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Lycopene: A novel anti-oxidant and anticancer agent

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ABSTRACT

Prostate cancer is a major public health problem in nations that have an affluent culture with an aging population. Over the last decade the development of chemopreventive agents has gained wide recognition. Among the landmark epidemiologic findings during this period has been the association between the consumption of tomato products and a lower risk of prostate cancer. Lycopene, a carotenoid consumed largely from tomato products, may be the component responsible for lowering the risk of prostate cancer. Lycopene is the most potent antioxidant among various common carotenoids. However, many research, laboratory and clinical studies are now underway with the goal of assessing the ability of pure lycopene to serve as a chemopreventive agent for prostate and other malignancies. The present study focuses on the detail about lycopene. In the near future, lycopene can be used in clinical and epidemiologic studies, providing hope that the next generation will benefit from this knowledge and thus experience a lower risk of prostate cancer.

Keywords: Lycopene, Tomatoes, Antioxidant, Anticancer.

INTRODUCTION

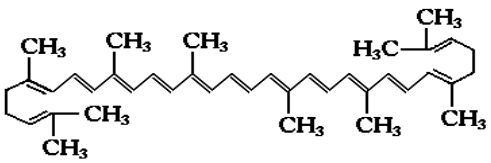
Lycopene, a carotenoid without provitamin- An activity, is present in many fruits and vegetables. It is a red, fat-soluble pigment found in certain plants and microorganisms, where it serves as an accessory light-gathering pigment and protects these organisms against the toxic effects of oxygen and light.Other sources include apricot, cranberry, grapes, pink grapefruit, guava, papaya, peaches, and watermelon.

Lycopene and other carotenoids are natural pigments synthesized by plants and microorganisms. The most-established natural roles of carotenoids are to protect cells against photosensitization and to serve as light-absorbing pigments during photosynthesis[1]. Some dietary carotenoids, such as ß-carotene, provide an important source of vitamin A; however, the majority of carotenoids, including lycopene, do not exhibit provitamin A activity. Lycopene is a carotenoid present in high concentrations in tomatoes and tomato products and is responsible for the characteristic red color of these foods. The recent associations between tomato products, lycopene, and disease risk have stimulated a greater effort to understand these relationships through cell culture and animal studies, as well as human metabolic studies[2, 9].

Botanical Origin: The fruit is obtained from the plant known as Lycopersicon esculentum Mill.

Chemistry and structure

Molecular Structure of Lycopene:



Molecular Formula: $C_{40}H_{56}$
Molecular Weight: 536.87

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- Lycopene is a 40 carbon acyclic carotenoid containing 11 conjugated double bonds.
- The chemistry of lycopene is unique because it has no pro-vitamin A activity, as compared with other carotenoids, such as alpha-carotene and beta-carotene.
- Lycopene is lipophilic and it is insoluble in water. Lycopene is the most abundant carotenoid in tomatoes (0.9 to 4.2 mg per 100 g), followed by beta-carotene, gamma-carotene, phytoene, and other minor carotenoids.
- It is touted as the highest overall single oxygen-quenching carotenoid.
- Lycopene is resistant to heat-induced geometrical isomerization in the processing of tomatoes.
- Mechanical treatment with heat helps release lycopene from the tomato matrix, improving bioavailability (as seen with processed commercial tomato products versus fresh tomatoes).
- The absorption of lycopene is enhanced by fat.
- Natural sources primarily contain the all-trans form of lycopene.
- The cis form of lycopene is more bioavailable and is less likely to precipitate and form the crystals affecting solubility.

More than 600 carotenoids have been characterized and share common structural features, such as the polyisoprenoid structure and a series of centrally located conjugated double bonds[10, 11]. The color and photochemical properties of each carotenoid are determined by its structure[11]. In addition, the structure also contributes to the chemical reactivity of carotenoids toward free radicals and oxidizing agents, which may be relevant to *in vivo* biological functions in animals[11]. Lycopene is a forty carbon ($C_{40}H_{56}$) acyclic carotenoid with 11 linearly arranged conjugated double bonds. Lycopene lacks the ß-ionone ring structure and is therefore devoid of provitamin A activity. Because of the highly conjugated nature of lycopene, it is particularly subject to oxidative degradation and isomerization. Chemical and physical factors known to degrade other carotenoids, including exposure to light, oxygen, elevated temperature, extremes in pH, and active surfaces, apply to lycopene as well[12, 16].

