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LYCOPENE

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Abstract:

The recent research for new anticancer drugs focuses on natural compounds from the regular human diet because these compounds rarely exhibit severe side effects yet efficiently act on a wide range of molecular targets involved in carcinogenesis. One promising compound is the tomato-derived carotenoid lycopene. Its antioxidant effect includes a considerable reactive oxygen species scavenging activity, which allows lycopene to prevent lipid per oxidation and DNA damage. Simultaneously, lycopene induces enzymes of cellular antioxidant response element transcription system. As another chemopreventive strategy, lycopene induces gap junctional communication, which is suppressed carcinogenesis. Besides anticancer activity, it is also beneficial in cardiovascular diseases, osteoporosis, bone health, male infertility, skin protection, age related macular degeneration prevention, Alzheimer's disease, amyotrophic lateral sclerosis, asthma caused by exercise, immune stimulation, viral disease and DNA damage. Vegetables and fruits like red tomatoes, red fleshed watermelon, red guavas and red grapefruit are the good sources of lycopene. It is a non-toxic and is commonly found in the diet. Average daily intake levels of lycopene range from 0.70 to 25.20 mg/day. Therapeutic dosage of lycopene range from 6-60 mg daily. It is available in different dosage forms such as tablets, capsules, syrups and granulated powders with multivitamin combination.

Introduction

Lycopene, a red carotenoid pigment, $C_{40}H_{56}$ found in blood, the reproductive organs, tomatoes and palm oils[1]. It is a carotenoid without provitamin A activity and 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 protect the organisms against the toxic effect of oxygen and light[2]. As an antioxidant its consumption can reduce the risk of some cancers. The FDA has approved Generally Recognized as Safe (GRAS) status to lycopene. Recently the FDA has also given a limited health claim declaration for lycopene, stating "very limited and preliminary scientific research suggests that eating one of the cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer"[3].

Sources of Lycopene

Ripe red tomatoes provide one of the best source of lycopene. Dried red tomatoes may contain as much as 50mg of lycopene per 2.2lbs.Cooking tomatoes makes the lycopene more accessible for use by the human body. So consuming cooked tomato sauces, tomato ketchup, tomato soup, stewed tomatoes and other cooked tomato dishes are excellent sources of lycopene. Red fleshed watermelon yields almost 13,000mcg of lycopene in a 1/4melon wedge. Other red tinged fruits such as guavas and red grapefruit also contain lycopene in small amount, about, 1,700mcg in a half a grapefruit .Rose hips also contain lycopene along with vit. C. The tomato sauce mixed with little olive oil to make pasta sauce yields more usable lycopene. A little butter on the grapefruit halve will make the lycopene more usable for body[4]. Lycopene β-cyclase (β-LCy) is the key enzyme that modifies the linear lycopene molecule into cyclic β-carotene, is indispensable carotenoid of the photosynthetic apparatus and a important source of vitamin A in the human and animal nutrition. It is commercially used in the cosmetic and pharmaceutical industry as well as an additive in food stuffs. The complementary DNA cloning and expression of lycopene β-cyclase (LCy) obtained from Ficus carica in E. coli is responsible for a new gene for β-carotene production or as part of the biosynthetic pathway of astaxanthin[5]. The study results shows that the lycopene (15.33+±.24mg per

100gm) and β-carotene (10.37±.46mg per 100gm) content found to be highest at 5 days post breaker and 10 days post breaker stage respectively[6].

Structure of Lycopene

Lycopene is a symmetrical tetraterpene assembled from 8 isoprene units .it is a member of the carotenoid family of compounds, because it consists entirely of carbon and oxygen. In its natural, all trans form, the molecule is straight and long, constrained by its system of eleven conjugated double bonds. When exposed to light or heat, lycopene can undergo isomerization to any of a no. of cis-isomers, which have a bent rather than a linear shape[7].

Physical Properties

Lycopene has a molecular formula C40H56 . Its molar mass is 536.87g/mol. It is a deep red solid in colour, having melting point 172-173C. It is insoluble in water but soluble in organic solvents and oils[8]. The content of lycopene and vitamin C of nector of guava (Psidium guajava L.) decreases with the processing and storage at 10°C for 120 days[9].

