

LYCOPENE AND IT'S IMPORTANCE IN TREATING VARIOUS DISEASES IN HUMANS

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Article Received on: 09/06/11 Revised on: 10/07/11 Approved for publication: 11/08/11

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ABSTRACT

Lycopene is present in many fruits and vegetables, with tomatoes and processed tomato products being among the richest sources. This review highlights the scientific documentation of lycopene as a therapeutic agent. Lycopene may alleviate chronic diseases such as cancer and coronary heart disease. Lycopene has also been found effective in the treatment of eye diseases, male infertility, inflammation, and osteoporosis. Experimental, clinical, and epidemiological studies have also established its role in the management of diabetes and hepatoprotection. Uses of lycopene have been studied extensively through epidemiological and biochemical investigations of its properties and its bioavailability from tomato-based diets. No adverse events have been reported in association with the consumption of lycopene-containing foods.

KEYWORDS: Lycopene, Carotenoids, Chronic Diseases, antigenotoxicity

INTRODUCTION

Lycopene is a bright red carotenoid pigment found in tomatoes and other red fruits. Lycopene was first discovered by DUGGAR. Its name is derived from the tomato's species classification, *Solanum lycopersicum*. In plants, algae, and other photosynthetic organisms¹, lycopene is an important intermediate in the biosynthesis of many carotenoids, including beta carotene, which are responsible for pigmentation, photosynthesis, and photoprotection. Structurally, it is a tetraterpene assembled from eight isoprene units, composed entirely of carbon and hydrogen, and is insoluble in water. Lycopene's eleven conjugated double bonds give it its deep red colour and are responsible for its antioxidant activity. Due to its strong colour and non-toxicity, lycopene is useful the food colouring.

Lycopene is not an essential nutrient for humans, but it is commonly found in the diet, mainly from dishes prepared with tomato sauce. When absorbed from the stomach, lycopene is transported in the blood by various lipoproteins and accumulates in the liver, adrenal glands, prostate and testes. Of all the carotenoids, lycopene is one of the most potent antioxidants; particularly able to quench singlet oxygen and peroxy radicals, both of which are thought to be responsible for damaging DNA in a process which can lead to the initiation of cancer. Because of this ability, lycopene is being investigated as a potential agent for the prevention of some types of cancers, particularly prostate cancer.

Structure and Physical properties

Lycopene is a symmetrical tetraterpene assembled from 8 isoprene units. It is a member of the carotenoid family of compounds, and because it consists entirely of carbon and hydrogen, it is known as a carotene¹. All-*trans* form, the molecule is long and straight, constrained by its system of eleven conjugated double bonds. Each double bond in this extended π electron system reduces the energy required for electrons to transition to higher energy states, allowing the molecule to absorb visible light of progressively longer wavelengths. Lycopene absorbs all but the longest wavelengths of visible light, so it appears red. When heated or exposed to light, all-*trans* lycopene can undergo isomerization to any of a number of *cis*-isomers. Lycopene is insoluble in water, and can be dissolved only in organic solvents and oils.

Biosynthesis

The biosynthesis of lycopene in eukaryotic plants and in prokaryotic cyanobacteria is similar. Synthesis begins with mevalonic acid, which is converted into dimethylallyl pyrophosphate. This is then condensed with three molecules of isopentenyl pyrophosphate (an isomer of dimethylallyl pyrophosphate), to give the twenty carbon geranylgeranyl pyrophosphate. Two molecules of this product are then condensed in a tail-to-tail configuration to give the forty carbon phytoene, the first committed step in carotenoid biosynthesis. Through several desaturation steps, phytoene is converted into lycopene. The two terminal isoprene groups of lycopene

can be cyclized to produce beta carotene, which can then be transformed into a wide variety of xanthophylls.