As a polyene, lycopene readily undergoes a *cis-trans* isomerization. As a result of the 11 conjugated carbon-carbon double bonds in its backbone, lycopene can theoretically be arranged in 2048 different geometrical configurations. Although a large number of geometrical isomers are theoretically possible for all-*trans* lycopene, Pauling and Zechmeister *et al*[17, 18] have found that only certain ethyl-

enic groups of a lycopene molecule can participate in *cis-trans* isomerization because of steric hindrance. Interconversion of isomers is thought to take place with exposure to thermoenergy, absorption of light, or by involvement in specific chemical reactions. *Cis* isomers of lycopene have chemical and physical characteristics distinctly different from their *all-trans* counterparts. Some of the differences observed as a result of a *trans*-to-*cis* isomerization reaction include lower melting points, decreased color intensity, a shift in the lambda max, smaller extinction coefficients, and the appearance of a new maximum in the ultraviolet spectrum[19]. To avoid underestimating the quantitative measurement of lycopene *cis*-isomers, the appropriate wavelength maximum and extinction coefficient should be applied. Because of the difficulty in identifying individual *cis* forms, quantitative data for isomer content of biological samples are generally estimated values.

Mechanism of Action

Antioxidant Activity

Consumption of carotenoids rich food has been associated with several health benefits including their ability to protect against oxidative damage[20]. Lycopene is the most potent antioxidant to prevent oxidation damage of the chromosome.

- Oxidative stress is recognized as one of the major contributors of increased risk of cancer, and in chemical assays.
- Lycopene can trap singlet oxygen and reduce mutagenesis in the Ames test.
- The antioxidant activity of carotenoids in multilamellar liposomes has been assayed by inhibition of formation of thiobarbituric acid-reactive substances.
- Lycopene's configuration enables it to inactivate free radicals.
- The free radicals are ready to react with cell components and cause permanent damage. Oxygen-derived free radicals are the most reactive species.
- These toxic chemicals are formed naturally as by-products during oxidative cellular metabolism.
- As an antioxidant, lycopene has a singlet-oxygen-quenching ability.

Hypocholesterolemic Activity

- Lycopene inhibits *de novo* cellular cholesterol synthesis from acetate upto 63% & following 73% cell incubation.
- Unlike LDL-derived cholesterol, which also suppresses macrophage LDL receptor activity, lycopene increase the activity of the macrophage LDL receptor. Hence the plasma LDL cholesterol concentration reduces (upto 14%).
- It has inhibitory effect on macrophage 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase, the rate-limiting enzyme in cholesterol synthesis.
- These observations have implications for heart disease prevention through modification of the processes of cellular atherogenesis resulting in unstable plaque formation.

Extraction

Lycopene rich product taken in the group consisting of tomato, pink grapefruit, watermelon, guava and papaya, etc. The impurities and water from the product are removed by subjecting the product to at least one washing with boiling ethanol (70% – 80%). Extracting the purified product by subjecting product to at least one extraction with boiling ethanol having an alcohol content 92 %. Recovering the ethanol solution and cooling the solution upto a temperature room temperature to obtain lycopene crystals. Filter the solution to recover the lycopene crystals[21].

Pharmacokinetics

- After ingestion, 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 lycopene and allow it to permeate the intestinal mucosal cells by a passive transport mechanism.
- Lycopene is incorporated into chylomicrons and released into the lymphatic system.
- In blood plasma, lycopene is eventually distributed into the very low density lipoprotein (VLDL) and low density lipoprotein (LDL) fractions.
- Lycopene is mainly distributed to fatty tissues and organs such as the adrenal glands, liver, and testes.
- Lycopene is carried in the plasma entirely by lipoproteins, and no other lycopene-specific binding or carrier proteins have been identified so far.
- Few metabolites of lycopene have been identified in human tissues & plasma as 5, 6-dihydroxy-5,6-dihydro-lycopene which may be a product of an oxidation reaction via a transitional lycopene epoxide.
- Lycopene supplementation appears to interact with the metabolism of linoleic acid, the "essential" fatty acid, resulting in decrease in its plasma concentration.

