

LYCOPENE: IT'S ROLE AS PROSTATE CANCER CHEMOPREVENTIVE AGENT

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ABSTRACT

Current researches for new anticancer drugs focuses more on the natural compounds such as physicochemical constituent from the regular human diet. Because of the lack of severe side effects yet efficiently can act on a wide range of receptors or molecular targets involved in carcinogenesis. One such compound is the tomato derived carotenoid lycopene. Lycopene which is basically a carotenoid phytoconstituent has remarkable chemopreventive and anti-proliferative activity. People with a sound diet of lycopene may have a less risk of cancers especially prostate cancer which is most impeding for the males of age 40-50 years. Antioxidative property of the lycopene includes a considerable reactive oxygen species (ROS) scavenging activity, which allows lycopene to prevent lipid peroxidation and DNA damage [1]. As another chemopreventive strategy, lycopene reduces the risk of prostate cancer by diverging its effect on the plasma Insulin like growth factor, on Connexins, and the most acceptable one, by quench of free radicals. Lycopene also has a synergistic effect with other natural antioxidant that might be important for its future application in anticancer treatment.

Keywords: Chemopreventive, Antioxidant, Connexions, Synergistic effect.

INTRODUCTION

Chemistry of lycopene

Lycopene is a member of a group of naturally occurring pigments called carotenoids¹. Carotenoids usually occurs in plants and not in animals, hence animals rely on ingestion for their source of these biomolecules. In plants the main function of these carotenoids is to serve as light absorbing oxidative pigment and also protect cells against photo oxidative damage during the process of photosynthesis².

Tomatoes and tomato-based products are the major sources of natural lycopene in the human diet. It is the major colouring pigment of tomato usually occurs in all trans form (35-96% of the total lycopene) and low levels of cis-lycopene (1-22% of the total lycopene).

Lycopene for food use can also be manufactured by chemical synthesis or can be produced by fermentation of *Blakeslea trispora*³.

Synthetic lycopene occurs as a red to dark violet crystalline powder. It is practically insoluble in water and nearly insoluble in methanol and ethanol, but is freely soluble in chloroform and tetrahydrofuran.

Lycopene is sparingly soluble in ether, hexane, and vegetable oils. A 1% solution of lycopene in chloroform is clear and has intensive orange-red colour. A solution in hexane shows an absorption maximum at approximately 470 nm³. Other significant sources of lycopene include pink grapefruit, watermelon, Papaya, pink guava, and apricots.

Lycopene is a highly unsaturated straight chain hydrocarbon with a total of 13 double bounds, of which 11 are conjugated. The chemical name of Lycopene is 2,6,10,14,19,23,27,31-octamethyl-2,6,8,10,12,14,16,18,20,22,24,26,30-dotriacontatridecaene. Common names include Ψ , Ψ - carotene, all-trans-lycopene, and (all-E)-

lycopene. The chemical formula is $C_{40}H_{56}$ and the molecular weight of is 536.9⁴.

Lycopene as such is unstable when exposed to light, heat, and oxygen. Exposure to light and heat triggers its isomerization from the *trans* to *cis* configuration. The *cis*-isomers of lycopene have different physico chemical characteristics than all-*trans*-lycopene. Some of these differences include lower melting points, lower specific absorption, and a shift in the absorption maximum. Lycopene can also undergo oxidative damage when exposed to oxygen with the formation of many different oxidative products. To prevent isomerization and oxidation, synthetic lycopene is kept under inert gas in light proof containers (amber colour) and stored in a cool place⁴.

