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Lycopene, a powerful antioxidant

by

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Abbreviations:

DMAPP, dimethylallyl pyrophosphate; **FPP,** farnesyl pyrophosphate; **GGPP,** geranylgeranyl pyrophosphate synthase; **GGPS,** geranylgeranyl pyrophosphate synthase; **GJC,** gap junction communication; **GPP,** geranyl pyrophosphate; **$GS^{\bullet}$,** glutathiyl radical; **HDL**, high density lipoprotein; **IPP**, isopentenyl pyrophosphate; **LDL,** low density lipoprotein; **LCY,** lycopene cyclase; **MPTA**, 2-(4-methyl-phynoxy)triethylamine; **MVA,** mevalonic acid; **NFZ,** norflurazone; **$NO_2^{\bullet}$**, nitrogen dioxide; **$^1O_2$**, singlet oxygen; **$O_2^{\bullet -}$,** superoxide radical; **PDS,** phytoene desaturase; **PPPP,** prephytoene pyrophosphate; **PSY,** phytoene synthase; **$RS^{\bullet}$**, alkylthiyl radical; **$RSO_2^{\bullet}$**, thiylsulfonyl radical; **$TO^{\bullet}$**, tocopheroxyl radical; **TOH**, tocopherol; **ZDS,** ζ-carotene desaturase; **VLDL,** very low density lipoprotein.

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Abstract

Lycopene is a red pigment naturally found in plants and is part of a large class of plants compound called carotenoids. The synthesis of lycopene has also been found in some photosynthetic organisms like algae, some types of fungus, and some bacteria. It is currently considered one of the most efficient antioxidants; protecting against free radicals that damage critical parts of the cell, including lipids, membrane lipoproteins, proteins, and DNA. The conventional method used in detection of lycopene is high-performance liquid chromatography. Increased levels of lycopene have been associated with prevention prostate cancer and coronary heart disease. Therefore, it is important to understand the characteristics and mechanisms of action as well as functions of lycopene for using it as a tool in prevention of human pathologies.

Introduction

Lycopene is an acyclic unsaturated carotenoid that conveys bright red color to many plants, especially in tomato, guava, rosehip, watermelon and pink grapefruit and is the most common carotenoid in the human body. Its name is obtained primarily from tomato (*Lycopersicon esculentum*) [1]. It is considered to be an antioxidant that can donate electrons to quench and neutralize free radical oxygen molecules that are known to accelerate aging and damage cells. In addition, lycopene has recently been shown to play an important role in reducing the risk of prostate cancer and cardiovascular disease [14, 17-18]. A high intake of lycopene can absorb carcinogens found in the daily environment before they can affect the body's cells. This review paper will mainly focus on lycopene chemistry, biochemistry, routes of formation, detection, and biological health aspects.

Routes of lycopene formation

Carotenoids are organic pigments naturally occurring in plants and some other photosynthetic organisms like algae, some types of fungus, and some bacteria, but not animals [2]. Plant carotenoids are found embedded in membranes of chloroplasts and chromoplasts. The structures of some common plant carotenoids and a simplified biosynthetic pathway are illustrated in **Figure 1**. Carotenoids are characterized by a large 40-carbon atom polyene chain, sometimes terminated by rings. In the first step, the enzyme geranylgeranyl pyrophosphate synthase (GGPS) catalyzes three successive condensation reactions. The first of them is the condensation of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) to form geranylgeranyl pyrophosphate (GGPP). The synthesis of carotenoids begins with the two-step conversion of two molecules of GGPP into prephytoene pyrophosphate (PPPP) and then into phytoene catalysed by phytoene synthase (PSY). Phytoene is the first lipophilic compound in the carotenoid pathway. A sequential of desaturation reactions of phytoene results in the synthesis of phytofluene, ζ-carotene, neurosporene, and lycopene, which is then converted by lycopene cyclase (LCY) into β-carotene, a molecule which is broken down in animals to form vitamin A. Carotenoids where some of the double bonds have been oxidized are known as xanthophylls, the un-oxidized carotenoids are known as carotenes [3].