Bioavailability of Lycopene

Differences in bioavailability of lycopene may account, in part, for the relatively poor correlations between blood lycopene concentrations and estimated dietary intake. Carotenoids are strongly bound to intracellular macromolecules in many foods, and absorption therefore may be limited unless released from the food matrix[22]. Heating tomato juice was shown to improve the uptake of lycopene in humans[23].

Gartner *et al*. reported that lycopene bioavailability from tomato paste, a processed product, was higher than from fresh tomatoes when both were consumed with corn oil[24]. These observations seem to be the result of thermal weakening and disruption of lycopene–protein complexes, rupturing of cell walls, and/or dispersion of crystalline carotenoid aggregates. Likewise, various food-processing operations such as chopping and pureeing, which result in a reduction in physical size of the food particle, will also enhance lycopene bioavailability[25, 26].

Lycopene bioavailability was recently studied after a single dose of fresh tomatoes or tomato paste by measuring carotenoid concentrations in the chylomicron fraction of the systemic circulation[24]. Each source of lycopene (23 mg) was consumed with 15 g of corn oil.

Tomato paste was found to yield a 2.5-fold greater total *all-trans* lycopene peak concentration and a 3.8-fold greater area under the curve than fresh tomatoes. When compared with fresh tomatoes, ingestion of tomato paste resulted in a significantly higher area under the curve for *cis* lycopene isomers. Recent data in our laboratory from a pilot clinical trial of lactating women showed greater concentration of lycopene in human milk for those consuming tomato sauces compared to fresh tomatoes[26]. These observations support the conclusion that food processing and cooking enhances lycopene bioavailability. Digestive processes will certainly influence lycopene bioavailability. Several factors affect initial carotenoid release from the physical food matrix and transfer and distribution into lipid droplets within the stomach and proximal duodenum[28]. Perhaps of major importance, dietary lipids may serve a critical role in dissolution and subsequent absorption of a very hydrophobic carotenoid such as lycopene. Pancreatic lipases and bile salts act upon the carotenoid-containing lipid droplets entering the duodenum and form multilamellar lipid vesicles containing the carotenoids[29]. The transfer of lycopene, like other carotenoids, from the micelle into the mucosal cells appears to occur via passive diffusion[30, 31]. Factors such as the structural features of the carotenoid, the dietary fat content, fatty acid patterns, fiber, and other food components may influence the carotenoid content of micelles and subsequent mucosal transfer[29].

Chylomicrons are responsible for carrying carotenoids from the intestinal mu-

cosa to the blood stream via the lymphatics[29]. Little is known about how lycopene in chylomicrons is subsequently accumulated by the liver and other tissues, repackaged in lipoproteins, and returned to the circulation. Lycopene is carried in the plasma entirely by lipoproteins, and no other lycopene-specific binding or carrier proteins have been identified thus far[29, 32]. However, it is likely that dietary and pharmacologic agents that influence lipoprotein metabolism will influence circulating lycopene concentrations.

Lycopene from food processing

Consumers use the intensity of the red color as an index of quality for tomato products. Therefore, reducing the loss of lycopene throughout the production process and during storage has always been an important issue for food processors. Exposure to thermal treatments during food-processing operations causes well-documented changes in the physiochemical stability of carotenoids.

Boskovic and Cano *et al*[33, 34] observed that processing and extended storage of dehydrated tomato products resulted in a loss of *all-trans* lycopene content by up to 20%. Food-processing techniques, such as canning and freezing, led to a significant reduction in lycopene and total carotenoid content of papayaslices. In contrast, many studies have found that hydrocarbon carotenoids such as lycopene,carotene, and ß-carotene in processed fruits and vegetables are fairly heat resistant[35, 36].

According to Khachik *et al*[35], most of these carotenoids remain stable after bench-top food preparation. Saini and Singh[37] also reported that thermal processing had no effect on the lycopene content in juices made from several high-yield tomato hybrids. Zanori *et al*[38] recently reported that despite the oxidative and thermal severity of the drying process, reflected in the 5-hydroxymethyl-2-furfural and ascorbic acid values, lycopene displayed high stability during drying of tomato halves.