The unique nature of this phytochemical constituent makes it a very potent antioxidant which is twice as potent as β carotene and ten

times that of α tocopherol in terms of its singlet oxygen quenching ability. The molecule lacks the terminal β ionic rings, and unlike beta carotene lacks pro vitamin A activity. The presence of such a highly conjugated double bonds, allows lycopene and all other carotenoids to isomerise it and thus numerous combinations of *cis* and *trans* isomers are possible. Lycopene usually occurs in a *trans* isomeric form, it can undergo high thermo chemical reaction induced *cis* isomerisation. *Trans* form of the molecule is highly stable, good bioavailable, and has higher antioxidant potential as compared to its *cis* form⁵. The *cis*-forms are available in sound in the human serum and all the *trans*-forms are converted to *cis* forms in the body. Various *cis* isomers of lycopene have been identified in processed tomatoes products and biological fluids and tissues.

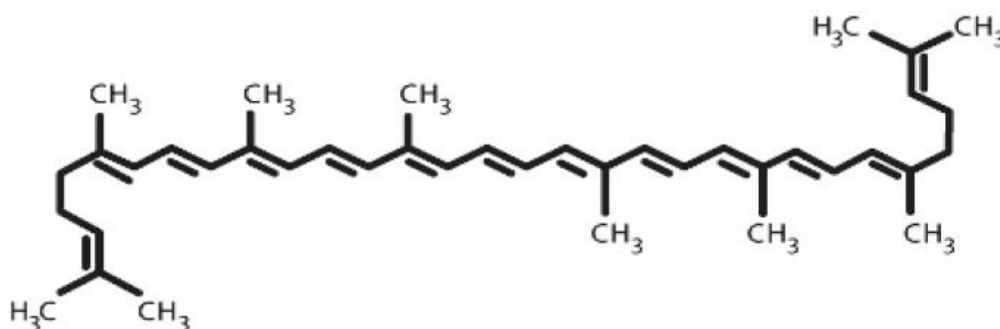


Fig. 1: Skeletal formula of lycopene

The antioxidative properties of this phytochemical constituent have been suggested as being mainly responsible for their beneficial effects. Recent studies also show that these molecules may mediate their effect via other mechanisms such as gap functions communication, cell growth regulation, modulation of gene expression and immune response, and modulation of phase 1 and 2 drug metabolizing enzymes. Lycopene reacts with oxygen free radicals by either transfer of the unpaired electrons leaving the carotenoid in an unstable excited triplet state, the excess energy being dissipated as heat or by bleaching of the carotenoids. Lycopene has been demonstrated to not only scavenge oxygen free radical species, for example peroxy radicals, but also interact with reactive oxygen species such as hydrogen peroxide and nitrogen dioxide and in

this manner protect cells from oxidative damage⁵. The oxidative weapons are free radicals, the molecules with an unpaired electron on the outer shell. There are intrinsic defense mechanism against cellular damage by these free radicals including the enzymes glutathione peroxidase and superoxide dismutase.

Extraction of lycopene

The extract from tomato is a lycopene-rich extract prepared from the ripe fruits of tomato (*Lycopersicon esculentum* L.). The crude product is manufactured by crushing tomatoes, to produce tomato juice that is then separated into serum and pulp. The pulp is then subsequently extracted using ethyl acetate as a solvent⁶. Ethyl acetate as such is organic solvent will partition the hydrophobic molecule. The final

extract consists of tomato oil in which lycopene together with a number of other constituents that occur naturally in tomato, are dissolved and dispersed. These constituents include fatty acids and acylglycerols, unsaponifiable matter, water soluble matter, phosphorous compounds, and phospholipids. The final product is obtained after solvent evaporation under vacuum at 40-60°C. Lycopene extract from tomato contains carotenoids (5-15% w/w) as well as non-carotenoid components. The carotenoid fraction of the tomato extract consists mainly of total lycopenes, of which ~86 % is all-*trans*-lycopene, ~6% is 5-*cis*-lycopene, ~2% is 9-*cis*-lycopene and ~2% is 13-*cis*-lycopene, and ~4% are other carotenoids. The major non-carotenoid components of the extract include fatty acids

and acylglycerols (69-74%), phospholipids (8.9-14%), and waxes (5-8.4%). Lycopene extract from tomato may also be used in food supplements⁶.