Role in Photosynthesis

Lycopene are important pigments found in photosynthetic pigment-protein complexes in plants, photosynthetic bacteria, fungi, and algae. They are responsible for the bright colours of fruits and vegetables, perform various functions in photosynthesis, and protect photosynthetic organisms from excessive light damage. Lycopene is a key intermediate in the biosynthesis of many important carotenoids, such as beta-carotene, and xanthophylls².

Bioavailability and Pharmacokinetics

Lycopene ingested in its natural trans form is poorly absorbed; heat processing tomatoes and tomato products induces isomerization of lycopene from all-trans to cis configuration, in turn increasing its bioavailability³. Also, because lycopene is a fat-soluble compound, absorption into tissues is improved when it is consumed with oil. Its concentration in body tissues is higher than all other carotenoids. Lycopene is mainly distributed to fatty tissues and organs such as the adrenal glands, liver, and testes. In contrast to other carotenoids, lycopene's serum values are not regularly reduced by smoking or alcohol consumption, although levels decrease with increasing age⁴. In one study, serum concentrations of lycopene increased after consumption of heated tomato juice mixed with oil, with a peak at 24–48 h after ingestion. Heating tomato juice resulted in trans-to-cis isomerization of lycopene, and on ingestion of this juice, the cis isomers of lycopene appeared to predominate in human serum over the all-trans isomers. Lycopene is incorporated into lipid micelles in the small intestine. These micelles are formed from dietary fats and bile acids and help to solubilize the hydrophobic form of lycopene and allow it to permeate the intestinal mucosal cells by a passive transport mechanism. In blood plasma, lycopene is eventually distributed into the very low and low-density lipoprotein fractions⁵.

Dietary sources

Since humans are unable to synthesise carotenoids de novo, but 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)⁶. Of the tomato products, juice, ketchup, soup, pizza, spaghetti sauces are the major contributors in the diet (Table 1). All-trans is the predominant isomeric form of lycopene in raw tomatoes but *trans* to *cis* isomerization occurs during cooking/food processing and storage⁷.

Lycopene and its biological action

Although not considered an essential nutrient, research has shown that lycopene may have various benefits for human health. As a major carotenoid in human blood, lycopene protects against oxidative damage to lipids, proteins, and DNA. Lycopene is a potent quencher of singlet oxygen (a reactive form of oxygen), which suggests that it may have comparatively stronger antioxidant properties than other major plasma carotenoids⁸. Lycopene has been found to be a potent and specific inhibitor of cancer cell proliferation^{9,10} which is regulated by an elaborated cellular process called "cell cycle." Rapid and uncontrolled cell division is a hallmark of cancer cell metabolism; lycopene's activity in retarding cell cycle progression may explain its demonstrated activity in retarding the spread of certain types of cancer. Lycopene was found to induce the formation of the protein connexin 43, one of the major building blocks of these channels, and thereby to restore gap junctions¹¹. Lycopene induces Phase II enzymes which help to eliminate carcinogens and toxins from the body. The change in the levels of so many regulatory proteins is related to lycopene's ability to modulate various transcription factors which are key players in the process of new cellular protein synthesis¹².

Lycopene effect on various diseases

Tomato lycopene preventing osteoporosis

Osteoporosis is a major metabolic bone disease that primarily affects women and men over the age of 50 because of the loss of estrogen at menopause in women and low levels of the sex hormone testosterone in men. One of the risk factors for osteoporosis that is of wide interest and will be reviewed here is oxidative stress cause by reactive oxygen species (ROS). Ongoing clinical study is researching on the role of lycopene as a nutritional supplement in the prevention of osteoporosis in postmenopausal women. Antioxidant such as lycopene interact with ROS and mitigate their damaging effects on bone cells there by preventing the development of osteoporosis¹³.

Lycopene on breast cancer

Some studies have found no significant association between dietary lycopene intake and breast cancer, others have found a positive relationship between lycopene in breast tissue and breast cancer risk¹⁴. The Breast Cancer Serum Bank in Columbia, Missouri were analyzed to evaluate the relationship of levels of carotenoids (including lycopene), selenium and retinol with breast cancer. Only lycopene was found to be associated with a reduced risk for developing breast cancer¹⁵.