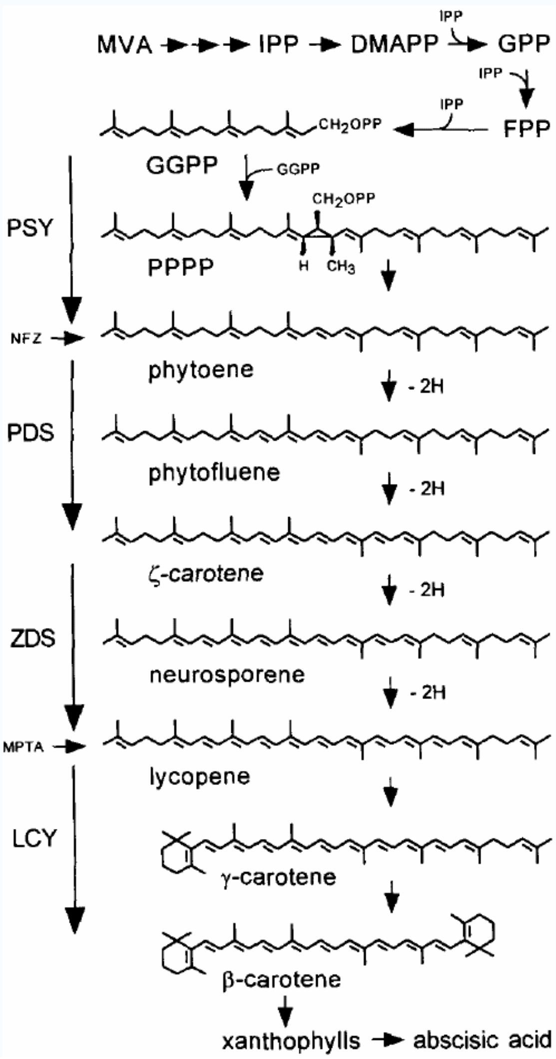

Figure 1. Carotenoid biosynthesis in cyanobacteria and plants. MVA, mevalonic acid, is derived from acetyl-CoA and is decarboxylated to isopentenyl pyrophosphate, IPP. The first steps of the pathway are condensation reactions that result in the formation of geranylgeranyl diphosphate (geranylgeranyl pyrophosphate, GGPP). DMAPP, dimethylallyl pyrophosphate; GPP, geranyl pyrophosphate; FPP, farnesyl pyrophosphate; PPPP, prephytoene pyrophosphate; PSY, phytoene synthase; PDS, phytoene desaturase; ZDS, ζ-carotene desaturase; LCY, lycopene cyclase; NFZ, norflurazone and MPTA, 2-(4-methyl-phynoxy) triethylamine are bleaching herbicides that can inhibit both cyclization reactions. Abscisic acid is defined as a plant hormone that mainly acts to inhibit growth, promotes dormancy, and to help the plant tolerate stressful conditions [3].

Physical and chemical properties

Lycopene is a 40-carbon acyclic carotenoid with 11 linearly arranged conjugated double bonds. Its molecular formula is $C_{40}H_{56}$ and its molecular weight is 536.88 Daltons. According to the structural formula of lycopene represented in **Figure 1,** its chemical name is 2,6,10,14,19,23,27,31-octamethyl-2,6,8,10,12,14,16,18,20,22,24,26,30-dotriacontatridecane and also known as psi-carotene[1].

Many of the general physical and chemical properties of carotenoids are presented in **Figure 2.** Lycopene, as with other carotenoids, is a natural fat-soluble pigment. The best known property of carotenoids is their ability to absorb light in the 400-500 nm region of the visible spectrum. This physical property conveys the characteristic red/yellow color of the pigments. In addition to absorbing light directly, it can be excited by the transfer of energy from a suitable triplet state sensitizer (^{3}sen) or the transfer of the excitation energy from singlet oxygen ($^1O_2$); it then becomes a triplet state species (^{3}carotenoid). The ability to quench $^1O_2$ is a function of the effective number of conjugated double bonds [4].

When lycopene is oxidized, for example, by reacting with bleaches or acids, the double bonds between carbon atom will be broken, cleaving the molecule into smaller molecules each double-bonded to an oxygen atom. Although C=O bonds are also chromophoric, the much shorter molecules are unable to absorb enough light to appear colorful. A similar effect occurs if lycopene is reduced; reduction may saturate and join lycopene molecules, converting the double bonds to single bonds as a result [4]. In addition, rotation of any of its 11 conjugated double bonds allows for the formation of a number of *cis*-geometrical isomers. Even though most

[1] http://www3.cancer.gov/prevention/agents/Lycopene.html. accessed on Feb 12, 2005

lycopene found in nature is in the *all-trans* form, most lycopene in the body is in the *cis*-isomer. This information raised the hypothesis that the *cis* isomers are more readily absorbed [5].

