PERGAMON

Phytochemistry 54 (2000) 233–236

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

Molecules of Interest

Is lycopene beneficial to human health?

Peter M. Bramley

School of Biological Sciences, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK

Accepted 15 March 2000

Abstract

Since humans cannot synthesise carotenoids de novo, we depend upon the diet exclusively for the source of these micronutrients. Although the necessity for β-carotene, as the precursor of vitamin A has been recognised for many years, it is lycopene that has attracted substantial interest more recently. Lycopene is the red-coloured carotenoid predominantly found in tomato fruit, but in few other fruits or vegetables. It has claimed that it may alleviate chronic diseases such as cancers and coronary heart disease. This possibility has been studied extensively, by epidemiological studies and biochemical investigations of its properties and its bioavailability from tomato-based diets. This article summarises the current state of knowledge of the properties of lycopene, its possible role in human health and areas for future research. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Lycopene; Carotenoids; Tomato; Diet; Chronic diseases; Cancer; Coronary heart disease

1. Introduction

Lycopene (φ,φ-carotene, Fig. 1) is one of over 600 carotenoids found in nature. It accumulates in relatively few tissues, and can most easily be seen in ripe tomato fruit, watermelon and pink grapefruit, giving them a characteristic red pigmentation. In contrast, it is found in only minute amounts in photosynthetic tissues. Although used as food colorant for many years, it is only recently that it has been the subject of intense study with respect to its antioxidant activity and potential in alleviating chronic diseases such as certain cancers and coronary heart disease (CHD). In turn, this has led to the idea of increasing levels of lycopene in crops, particularly the tomato, by genetic crosses or genetic manipulation in order to increase the amount of lycopene in a typical diet.

2. Structure, properties and biosynthesis

Lycopene is an acyclic carotene with 11 conjugated double bonds, normally in the all-*trans* configuration (Fig. 1). However, the double bonds are subject to isomerisation, and various *cis* isomers (mainly 5, 9, 13 or 15-) are found in plants, and also in plasma (Holloway et al., 2000).

The long chromophore in the polyene chain accounts for the red colour of lycopene (λ_{max} 472 nm) and also for its powerful antioxidant activity. It is able to react with singlet oxygen and various radical cations and has the highest TEAC (Trolox-equivalent antioxidant capacity) value of all carotenoids (Rice-Evans et al., 1997).

Lycopene is synthesised via a series of four desaturation reactions from the colourless carotene, phytoene (7,8,11,12,7′,8′,11′,12′-octahydro-φ,φ-carotene). These reactions occur in the plastids of higher plants and are catalysed by two membrane bound desaturases

E-mail address: p.bramley@rhbnc.ac.uk (P.M. Bramley).

PII: S0031-9422(00)00103-5

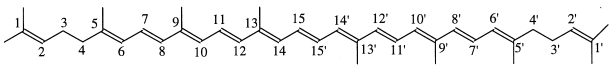

Fig. 1. Structure and numbering of lycopene.

(reviewed by Harker and Hirschberg, 1998). Lycopene itself is cyclised to ε- and β-carotenes, both of which are precursors of the xanthophylls, found in the photosynthetic apparatus. The genes for virtually all these enzymes have been cloned and can now be used for plant transformations. Such an approach can lead to plants, particularly tomato, with elevated levels of lycopene (Bramley, 1997).

3. Dietary sources

Since humans are unable to synthesise carotenoids de novo, we obtain them exclusively from the diet. At least 85% of our dietary lycopene comes from tomato fruit and tomato-based products, the remainder being obtained from watermelon, pink grapefruit, guava and papaya (Table 1). Of the tomato products, juice, ketchup, soup and pizza and spaghetti sauces are the major contributors in the diet (Table 1). The range of values is related to varietal differences and the effects of growth conditions on carotenoid synthesis. The configuration of lycopene in these crops is predominantly all-*trans*, although processed tomato products contain between 1.7% and 10.1% *cis* isomers. Processing also affects the matrix of the tomato product (Shi and Le Mageur, 2000).

4. Uptake, metabolism and tissue distribution in humans

Uptake of carotenoids from the diet has been studied for many years (reviewed by Rao and Agarwal, 1999). The bioavailability of dietary lycopene appears to be dependent upon several factors. It is absorbed better from heat processed foods than unprocessed sources and also from lipid-rich diets (Bohm and Bitsch, 1999). *Cis* isomers are more bioavailable than the all-*trans* form (Boileau et al., 1999). This may be because *cis* isomers are more soluble in bile acid micelles and so preferentially incorporated into chylomicrons. It has been suggested that individual carotenoids antagonise absorption of each other, e.g. canthaxanthin inhibits lycopene uptake (Blakely et al., 1994). Once ingested, lycopene then appears in plasma, initially in the VLDL and chylomicron fractions and later in LDL and HDL. The highest levels are found in LDL. Serum concentrations, however, vary enormously, from 50 to 900 nM, with large interperson variations. Lycopene is found in most human tissues, but is not deposited uniformly (Table 2). These differences suggest that there are specific mechanisms for the preferential deposition of lycopene, particularly in the adrenals and testes.