Prostate cancer

Prostate cancer is the most common male cancer in developed countries and is increasing in the developing world. One study of 404 patients in China, 130 of whom had prostate cancer, suggested that those who had the highest intakes of green tea or lycopene, independently, had an inverse association with developing prostate cancer. In addition, those ingesting both green tea and lycopene had an even greater inverse association, suggesting there may be synergistic effects¹⁶. Clinical investigation of elderly men, lycopene inhibited progression of benign prostate hyperplasia¹⁷. At less than 1 μ M concentration, lycopene was shown to inhibit human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression, specifically in prostate cancer cells, without evidence of toxic effects or apoptosis of cells. Studies using human and animal cells have identified a gene, connexin 43, whose expression is up-regulated by lycopene, allowing direct intercellular gap junction communication (GJC). GJC is deficient in many human tumors, and its restoration or up-regulation is associated with decreased proliferation¹⁸. In order to study the relationship between tomatoes, tomato products, lycopene and cancers of the upper aerodigestive tract (UADC; oral cavity, pharynx, larynx, esophagus) a case control study was carried out in Uruguay. Tomato intake was associated with a reduction in risk of upper aero digestive tract cancer¹⁹.

Lycopene effect on ovarian and cervical health

Intake of dietary lycopene may also play a role in the prevention of ovarian and cervical cancers. From a population-based study of 549 cases of ovarian cancer and 516 controls, researchers estimated consumption of several antioxidant vitamins and carotenoids including lycopene. Intake of lycopene was significantly and inversely associated with risk for ovarian cancer, predominately in postmenopausal women. The food most strongly associated with a decreased risk for ovarian cancer were raw carrots and tomato sauce²⁰. In a study involving 147 confirmed cervical cancer patients and 191 non-cancerous subjects, only lycopene was found to significantly decrease cancer²¹. In another study of non-Hispanic, black women, higher levels of lycopene in the blood were found to have a decreased risk of developing cervical cancer²².

Lycopene and longevity

Lycopene may also improve longevity in women. In a study examining plasma lycopene and longevity in nuns, lycopene and other carotenoids were measured in 94 participants, ages 77 to 99 years, living in the same convent. After six years of follow-up, only 13% of those with low plasma lycopene were still alive, while 48% of

those with moderate lycopene and 70% of those with high lycopene were living²³.

Effect of lycopene on diabetes

In a clinical study investigating the role of lycopene in diabetic patients (N=133), lycopene reduced the risk of diabetic retinopathy²⁴.

Effect of lycopene on liver protection

Lycopene and tomato extraction supplementations significantly decreased the number of altered hepatic foci expressing the placental form of glutathione S-transferase in the livers of HFD-fed rats. This was associated with significant lower proliferating cell nuclear antigen positive hepatocytes and cyclinD1 protein, as well as decreased activation of extracellular signal-regulated kinase and nuclear NF-kappaB. Although both lycopene and tomato extraction supplementations reduced HFD-induced lipid peroxidation in the liver, researchers observed significantly decreased cytochrome P450 2E1, inflammatory foci and mRNA expression of proinflammatory cytokines (TNF-alpha, IL-1beta and IL-12) in the HFD+TE fed group, but increased nuclear NF-E2-related factor-2 and heme oxygenase-1 proteins in the HFD+lycopene fed group, relative to HFD feeding alone. Data indicated lycopene and TE can inhibit NASH-promoted hepatocarcinogenesis mainly as a result of reduced oxidative stress²⁵.

Role of lycopene in the treatment of Hepatitis C

Hepatitis C virus infection and hepatocellular carcinoma are growing health problems around the globe. *In vitro*, animal, and clinical studies suggest that lycopene may attenuate liver injury and possibly prevent the development of hepatocellular carcinoma²⁶.