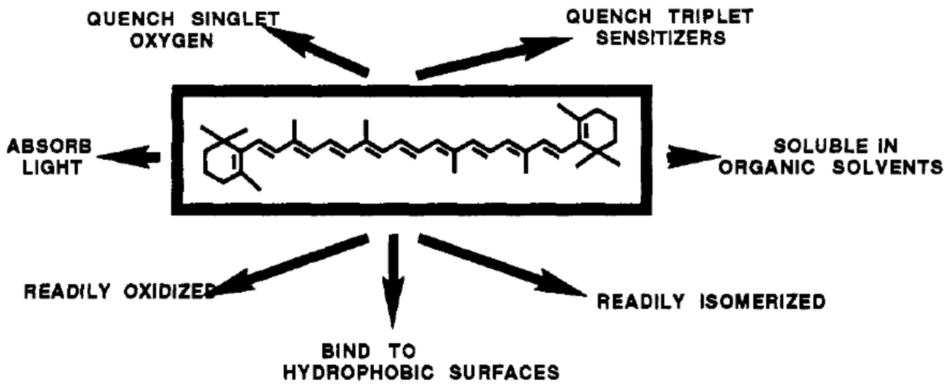

Figure 2. General physical and chemical properties of carotenoids [4].

Reactions of lycopene with radical species

It has been reported that lycopene is the most efficient biological carotenoid $^1O_2$ quencher. It exhibits the highest physical quenching rate constant (k_q) with $^1O_2$ = 3.1 x 10^{10} M^{-1} s^{-1} compared to other carotenoids. Among several carotenoids, the $^1O_2$ quenching ability decreased in the following order: lycopene, γ-carotene, astaxanthin, canthaxanthin, α-carotene, β-carotene, bixin, zeaxanthin, lutein, cryptoxanthin and crocin [6, 7].

Lycopene can react with radicals in many ways. It has been demonstrated that when *all-trans* lycopene reacts with the superoxide radical ($O_2^{\bullet-}$) or nitrogen dioxide ($NO_2^{\bullet}$), electron transfer occur with the formation of the radical anion as shown in **reaction (1)** [8] and formation of the radical cation as shown in **reaction (2)** with the rate constant 1.9 x 10^7 M^{-1} s^{-1} [9, 10].

$$\text{Lycopene} + O_2^{\bullet-} \rightarrow \text{lycopene}^{\bullet-} + O_2 \quad \textbf{(1)}$$

$$\text{Lycopene} + NO_2^{\bullet} \rightarrow \text{lycopene}^{\bullet+} + NO_2^{-} \quad \textbf{(2)}$$

It was also reported that lycopene reacts very rapidly with alkylthiyl radical ($RS^{\bullet}$), glutathiyl radical ($GS^{\bullet}$), and thiylsulfonyl radical ($RSO_2^{\bullet}$) as shown in **reaction (3-5)** with the absolute rate constants for lycopene radical formation of $1.6 \times 10^9\ M^{-1}\ s^{-1}$, $4.8 \times 10^8\ M^{-1}\ s^{-1}$, and $1.26 \times 10^9\ M^{-1}\ s^{-1}$ respectively**.** In contrast to scavenging of $NO_2^{\bullet}$ mechanism the $RS^{\bullet}$ and $GS^{\bullet}$ react *via* a radical addition process by adds itself to the electron-rich lycopene to generate lycopene-radical adduct with an unpaired electron located on the lycopene portion. The $RSO_2^{\bullet}$ radical undergoes both radical addition, forming an intermediate lycopene adduct radical, and electron abstraction, forming lycopene radical cation. Both lycopene adduct radical and lycopene radical cation decay biomolecularly [10].

$$RS^{\bullet} + \text{lycopene} \rightarrow [\text{RS-lycopene}]^{\bullet} \quad \textbf{(3)}$$

$$GS^{\bullet} + \text{lycopene} \rightarrow [\text{GS-lycopene}]^{\bullet} \quad \textbf{(4)}$$

$$RSO_2^{\bullet} + \text{lycopene} \rightarrow [RSO_2\text{-lycopene}]^{\bullet} \rightarrow RSO_2^{-} + \text{lycopene}^{\bullet +} \quad \textbf{(5)}$$

In addition, it has been clearly demonstrated that lycopene radical cation could be reduced by tocopherol (TOH) with the formation of tocopheroxyl radical ($TO^{\bullet}$) according to **reaction (6)** [11].

$$\text{Lycopene}^{\bullet +} + TOH \rightarrow \text{lycopene} + TO^{\bullet} + H^{+} \quad \textbf{(6)}$$