Little is known about the metabolism or degradation of lycopene in mammals. A number of oxygenated metabolites have been found in plasma and tissues, e.g. 2,6-cyclolycopene-1,5-diols (Khachik et al., 1992). It has been suggested that these oxygenated lycopenes are products of in vivo oxidation, or have physiological roles per se.

5. Role of lycopene in human health

Three main research directions have been used to study the role of lycopene in humans: epidemiology (including bioavailability), the effect of lycopene on tumour proliferation and biochemical/immunological mechanisms of lycopene action.

Several epidemiological studies have been published which show an inverse correlation between tomato-

Table 1
Lycopene content of fruit and tomato products[a]

Fruit or tomato product	Lycopene content (μg/g wet weight)
Fresh tomato	8.8–42.0
Watermelon	23.0–72.0
Pink guava	54.0
Pink grapefruit	33.6
Papaya	20.0–53.0
Tomato sauce	62.0
Tomato paste	54.0–1500.0
Tomato juice	50.0–116.0
Tomato ketchup	99.0–134.4
Pizza sauce	127.1

[a] Data taken from: Scott and Hart (1995), Tonucci et al. (1995), and Rao and Agarwal (1999).

Table 2
Lycopene levels in human tissues[a]

Tissue	Lycopene (nmol/g wet weight)
Adipose	0.2–1.3
Adrenal	1.9–21.6
Brainstem	Not detectable
Breast	0.8
Colon	0.3
Liver	1.3–5.7
Lung	0.2–0.6
Ovary	0.3
Prostate	0.8
Skin	0.4
Stomach	0.2
Testis	4.3–21.4

[a] Data taken from: Schmitz et al. (1991), Stahl et al. (1992), and Clinton et al. (1996).

Table 3
Epidemiological studies involving lycopene, lycopene-containing foods and chronic diseases

Disease	Major conclusion	Reference
Prostate cancer	Intake of tomato products inversely associated with prostate cancer	Giovannucci et al. (1995); Clinton et al. (1996)
Digestive tract cancer	Reduced risk with high tomato intake	Franceschi et al. (1994)
Bladder cancer	Serum lycopene associated with decreased risk	Helzlsour et al. (1989)
Skin cancer	Decrease in skin lycopene on exposure to light	Ribago-Mercado et al. (1995)
Breast cancer	Serum lycopene associated with decreased risk	Dorgan et al. (1998)
Cervical cancer	Lycopene level showed inverse risk	Sengupta and Das (1999)
Cardiovascular disease	Adipose tissue lycopene associated with lower risk, low serum lycopene with increased mortality	Kohlmeier et al. (1997); Kristenson et al. (1997)

rich diets and the incidence of several cancers and CHD (Table 3). However, a simple extrapolation of lycopene levels in the diet to reduction in chronic diseases is likely to be misleading and the view that lycopene is the sole anticancer compound in tomato-rich diets should be viewed with caution until more studies are carried out. Several groups have showed inhibition by lycopene of cancer cell growth in tissue culture experiments (e.g. Dorgan et al., 1998). Lycopene induces gap junctional communication between cells, which may be a basis for protection against cancer development (Zhang et al., 1991), a property that is independent of its antioxidant property. The mode of action of lycopene in alleviating CHD is thought to be due to its antioxidant properties, leading to the protection of serum lipoproteins to oxidation, although conclusive studies have yet to be reported (Rice-Evans et al., 1997).

6. Future studies

Lycopene is a promising candidate as a dietary component than can reduce cancer risk and CHD in humans. Its potential role in human health warrants further investigation in several areas before we can be sure of its importance for human health. These include:

- Factors than influence uptake from the diet, including interaction with other carotenoids
- Metabolism in humans and the possible roles of metabolites and *cis*/*trans* isomers
- Mechanisms for direct and indirect modulation of the cancer cascade
- Evidence-based intervention studies with humans
- Mechanism for the deposition of lycopene in human tissues
- The effect of lycopene on immune systems.

References

Blakely, S.R., Brown, E.D., Babu, U., Grundel, E., Mitchell, G.V., 1994. Bioavailability of carotenoids in tomato paste and dried spinach and their interactions with canthaxanthin. FASEB J. 8, 192.

Bohm, V., Bitsch, R., 1999. Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status and the antioxidant capacity of human plasma. Eur. J. Nutr. 38, 118–125.

Boileau, A.C., Merchen, N.R., Wasson, K., Atkinson, C.A., Erdman Jr., J.W., 1999. *Cis*-lycopene is more bioavailable than *trans*-lycopene in vitro and in vivo in lymph-cannulated ferrets. J. Nutr. 129, 1176–1181.

Bramley, P.M., 1997. The regulation and genetic manipulation of carotenoid biosynthesis in tomato fruit. Pure Appl. Chem. 69, 2159–2162.