Lycopene and pregnancy

Antioxidants have been suggested to play a role in preeclampsia. In one study, placental tissue, maternal serum, and umbilical cord venous blood levels of four dietary carotenoids (including lycopene) were compared in 22 normal pregnant women and 19 women with preeclampsia. Levels of beta-carotene, canthaxanthin, and lycopene in placenta in preeclamptic women were lower than from those with normal pregnancy, as were beta-carotene and lycopene levels of maternal serum. These findings suggest that oxidative stress or dietary antioxidants may affect preeclampsia²⁷.

Asthma

Case control studies have shown that dietary supplementation or adequate intake of lycopene and vitamin A rich foods may be beneficial in asthmatic subjects²⁸.

Obesity

The adipose tissue secretes a large quantity of proteins called adipokines (including cytokines and chemokines) which play a role in the general physiology of the body. Obesity, characterized by a massive development of the adipose tissue leads to low grade inflammation notably due to an increased production of cytokines and chemokines. This inflammatory state would contribute to the development of insulin resistance at the origin of type 2 diabetes. As lycopene is mainly stored in the adipose tissues, researchers have developed the hypothesis that lycopene could reduce the production of cytokines and chemokines by the adipose tissue which would reduce the risk of developing pathologies linked with obesity²⁹.

Lycopene on male infertility

Excessive ROS-containing free-oxygen radicals have been identified as one of the causes of male infertility. Lycopene is a component of the human redox defense mechanism against free radicals. It is found in high concentrations in the testes and seminal plasma, and decreased levels have been demonstrated in men suffering from infertility. Oral administration of lycopene to men with infertility significantly improved the sperm concentration in 66% of cases and motility in 73% of cases³⁰.

Coronary heart disease

Coronary heart disease (CHD) is one of the primary causes of death in the world. The emphasis of research so far has been on the relationship between serum cholesterol levels and the risk of CHD. More recently, oxidative stress induced by reactive oxygen species (ROS) is also considered to play an important part in the etiology of this disease. The evidence in support of the role of lycopene in the prevention of CHD is primarily from the epidemiological observations of normal and at-risk populations. The most impressive population-based evidence comes from a multi-center case-control study in which subjects from 10 European countries were evaluated for a relationship between their antioxidant status and acute myocardial infarction. After adjusting for a range of dietary variables, only lycopene levels were found to be protective³¹. Recently a prospective, nested, case-control study was conducted by Harvard University researchers on 39,876 women. The study showed that higher plasma lycopene concentrations are associated with a lower risk of cardiovascular disease in middle-aged and elderly women³².

Atherosclerosis

Serum lycopene concentration may play a role in the early stages of atherosclerosis. Increased thickness of intima-media (the innermost lining of a blood vessel, including the middle, muscular layer in the wall of the

blood vessel) has been shown to predict coronary events. A low serum lycopene concentration, prevalent in eastern Finland, was associated with an increased thickness of the intima-media³⁴. Italian researchers report an inverse correlation between blood level of lycopene and the severity of atherosclerosis. Their study involved 11 healthy subjects with no indication of hypertension or atherosclerosis, 11 patients with hypertension, and 11 patients with hypertension and peripheral vascular disease (intermittent claudication). All participants had their blood plasma level of lycopene, gamma-tocopherol, alpha-tocopherol, beta-carotene, and coenzyme Q10 (ubiquinone) measured. The maximum thickness of the wall, provides a reliable indication of the extent of atherosclerosis. As expected intima media thickness max was significantly higher (2.56 mm) in patients with peripheral vascular disease (PVD) than in controls (1.05 mm) and in patients with uncomplicated hypertension (1.24 mm). The researchers also found a significant inverse association between intima media thickness max and lycopene levels. The researchers found no association between intima media thickness max and blood levels of alpha-tocopherol, gamma-tocopherol, beta-carotene or coenzyme Q10. They speculate that lycopene may be protective against atherosclerosis³³.