The food level of the extract, expressed as lycopene added to food, may vary from 2 mg/l in bottled water to 130 mg/kg in ready-to-eat cereals. Lycopene in the tomato extract was shown to be stable when stored at room temperature 27-30°C and at 4°C for up to 37 months. When used as a food colour, lycopene remains stable in the food matrix under appropriate storage conditions. Lycopene stability depends on the particular food to which it is added, as well as on the manufacturing process.

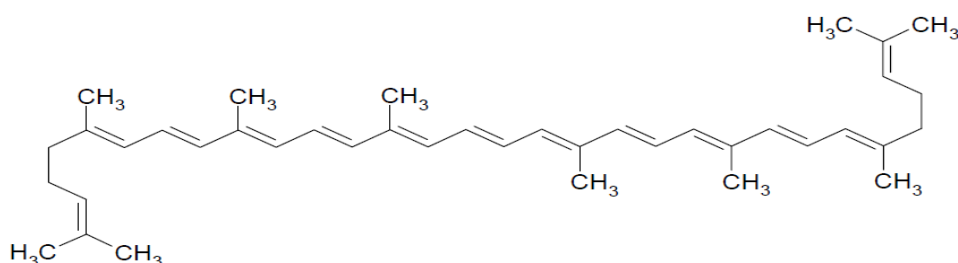


Fig. 2: All-Trans-Lycopene

PROSTATE CANCER PREVENTING ACTIVITY OF LYCOPENE

Lycopene's mechanism of action in affecting prostate health is unknown. Several theories are being explored⁷.

1. The first proposes an association between lycopene and insulin growth factor (IGF)

High levels of insulin growth factor are linked to a greater risk of prostate cancer. Increased lycopene consumption is inversely related to insulin growth factor levels. It is more efficient than any other carotene in inhibiting the insulin like growth factors type 1 (IGF1) induced proliferation of a number of tumour cell lines⁷. IGFs are important growth factors in the process of formation of tumour and tumour cell proliferation. Insulin growth factor and growth hormone are colligated with each other. When growth hormone is secreted from the anterior pituitary part it induces the production of Insulin like Growth Factor (IGF) by the liver and secretion of IGF inhibits the secretion of GH by feedback mechanism. IGF are proteins of high sequence similarity with the insulin and has two cells surface receptors, IGF 1 & IGF-2 of which, IGF-1 are postulated here now. There is a

strong positive association between IGF-I levels and prostate cancer risk in males.

1.1 General Physiology of INSULIN LIKE GROWTH FACTOR 1

IGF-1 is a protein also called as Somatomedin C, is encoded by IGF-1 gene and the actions elicited by it are called as Non Suppressable Insulin Like Activity (NSILA). It is required in the childhood growth and cell proliferation. IGF-1 evokes its activity by its binding to IGF-1 receptor (IGF1R), a Tyrosine Kinase Receptor which broaches intracellular signaling. IGF1 is the most virile stimulator of Akt signal pathway which is useful in cell proliferation and an inhibitor of programmed cell death i.e. apoptosis. Akt, also known as protein kinase B is a serine/threonine protein kinase that fiddles a critical role in cell cycle and cell proliferation as follows: Bcl-2 associated death protein (BAD) is involved in the cell apoptosis and forms a heterodimer with B cell lymphoma2 (Bcl-2) by triggering a BAX triggered apoptosis. Thus cell apoptosis is evoked. The de-phosphorylated BAD is active and evokes apoptosis. The Akt phosphorylates the BAD and thus dissever the BAD from the Bcl2 associated heterodimer

complex thus inactivating its function of apoptosis⁸.

Cellular effect of lycopene, showed that growth inhibition by the lycopene involves interference in the mitogenic pathway of IGF-I. It is also found that IGF-I-stimulated cell growth was inhibited by physiologic concentrations of lycopene that were lower than those needed for inhibition in unstimulated cells. These findings warranted the examination of the effect of lycopene on the IGF signaling pathway.