Clinton, S.K., Emenhiser, C., Schwartz, S.J., 1996. *Cis–trans* lycopene isomers, carotenoids and retinol in the human prostate. Cancer Epidemiol. Biomarkers Prev. 5, 823–833.

Dorgan, J.F., Sowell, A., Swanson, C.A., Potischman, N., Miller, R., Schussler, N., Stephenson Jr., H.E., 1998. Relationship of serum carotenoids, retinol, α-tocopherol and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri. Cancer Causes Control 9, 89–97.

Franceschi, S., Bidoli, E., LaVeccia, C., Talamini, R., D'Avanzo, B., Negri, E., 1994. Tomatoes and risk of digestive tract cancers. Int. J. Cancer 59, 181–184.

Giovannucci, E., Ascherio, A., Rimm, E.B., Stampfer, M.J., Colditz, G.A., Willett, W.C., 1995. Intake of carotenoids and retinol in relation to risk of prostate cancer. J. Natl. Cancer Inst. 87, 1767–1776.

Harker, M., Hirschberg, J., 1998. Molecular biology of carotenoid biosynthesis in photosynthetic organisms. Methods Enzymol. 297, 244–263.

Helzlsouer, K.J., Comstock, G.W., Morris, J.S., 1989. Selenium, lycopene, α-tocopherol, β-carotene, retinol and subsequent bladder cancer. Cancer Res. 49, 6144–6148.

Holloway, D.E., Yang, M., Paganga, G., Rice-Evans, C.A., Bramley, P.M., 2000. Isomerization of dietary lycopene during assimilation and transport in plasma. Free Rad. Res. 32, 93–102.

Khachik, F., Beecher, G.R., Goli, M.B., Lusby, W.R., Smith, J.C., 1992. Separation and identification of carotenoids and their oxidative products in extracts of human plasma. Anal. Chem. 64, 2111–2122.

Kohlmeier, L., Kark, J.D., Gomez-Garcia, E., Martin, B.C., Steck, S.E., Kardinaal, A.F.M., Ringstad, J., Thamm, M., Masaev, V., Riemersma, R., Martin-Moreno, J.M., Huttunen, J.K., Kok,

F.J., 1997. Lycopene and myocardial infarction risk in the EURAMIC study. Am. J. Epidemiol. 140, 618–626.

Kristenson, M., Zieden, B., Kucinskiene, Z., Elinder, L.S., Bergdahl, B., Abaraqvicius, A., Razinkoviene, L., Calkauskas, H., Olsson, A., 1997. Antioxidant state and mortality form coronary heart disease in Lithuania and Swedish men: concomitant cross sectional study of men aged 50. Brit. Med. J. 314, 629–633.

Rao, A.V., Agarwal, S., 1999. Role of lycopene as antioxidant carotenoid in the prevention of chronic diseases: a review. Nutr. Res. 19, 305–323.

Ribago-Mercado, J.D., Garmyn, M., Gilchrest, B.A., Russell, R.M., 1995. Skin lycopene is destroyed preferentially over β-carotene during UV irradiation in humans. J. Nutr. 125, 1854–1859.

Rice-Evans, C.A., Sampson, J., Bramley, P.M., Holloway, D.E., 1997. Why do we expect carotenoids to be antioxidants in vivo? Free Rad. Res. 26, 381–398.

Schmitz, H.H., Poor, C.L., Wellman, R.B., Erdman, Jr. J.W., 1991. Concentrations of selected carotenoids and vitamin A in human liver, kidney, and lung tissue. J. Nutr. 121, 1613–1621.

Scott, K.J., Hart, D.J., 1995. Development and evaluation of an HPLC method for the analysis of carotenoids in foods and the measurement of carotenoid content of vegetables and fruits commonly consumed in the UK. Food Chem. 54, 101–111.

Sengupta, A., Das, S., 1999. The anti-carcinogenic role of lycopene, abundantly present in tomato. Eur. J. Cancer Prevention 8, 325–330.

Shi, J., Le Mageur, M., 2000. Lycopene in tomatoes: chemical and physical properties affected by food processing. Crit. Rev. Food Sci. Nutr. 40, 1–42.

Stahl, W., Schwarz, W., Sundquist, A.R., Sies, H., 1992. *Cis–trans* isomers of lycopene and β-carotene in human serum and tissues. Archiv. Biochem. Biophys. 294, 173–177.

Tonucci, L.H., Holden, J.M., Beecher, G.R., Khachik, F., Davis, C.S., Mulokozzi, G., 1995. Carotenoid contents of thermally processed tomato-based food products. J. Agric. Food Chem. 43, 579–586.

Zhang, L-X., Conney, R.V., Bertram, J.S., 1991. Carotenoids enhance gap junctional communication and inhibit lipid peroxidation in C3H/1077/2 cells: relationship to their cancer chemopreventative action. Carcinogenesis 12, 2109–2114.