Additionally, Nguyen and Schwartz[39] recently reported that processing does not have a significant effect on the stability of lycopene, independent of product type, moisture content,container type, tomato variety, and severity of heat treatments.

Although lycopene may be fairly stable during standard food processing procedures, less is known about its impact on isomerization. Studies have shown that heating tomato juice and bench-top preparation of a spaghetti sauce from canned tomatoes increases *cis*-isomer concentrations[40, 41]. In contrast, Khachik *et al*[36] observed that common heat treatments during food preparation, such as microwaving, steaming, boiling, and stewing, did not significantly change the distribution of carotenoids in tomatoes and green vegetables. Other studies have also reported low levels of lycopene *cis* isomers in thermally processed tomato products[39, 42].

Recently, Nguyen and *et al*[43] reported that during typical cooking of tomatoes, factors such as genotypic differences in overall carotenoid composition, the presence of oil, and physical changes to tomato tissues did not influence the thermal isomerization of *all-trans* lycopene, all-*trans* carotene, or prolycopene. Additional information needs to be gathered on the thermal behavior of lycopene before definitive answers can be offered regarding its physical state and stability during processing and cooking. Nevertheless, it is evident that lycopene is more stable in native tomato fruit matrices than in isolated or purified form due to the protective effects of cellular constituents such as water[44].

Assay for Lycopene

- Because of its instability, lycopene concentrations of reference standard preparations were determined spectroscopically and chromatographically prior to use in order to assign accurate lycopene strength.
- After diluting the stock standard solution in petroleum ether, the lycopene concentration was determined spectroscopically at 472 nm using an extinction coefficient of $E^{1\%}_{1cm} = 3450$.
- The reference standard preparation was further characterized chromatographically by determining the area % of the lycopene peak versus total peak area.
- Antioxidant stabilizers were tested for efficacy in retarding the degradation of lycopene in standard and sample preparations.
- Standards and samples were chromatographed to demonstrate that the method is suitable for the determination of lycopene in the presence of other carotenoids.

Lycopene and Prostate Cancer

Prostate cancer afflicts more than 10% of North American men and while this cancer is often curable by surgery or radiotherapy when confined to the prostate, in more than half of the patients the cancer recurs or spreads outside the gland at the time of diagnosis[45]. Lycopene has emerged from the scientific literature over the past few years, to bear significant potential for consideration in both the treatment and prevention of prostate cancer.

Numerous epidemiological studies and reviews have been carried out describing the role of lycopene in association with the prevention of prostate cancer[46]. One of the earliest epidemiological studies viewing an inverse relationship between the consumption of tomatoes and tomato products and the risk of prostate cancer was published in 1995[47]. In this study the valuable properties of tomato products was attributed to lycopene. Since then, several other epidemiological, experimental and tissue culture studies have been reported providing further evidence for the role of lycopene in prostate cancer.

Lycopene was the only antioxidant for which plasma lycopene was very powerfully related to lower prostate cancer risk (upper quintile odds ratio = 0.40; P, trend = 0.006 for aggressive cancer). In tissue distribution studies carried out in rats, lycopene was found in liver, testes, stomach, intestine and prostates of rats fed a tomato oleoresin diet[48].

Physiological levels of lycopene were also detected in prostate, lung, mammary gland and serum of male and female rats fed a diet containing a carotenoid mixture extracted from tomatoes[49]. Additional studies suggest that the cis-lycopene is the predominant isomer found in liver and that androgens modulate the metabolism of lycopene in the liver[50].

Rationalisation of the evidence for a reduction in prostate cancer risk has often been assigned to the antioxidant properties of lycopene[51] although recent evidence suggests that additional mechanisms beyond antioxidant property of lycopene may also be pertinent to prostate carcinogenesis.