2. Another proposed mechanism of action includes both inhibition of tumour growth and increased differentiation of normal cells⁸

Lycopene and other carotenoids cause this inhibition by increasing gap-junctional communication among healthy prostate cells and up regulation of connexin 43 (Cx43). Malignant prostate cells with a decrease or loss in junctional communication grow more slowly than cells with greater communication. Gap junctional intercellular communication (GJIC) and Cx43 expression levels could be useful intermediate endpoints in prostate cancer chemoprevention because they are decreased in prostate cancer cells. Therefore, chemo preventive agents modulating Cx43 expression and/or GJIC would be of great interest. Retinoid and carotenoids are potent up-regulators of

Cx43 and GJIC. In particular, lycopene increases GJIC by increasing expression of the gap junctional gene, Cx43⁸. This action correlates strongly with the ability of lycopene and other carotenoids to suppress neoplastic transformation in model cell culture systems. This action of carotenoids has been proposed to have mechanistic significance by enabling the transfer of growth-regulatory signals between normal growth-inhibited cells and pre neoplastic cells. Indeed, when neoplastic cells were forced into junctional communication with quiescent normal cells, the neoplastic cells became growth arrested in direct proportion to their extent of junctional communication. Progressive decreases in the expression of Cx43 with disease severity have been reported in the human prostate, and there is evidence in prostatic carcinoma cell lines that some of this loss of junctional communication may result from defects in assembly of Cx43 protein into gap junctions. When functional communication was restored in a human prostatic carcinoma cell line, cells had more normal differentiation, reduced proliferation, and suppressed tumorigenicity. Therefore, Cx43 and GJIC could be used as surrogate endpoint biomarkers (SEBs) or intermediate endpoints in phase II clinical chemoprevention trials for prostate cancer.

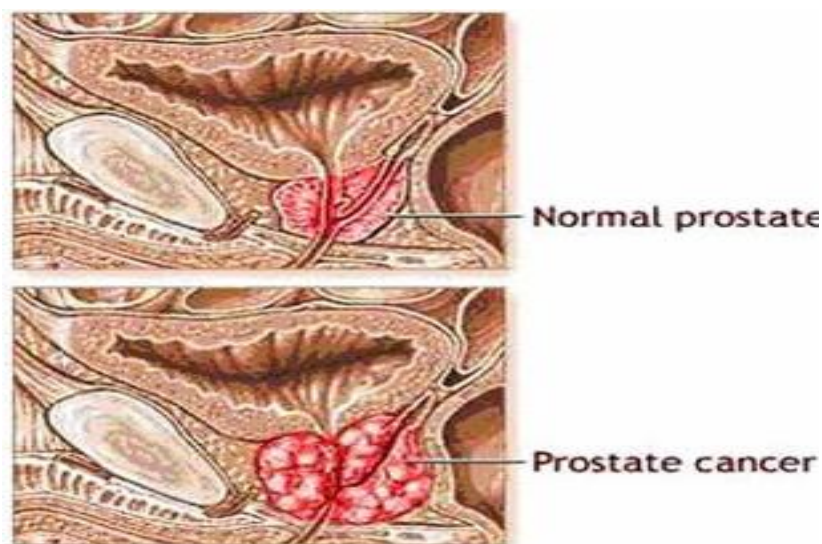


Fig. 3: Showing the difference between normal and cancerous cells of prostate

3. The most widely accepted theory involves Lycopene's antioxidant effect

Lycopene acts as a scavenger for singlet oxygen, which is theorized to damage DNA and cause cancer. Lycopene is naturally found in high concentrations in prostate cells, which may account for its specific effect on prostate cancer⁹. There is also some evidence that lycopene affects other reactive oxygen species, such as hydrogen peroxide and nitrogen dioxide.