Bioavailability

The research shows that the amount of lycopene in red colored tomatoes is 90% and the orange colored tomatoes contain 100%.The red tomatoes contain more all-trans variety whereas orange tomatoes contain more tetra-cis. The study said that the tetra-cis form is absorbed 2.5 times by the human body as compared to all-trans[10] Because lycopene is a fat soluble compound, absorption into tissues is improved when it is consumed with oil in one study, the serum concentration of lycopene increased after consumption of heated tomato juice mixed with oil with a peak at 24-48 hrs. after ingestion. Heating tomato juice resulted in trans to cis isomerization of lycopene and on ingestion of lycopene appeared to predominate in human serum over the all-trans isomers[11]. It has been suggested that a higher amount of carotenes solubilized into the oil phase of the food matrix would lead to a higher bioaccessibility.

The micronutrients distribution in a food matrix is better studied by using the structural characterization of the cryo-SEM with the molecular sensitivity of Raman Spectroscopy[12].

Biochemistry of Lycopene

Lycopene has both oxidative and nonoxidative properties that helps in giving it properties of fighting cancer. Due to each of beta ionone ring structure, it cannot vit. A .It also inactivates free radicals; these free radicals have a special property of reacting with body cells. These free radicals in turn create cell damage especially radicals generated from oxygen which are most damaging. It also reduces LDL oxidation and helps in reducing levels of blood cholesterol, and macular degenerative disease and cancers of lungs as well as cervix[13].

Extraction of Lycopene

Lycopene has extracted through a process that used chemical solvent .In this process chemicals are added to tomatoes to extract the chemical lycopene. The problem with this method is that this process is too long. So the suppliers of lycopene cannot keep up with the demand. To solve this problem a new method involves, supercritical fluid extraction .In this method, tomatoes are placed inside of a superficial gas extractor and the extractor removes the lycopene. This method of extraction produces a higher yield of lycopene extract than other methods[14]. Another method of extraction is the use of enzymes such as cellulase and pectinase. The increase in yield of lycopene by using enzymes is 132 microgram per gram in cellulase treated sample and 108 microgram per gram in case of pectinase treated samples[15]. Column chromatography can also be used for extraction of lycopene from tomatoes paste[16]. The ultrasonic assisted extraction (UAE) with response surface methodology (RSM) is the novel modified technique. Sonication technique enhanced the efficiency of relative lycopene lowered the extraction temperature and shortened the total extraction time. The extraction is done with the addition of oxygen free nitrogen flow and change of water route during the water bath sonication. The highest relative yield of lycopene obtained was 100% at 45°C with total extraction time of 50.0 min. and ratio of solvent to freeze dried tomato sample (w/w) of 80.0:1. Hence the current, improved UAE of lycopene promotes the extraction yield of lycopene and at the same time minimizes the degradation and isomerization of lycopene[17].The combined pressure heat treatments, high pressure

processing. (HPP:500-700 MPa, 3°C), pressure assisted thermal processing (PATP:500-700 MPa, 100°C) for up to 10 min. increases lycopene extractability[18].The samples dried by using Freeze drying method have higher antioxidant activity and high concentration of hydrophilic (phenolic, ascorbic acid and sugars) and lipophilic (tocopherols, chlorophylls, and lycopene) compounds[19].

Analysis of Lycopene

The analysis of lycopene in tomato paste is carried out by either high pressure chromatography (HPLC), spectrophotometry or by evaluating the colour. The instability of lycopene during process of extraction, handling and disposal of organic solvent makes the preparation of a sample for a delicate task. So the accurate and rapid assessment of lycopene focus on a "direct" determination o total lycopene content in different tomato pastes by means of the laser optothermal window (LOW) method at 502nm.This method has a good degree of reproducibility and a suitable method for routine assays of lycopene content in tomato pastes[20].

Pharmacokinetic and Pharmacodynamic of Lycopene

Carotenoids are absorbed like fats and transported via the lymphatic system into the liver. Absorption is dependent on the diet. Higher fat diet increases lycopene absorption while cholesterol lowering drugs reduce its absorption. 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. Like other carotenoid, lycopene is incorporated into the chylomicrons and released into the lymphatic system. In blood plasma, lycopene is eventually distributed into the very low and low density lipoprotein function. Lycopene is distributed to fatty tissues and organs such as adrenal glands, liver and testes[21].

