31
UK vegetarians, UK (n=99)	0.98 ± 0.45
Cambridge, UK (n=98)	0.72 ± 0.30
Potsdam, DE (n=98)	0.60 ± 0.30
Heidelberg, DE (n=99)	0.62 ± 0.31
The Netherlands, NL (n= 97)	0.54 ± 0.33
Denmark, DK (n=99)	0.58 ± 0.34
Malmö, SE (n=99)	0.46 ± 0.24
Umea, SE (n=99)	0.56 ± 0.37

SAFETY

There are no signs of any significant adverse biological effect by lycopene (even at high doses), neither from the numerous epidemiological studies nor from clinical studies evaluating various endpoints upon lycopene supplementation through protocols using tomato-based products or tomato-based capsules. The only side effect that might be observed with a long-term intake of relatively high doses (dose needed unknown) is lycopenodermia (carotenodermia), a harmless and reversible discolouration of the skin [3].

Using recently developed risk assessment procedures for nutrients for which a Tolerable Upper Intake Level (UL) could not be derived, an Observed Safe Level (OSL) of 75 mg/d has been suggested for lycopene [47].

Lycopene extracted from tomatoes is authorised as a food colouring agent in the EU and the US. In 1999 the Scientific Committee for Food (SCF) evaluated synthetic lycopene for use as a food colourant, but the available data at that time were not sufficient to allow for an acceptance [35]. Synthetic lycopene is currently not approved as a colouring agent or dietary ingredient in the EU but is considered Generally Recognised As Safe (GRAS) for nutritional purposes in the US. In Australia and New Zealand both natural and synthetic lycopene are permitted as food colours (food additive). In Japan tomato colour is permitted for use as food additive.

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