OTHER IRREFUTABLE EFFECTS OF LYCOPENE¹⁰

- Studies prove that it has been useful in lowering of hypertension, in particular mild hypertensive patient.
- Naturally lycopene is useful in the manufacturing of vitamin A. So, it is also helpful in the improved eyesight.
- It increases the High Density Lipid levels (HDL) which are useful for the absorption of Lower Density Lipids (LDL), thus preventing atherosclerosis, hypercholesteremia. As an anti oxidant it also helps cholesterol from being oxidised¹¹.
- Lycopene is also useful in treating oral leukoplakia, a condition which is precancerous mucous membrane condition, which is manifested by white patches.

REACTION AND FATE IN FOODS

The chemical structure of lycopene, particularly the straight chain of conjugated carbon-carbon double bonds, predisposes lycopene to get isomerize and degrade upon exposure to light, heat, and oxygen and the subsequent loss of its colouring properties this would render tomato extract ineffective as a food colour. The Committee received data on lycopene stability in

representative foods based on monitoring of the lycopene content in food and the colour of food during 5 days storage under fluorescent light and storage conditions appropriate for each food (room temperature, 4°C, or frozen)¹². The concentration of lycopene in different food products, to which the commercial product Lyc-O-Mato Oleoresin containing 6% lycopene was added, was in the range of 0.5 to 60 mg/kg (Table1). Equivalent commercial food products, which were either not coloured or coloured with control colorants such as β -carotene, were used as control samples. Both the test and control samples were analyzed for colour using a Hunter Colorimeter and for lycopene content using HPLC. Visual inspections and Hunter Colorimetry showed no significant changes in colour after 5 days of storage. The HPLC data showed that ninety-five percent of the added lycopene was recovered at the time of formulation and ninety percent 5 days after formulation. These results demonstrate that tomato extract is stable in a variety of foods under appropriate storage conditions.

Lycopene stability was also assessed in a fruit preparation containing apple and *Aloe vera* formulated with tomato extract. The level of lycopene in the product decreased from approximately 83 mg/kg to 77 mg/kg after four months of storage¹³.

FOOD SUPPLEMENTS FOR LYCOPENE¹⁴

Lycopene is found in many fruits and vegetables especially in tomatoes and watermelon, which may play an important role in reducing risks of prostate cancer.

Table 1: Lycopene stability in foods prepared with Lyc-O-Mato Oleoresin containing 6% lycopene¹³

Food	Lycopene level in food(mg/kg)	Control colorant level in food (mg/kg)
Orange gelatine	10-30	Yellow 6/Red (40)
Yellow cake	20-30	β -carotene(80)
Lemon beverage	3-60	Not coloured
Orange hard candy	5-20	Not coloured
Ice cream	10-20	Not coloured
Salad dressing	20-50	Not coloured
Margarine	0.5-1.0	β -carotene(2)

Table 2: List of food supplements and the amount of lycopene In Microgram/Gram wet weight

Source	Microgram/gram wet weight
Gac	2000-2,300
Raw Tomato	8.8-42
Water melon	23-72
Pink Grape fruit	3.6-34
Pink Guava	54
Papaya	20-53
Apricot	<0.1

HANDINESS AND DOSAGE

Lycopene is formulated along with the multivitamins. They are formulated as capsules. An intake of 5-10 mg, few times a week is ample for the one who doesn't take much more vegetables or fruits¹⁵⁻¹⁷. But, for those WHO have a decent diet of fruits and vegetables there isn't any need of running for the dietary supplements of lycopene.

CONCLUSION

Lycopene which is a carotenoid pigment has good irrefutable role in prevention of prostate cancer. Pragmatically approaches have adapted and leavened its vitality. So considering all the above essays it is to be noted that lycopene consumption is important to prevent the carcinogenesis and it is proved in various studies as stated above. This article evokes that it is better to have lycopene supplements than to have a surgery and that is proved in the studies stated .Thus "PREVENTION MAY BE BETTER THAN CURE"

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