Lycopene is currently considered one of the most efficient carotenoid at protecting against free radical that damage critical parts of the cell, including lipids, membrane lipoproteins, proteins and DNA. Lycopene may prevent the malignant transformation. Contact inhibition is one of the mechanism that controls excessive cell division. In this mechanism, a cell, in crowded surroundings, will stop multiplying. Special structure in the cell membrane, termed a

gap junction where most tumour cells exhibit fewer of these structures. Lycopene found to induce formation of a protein connexin , one of the major building blocks of these channels, and thereby to restore gap junction[22].

Interactions

Interaction with Drugs

Lycopene interact with some chemotherapeutic agents as well as with ciprofloxacin and olestra. Some drugs that lower cholesterol levels in the blood may also reduces the levels of lycopene. Examples are statins like lovastatin or atorvastatin. Nicotine and alcohol may lower lycopene in the body. Tomato based foods may prevent platelet aggregation and thrombosis. It synergises with the drugs that increase the risk of bleeding, e.g. aspirin, anti platelet drugs such as clopidogrel and non steroidal anti-inflammatory drugs such as ibuprofen and naproxen .Lycopene may interact with the infertility treatments, photosensitizing agents, or agents that affect the immune system[23].

INTERACTION WITH NUTRITIONAL SUPPLEMENTS

Concomitant intake of beta-carotene and lycopene may increase the absorption of lycopene. Medium chain glycerides may enhance the absorption of lycopene. The intake of pectin may decrease the lycopene absorption.

INTERACTION WITH FOODS

Dietary oils, such as olive oil, may enhance the absorption of lycopene while olestra may reduce the lycopene absorption[24].

INTERACTION WITH HERBS

Canthaxanthin has been shown to reduce lycopene uptake from dietary sources and it results in decreased in lycopene levels in the blood. Red palm oil may increase blood levels of lycopene. Theoretically, lycopene may increase the risk of bleeding when combined with herbs and supplements that are believed to increase the risk of bleeding. Lycopene may interact with herbs that affect fertility, photosensitizing agents or agents that affect the immune system[25].

Mechanism of Action

Lycopene at physiological concentrations can 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. A gene, connexin 43 in human body is up regulated by lycopene and which allows direct intercellular gap junctional communication (GJC). GJC is deficient in many human tumours and its restoration or up regulation is associated with decreased proliferation.

Side Effects and Toxicity

Lycopene is non- toxic and is commonly found in the diet. The prolonged and excessive intake of tomato juices, the skin and liver becomes colored orange yellow and elevated the lycopene in the blood. After two or three weeks, on a lycopene free diet the skin color returned to normal. The discoloration of the skin is known as lycopenodermia and is non toxic. Tomato and tomato based products may be acidic and irritate stomach ulcers[26].

Dosing of Lycopene

Average daily intake levels of lycopene range from 0.70 to 25.20mg/day but 50% of North Americans consume ≤ 1.86mg/day of lycopene. Based on human research human recommendations for the daily intake of lycopene suggests 7mg/day. At this level of intake, circulatory lycopene concentration is maintained at a level consistent with that shown to reduce lipid per oxidation and to result in other beneficial effects of lycopene[27]. Therapeutic dosages of lycopene range from 6-60 mg daily. Dosage cited in the literature include 6 mg for reducing the risk of lung-cancer in non smoking women, 12 mg for reducing the risk of lung-cancer in non smoking men, 30 mg for decreasing the growth of prostate cancer and preventing exercise-induced asthma and 60 mg for reducing LDL cholesterol[28].

Clinical Studies on Lycopene

Lycopene and Cancer

The specific antioxidant level may be helpful in the early detection of prostate cancer and the higher serum level of lycopene associated with greater odds of prostate cancer detection[29].The chemo preventive effects of lycopene