Biological properties of lycopene

In photosynthetic organisms, lycopene serves as an accessory light-gathering pigment and to protect these organisms against the toxic effects of oxygen and light while in non-photosynthetic organisms, carotenoids have been linked to oxidation-preventing mechanisms [12]. Animals are incapable of synthesizing carotenoids and must obtain them through their diet. Among the 600 known carotenoids in nature, only about 20 are found in human plasma and tissues. Lycopene is the major carotenoid found in human blood and tissues, and is found primarily in the testis, adrenal glands, liver, prostate, breast, colon, and lung. It has a half life about 2-3 days and was found to be transported in plasma by lipoprotein, primarily with LDL and VLDL but not HDL. The role of lycopene in preventing human pathologies is simply illustrated in **Figure 3.** Gap junction communication (GJC) are cell-to-cell channels that enable connecting cells to exchange low-molecular weight compounds like nutrients and signaling molecules. One feature of carcinogenesis is the loss of GJC. Lycopene increase GJC between cells and enhances the expression of connexin 43, a gene encoding major gap junction protein, and thereby upregulated GJC and acts as anticarcinogen [13].

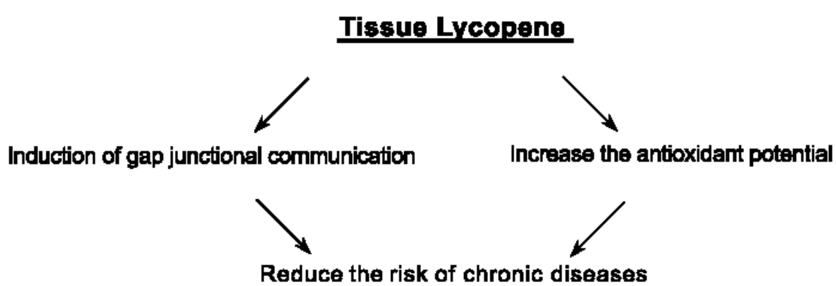

Figure 3. Cellular process of lycopene [13].

Furthermore, the ability of lycopene to act as a biological antioxidant and a scavenger of free radicals, often associated with carcinogenesis, is one key to the mechanism for its beneficial effects on human health. It may also interfere with oxidative damage to DNA and lipoproteins and inhibit the oxidation of LDL cholesterol [14].

So far, no adverse effects of lycopene use have been reported and it is considered to be safe [4]. However, since lycopene is a lipid-soluble antioxidant, it has been reported that concomitant intake of some cholesterol-lowering drugs such as probucol and cholestyramine significantly decrease serum concentration of lycopene due to impairment of gastrointestinal absorption [15].

Detection

A simple method for measurement of lycopene from tomato products can be performed by extracting the sample with hexane and then measuring on spectrophotometer at 472 nm ($E^{1\%}_{472\ nm}$ of all trans-lycopene = 3450 in hexane)[2]. For validation purposes the hexane extract of lycopene should be analyzed by HPLC. On the other hand, reverse-phase high-performance liquid chromatography is a procedure commonly used in the separation, identification and quantification of the components of a complex mixture. However, lycopene present in skin can act as antioxidant, protecting against UV radiation. A noninvasive technique detection of lycopene and other carotenoids in human skin by Raman spectroscopy, the measurement of the wavelength and intensity of inelastically scattered light from molecules, had been reported to provide a rapid screening of carotenoids in human skin in large populations and might be suitable for clinical studies correlating status with risk for cutaneous diseases [16].

Biological and health aspects

The ideal intake of lycopene is currently unknown; however, one study suggested that at least 5-10 g of fat in a meal is required for lycopene absorption and 6 mg/day of lycopene is beneficial for prostate cancer prevention [17].

Many epidemiological studies implicated lycopene in the prevention of cardiovascular disease and cancer [13, 17]. Recently, lycopene has been found to inhibit proliferation of several types of cancer, including those of breast, prostate, lung, and endometrium. It has also been reported that lycopene initiates cell cycle arrest and induction of apoptosis in LNCaP human prostate cancer cells [18]. The mechanism of action in affecting prostate cells is still unknown but the most widely accepted theory involves lycopene's antioxidant effect on scarvenging of $^1O_2$, which are theorized to damage DNA and cause cancer. Lycopene, therefore, may be used as

[2] http://www.nsf.org/business/ina/lycopene.asp?program=INA accessed on Feb 22, 2005

a potential chemopreventive/chemotherapeutic agent in some chronic diseases, particularly coronary heart disease and prostate cancer.

Summary

Lycopene is not produced in the body. The only way to obtain its benefits is eating foods rich in lycopene such as fruits and vegetables. Tomato and tomato products are the main foodstuffs contributing to the dietary intake of lycopene. Interest in lycopene is growing because of many recent studies suggest that consumption of foods rich in lycopene is associated with lower risk of prostate cancer and cardiovascular disease. Thus, lycopene is considered to be effective dietary supplement for health promotion and disease prevention.

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