Hypertension

Hypertension (HT), dislipidaemia, and homocysteinaemia are a major risk factors for cardiac, cerebral and renal diseases. Treatment of HT can reduce this increase risk, however, in 70% of hypertensives, BP is poorly controlled. In studies carried out on 30 HT subject aged 40-65 exhibited a significant decrease in systolic and diastolic blood pressure following supplementation with lycopene³⁶.

Lycopene and vision health

Maintaining healthy vision as people age is an important factor in maintaining their independence. According to the National Eye Institute, over half of all Americans age 65 and older are afflicted with cataracts³⁷. In one cross-sectional survey of 372 women and women aged 66 to 75 years in Sheffield, England, the risk of cortical cataract was lowest in participants with the highest plasma concentrations of lycopene. The researchers suggest that a diet rich in carotenoids may protect against cataract development³⁸.

Effect of lycopene on cancer

There have been a few experimental studies on the role of lycopene in preventing or treating cancer. Some evidence suggests that cancers of the pancreas, colon and rectum, esophagus, oral cavity, breast, and cervix could be reduced with increased lycopene intake^{38,40}.

Skin roughness

Antioxidant substances in the skin are expected to slow down photo ageing. We therefore developed the hypothesis that high levels of antioxidant substances may be correlated to lower levels of skin roughness. By utilizing modern optical non-invasive in vivo methods, the structures of the furrows and wrinkles as well as the concentration of lycopene were analyzed quantitatively on the forehead skin of 20 volunteers aged between 40 and 50 years. These findings indicate that higher levels of antioxidants in the skin effectively lead to lower levels of skin roughness, and therefore support our hypothesis³⁹.

Oral submucous fibrosis

Oral submucous fibrosis is a premalignant condition that has received considerable attention in the recent past because of its chronic debilitating and resistant nature. It is now strongly believed that there is a definite relation of the condition with the habit of areca nut chewing. Lycopene can and should be used as a first line of therapy in the initial management of oral submucous fibrosis⁴⁰.

CONCLUSION

As an antioxidant, lycopene has proved to be beneficial in mitigating a wide array of diseases. Constant intake of tomato and its products can provide the physiological system with a barrier to cope with various disease conditions. The wide availability of tomatoes and its products is an added advantage. As a nutritional supplement lycopene could be regularly incorporated in the diet to cut the risk of disease.

ACKNOWLEDGEMENT

My sincere thanks to all the people helped in making this paper.

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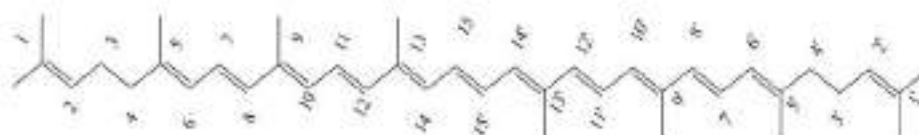
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Table 1: Lycopene content of fruit and tomato products and Table 2: Lycopene levels in human tissues

Fruit or tomato product	Lycopene content (mg/g wet weight)	Tissue	Lycopene (nmol/g wet weight)
Fresh tomato	8.8±42.0	Adipose	0.2±1.3
Watermelon	23.0±72.0	Adrenal	1.9±21.6
Pink guava	54.0	Brainstem	Not detectable
Pink grapefruit	33.6	Breast	0.8
Papaya	20.0±53.0	Colon	0.3
Tomato sauce	62.0	Liver	1.3±5.7
Tomato paste	54.0±1500.0	Lung	0.2±0.6
Tomato juice	50.0±116.0	Ovary	0.3
Tomato ketchup	99.0±134.4	Prostate	0.8
Pizza sauce	127.1	Skin	0.4
		Stomach	0.2
		Testis	4.3±21.4



STRUCTURE AND NUMBERING OF LYCOPENE.



LYCOPENE AND ITS BIOLOGICAL ACTION