associated with suppression of COX-2, PGE (2), and phosphorylated ERK1/2 protein so lycopene act as a chemo preventive agent against the growth and progression of colorectal cancer in a mouse xenograft model[30]. The administration of lycopene to N-methyl-N'-nitro-N-nitrosoguanidine-induced gastric carcinoma rats up regulated the antioxidant levels and immunity responsible for the anticancer effect[31].The described that the combination of chemo preventive agents such as selenium, alpha-tocopherol, isoflavones, lycopene, green tea polyphenols, calcium and resveratrol may be useful because mechanisms of action may be additive or synergistic[32]. The study suggests that, low fat diet, high intake of fruits, vegetables and lycopene rich foods and being physically active at middle found to be protective in Malaysia[33]. Lycopene induces enzymes of cellular antioxidant defence systems by activating the antioxidant response element transcription system and lycopene increases the gap junctional communication, which is suppressed during carcinogenesis[34].The four phytochemicals 1, 2, 3, 4, 6-penta-o-galloyl-beta-D-glucose, quercetin, curcumin and lycopene and hence the effects on expression of S-phase kinase-associated protein 2 (Skp2) in MDA-MB-231(Estrogen receptor, Human Epidermal Growth Factor2- negative) and BT474 (Estrogen receptor-2 positive) cells by the cell cycle progression and play an important role in treatment of breast cancer cells, especially ER/HER2-negative breast cancers[35].the study on various low molecular weight compounds (LMW) present on wild mushrooms having anti-breast cancer activity shows that the 4-O-caffeoylquinic, nariginand lycopene stand out the top-ranked potential inhibitors for aromatase, astrone sulfatase and 17-beta HSD1 respectively and the three –D docked conformations for these compounds are used[36]. The nutritional agents such as curcumin, genistin, resveratrol, epigallocatechin gallate and lycopene can modulate NF-kB and inflammatory pathways and there by reduces the cancer related symptoms in the patient[37].

LYCOPENE AND INFLAMMATION

Lycopene functions as a very potent antioxidant to suppress the induction of inflammatory cytokines, in pancreatic acinar cells stimulated with cerulean[38].The lycopne- Selenium-Serenoa repens (Ly-Se-SeR) association has a greater and stronger anti-inflammatory activity than Serenoa-repens (SeR) alone and this combination is more effective than SeR alone in reducing prostate weight and hyperplasia, augmenting apoptosis, and reducing cell

proliferation and growth factor expression[39]. The carotenoid supplementation for preterm infants raises plasma concentrations to those observed in Human- Milk(HM) fed term infants and may decrease inflammation[40].The ability of lycopene in inhibiting IL-8 production, NF-Kb/p65 nuclear translocation and redox signaling and in increasing PPARy expression is found in isolated rat alveolar macrophages exposed to cigarette smoke extract(CME)[41].The study suggests that lycopene has barrier integrity activity, and inhibitory activity on cell adhesion and migration to endothelial cells by blocking the activation of NF-Kb, CD14 and TLR4 expression and production of TNF-α and is useful as therapy for vascular inflammatory disease[42].

LYCOPENE AND CARDIOVASCULAR DISEASES

The study revealed that stronger positive amelioration of CVD risk factors observed following the intake of n-3PUFA enriched juice than after plain tomato juice consumption, which suggested a possible synergistic action between n-3PUFA and tomato antioxidants[43]. The high plasma concentration of beta-cryptoxanthin, lycopene and alpha-carotene may be associated with decreased carotid atherosclerosis in elderly men from Eastern Finland[44].

LYCOPENE AND IMMUNIZATION

The suckling pups exposed to lycopene in breast milk appear to develop normal innate and adaptive responses both systemically and at intestinal mucosal surfaces[45].

LYCOPENE AND NUTRITIONAL CONTENT

The present results showed that the symbiosis positively affected the growth and mineral nutrient content of tomato plants and enhanced the nutritional and nutraceutical value of tomato fruits through modifications of plant secondary metabolism, which led to increased levels of lycopene in fruits obtained from mycorrhizal plants[46].The tomato, carrot and boroccoli contributed to Increasing the concentrations of each carotenoid by more than 100% after 3 and 4 weeks of consumption, the oxidative markers did not show any variation except for Glutathione Peroxidase (GPx). The serum lycopene half life stronger than that of beta-carotene[47].