Cytotoxic and antiproliferative effects of lycopene are indicated in prostate cancer cells (PC-3, DU 145, LNCaP). Similar effects of lycopene are also demonstrated for other cancer cell lines. Suppression of insulin-like growth factor (IGF-I)-mediated cell signaling reported in mammary carcinoma cells that is associated with its effects on proliferation may also hold true in case of prostate cancer[52, 55]. Elevated IGF-1 levels are thought to be interrelated with an increased lifetime risk of developing prostate cancer. This finding, if confirmed clinically, provides a basis for the preventive properties of lycopene on prostate cancer development[56].

More recently, clinical reports have also been presented suggesting a therapeutic application for lycopene in prostate cancer treatment[57, 58]. It has been seen that pre-operative lycopene administration to men two weeks prior to radical prostatectomy was shown to decrease the number and size of cancerous foci in the prostate as well as associated high grade prostatic intra-epithelial neoplasia (PIN) in treated men as compared with control treated men[57].

A clinical study describes a single case response of hormone refractory prostate cancer to lycopene[58]. Extensive nodal disease was reported in a man whose serum PSA was 365 ng/ml in March 1999. After 2 years of daily lycopene (10 mg per day) and saw palmetto treatment (300 mg orally 3 times per day), the man was reported to be asymptomatic[58]. This study was uncontrolled with

respect to both placebo group, compliance and product quality and so there remains some questionability regarding definitive interpretation of the results. The patient in this study used saw palmetto in conjunction with lycopene and so, again, the compound of interest was not the sole product ultimately being tested. However, the outcome of these studies suggests a potential therapeutic role for lycopene as well as a use in the prevention of prostate cancer. As more evidence emerges in support of the anticancer and therapeutic benefits of lycopene, and as we begin to unravel more mechanistic detail of its activities, men living with prostate cancer are increasingly encouraged that an additional portion of tomato based foods can significantly benefit their fight against a disease which is the number one cancer affecting male population.

Clinical signification

1) Cancer

- Lycopene participates in a host of chemical reactions to prevent carcinogenesis by protecting critical cellular biomolecules, including lipids, proteins, and DNA.
- Benign prostate hyperplasia (BPH): Patients diagnosed with BPH or enlarged prostate are at increased risk of developing prostate cancer and are benefit from taking lycopene supplements.
- Other cancer such as oral, cervical, colon, esophageal, stomach & rectal can be significantly treated with lycopene.

2) Atherosclerosis

It reduces the Plasma LDL cholesterol concentrations & triglyceride levels, and increases high-density lipoprotein cholesterol. So it is mainly used in Atherosclerosis.

3) Inflammation

Lycopene reduces the production of inflammatory mediators, such as tumor necrosis factor-alpha.

4) Sun protection

Lycopene in combination with other carotenoids may help to reduce sunburn. In a combination of beta-carotene, lutein and lycopene ultraviolet-induce sunburn reduce.

5) Prevention of macular degeneration

Lycopene uses for the prevention for age related macular degeneration.

6) Exercise-induced asthma

Taking lycopene by mouth may reduce exercise-induced asthma.

7) Infertility

Taking lycopene seems to have a role in the management of idiopathic male infertility[20].

8) High blood pressure associated with pregnancy (pre-eclampsia)

Lycopene may reduce the development of pre-eclampsia and intra-uterine growth retardation in women having their first child[20].

9) Other Clinical Significance

- Helps with problems such as diabetes.
- Guards against aging of the skin.
- May prevent osteoporosis.
- Lycopene may be effective as a first-line therapy in treating oral submucous fibrosis.
- Can assist with fertility problems in men.

Side Effects

Lycopene supplements are generally well tolerated. But GI complaints, such as diarrhea, dyspepsia, gas, nausea, and vomiting are rarely observed.

Toxicities

No toxic effects were observed in rats treated with lycopene 2 g/kg/day for 28 days, an intake similar to approximately 200 mg of lycopene per kg of body weight per day in humans.

Interactions with Drugs

Drugs such as lovastatin, atorvastatin, cholestyramine, colestipol etc. that lower cholesterol levels in the blood may also reduce the levels of carotenoids such as lycopene.

Formulation

It is available is variety of formulation as lycopene tablet, capsule, syrup, paste, etc.

Therapeutic Dose

Usually it is given in 4 – 10 mg / per day.

Marketed

Lycopene products like Lycodee capsule & Lycodee Syrup are available in market.

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