LYCOPENE AND ANTIOXIDANT EFFECTS

The crop plants that dependent fully or partially as the animal pollinators contain more than 90% of vitamin C, a whole quantity of lycopene and almost the fully quantity of antioxidants beta-cryptoxanthin and beta-tocopherol, majority of the lipid, vitamin A and related carotenoids, calcium and fluorine, and a large proportion of folic acid[48].The combined treatment with lycopene and ellagic acid in addition to the 2,3,7.8-tetrachlorodibenzo-p-dioxide(TCDD) and prevented the development of TCDD- induced damages in sperm quality, testicular histology, and LPO[49].The study on the elderly patients of lumber osteophyte suggests that appropriate intake of antioxidants is important for inhibition of lumbar spine degeneration in a rapidly ageing society[50].The platinum-based compounds such as cisplatin, used in the treatment of solid tumors in elderly patients but their application is still limited due to risk in the cardiovascular toxicity, like myocardial ischemia, stroke and vascular thrombosis due to reactive oxygen species(ROS) production and subsequent induction of oxidative stress and switch to the prothrombic condition. But the use of antioxidants such as vitamin C, selenium, lycopene, melatonin and resveratrol have in implicated in cancer treatment by their property to suppress the oxidant injury[51]. The role of antioxidant carotenoids like retinolic acid (RA), all trans retinolic acid (ATRA), lycopene and beta-carotene in the production of Alzheimer's disease symptoms primarily through inhibition of amyloid beta (Aβ) formation, deposition and fibril formation either by reducing the levels of p35 or inhibiting corresponding enzymes has been studied[52].

LYCOPENE AND EYE HEALTH

The study of lycopene supplementation and other carotenoids like (lutein, lycopene and β-carotene) in preterm infants suggests that carotenoid supplementation may decrease inflammation and have protective effects of lutein on preterm retina health and maturation[53].

LYCOPENE AND DIABETES

The study on the patients with Type -2 Diabetes Mellitus showed that the physiological role of lycopene suppressed oxidative stress and enhance serum levels of IgM by increasing total antioxidant capacity (TAC) and inhibiting Malondialdehyde-LDL formation[54].

Lycopene Products

Lycopene is available in the different dosage forms such as tablets, capsules, syrups and granulated powders with other antioxidants and multivitamin combinations as:

Sr. No.	Brand Name	Dosage Form	Ingredients	Company Name
1	LYCOFIT[55]	Capsules	Lycopene 500m, vitamins	ORGANICS
2	LYC-O-MATO□□[56]	Softgel capsules	Lycopene15mg,	VITACOST
3	LYCOPENE-15[57]	Capsules	Lycopene 15mg, β-carotene	SEAGATE
4	LYCOPENE CREMA RINNOVENTE[58]	Skin cream	Lycopene, astaxanthin	LYNCOPENE SKIN CARE
5	LYCOPOM[59]	Capsules	Lycopene 250mg,other antioxidants	NEW CHAPTER
6	LYCOPENE-5[60]	Capsules	Lycopene 5mg	SEROYL/GENESTRA
7	LYCOPENE ANTIOXIDANT PROTECTION[61]	Capsules	Lycopene 20mg	SWANSON PREMIUM
8	LYCOFACTS[62]	Capsules	Lycopene 10%, Leutin, Vit.A	SIFAM PHARMACEUTICALS
9	GRAPEX[63]	Softgel capsules	Lycopene 2mg, Grape seed extract	UNIPHAR BIOTECH

10	REDOXFORTE[64]	Capsules	Lycopene, Vitamins	UNIROYAL BIOTECH
11	ZYFIT GOOD[65]	Nutritional Product	Lycopene, Vitamins, Green tea extract	ZIZA ORGANICS
12	VIT 2 FIT[66]	Capsules	Lycopene, Multivitamins	SAFE INTERNATIONAL
13	LYCOCELL[67]	Capsules	Lycopene 5mg, Multivitamins	MINT LIFESCIENCES
14	FUL-AID-PLUS[68]	Softgel Capsules	Lycopene 2mg, Leutin, Vitamins	MANKIND PHARMA
15	STAMINA-OD[69]	Tablets	Lycopene 10mg, Multivitamins	ICARUS HEALTHCARE
16	ADICO[70]	Syrup	Lycopene 1mg, Multivitamins	CC ORGANICS
17	LYRICH[71]	Capsules	Lycopene 2mg, Multivitamins	ZYTRAS LIFESCIENCES
18	HIPORT-N[72]	Capsules	Lycopene 5mg, Calcium Ascorbate	ARGON REMEDIES
19	LIFE FORCE MULTIPLE [73]	Capsules	Lycopene 3mg, Multivitamins	BIOALIGN
20	MULVIX ELIS[74]	Granulated Powder	Lycopene, Leutin, Vitamins	ELIS CORPORATE

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