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A REVIEW ON TOMATO LYCOPENE

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ABSTRACT: Lycopene, a non-provitamin a carotenoid, found in tomatoes, processed tomato products and other fruits, due to which red to pink coloration is observed. Among all the dietary carotenoids, lycopene is one of the most potent naturally and abundantly occurring antioxidant. Lycopene has unique structural features and chemical features which contribute to specific biological properties and pharmacological activities. The antioxidant potential of lycopene may be responsible for its associated health benefits. Dietary consumption of tomatoes and tomato products rich in lycopene are reported to be associated with a decreased risk of chronic diseases, like cancer and various cardiovascular diseases. Further investigations will be required to understand and evaluate mechanism whereby lycopene and its metabolites are proven to possess biological activities in human. This review summarizes the current understanding of lycopene with respect to its role in human health and prevention of various diseases.

INTRODUCTION: Chemistry of Lycopene: Lycopene is specifically an acyclic isomer of β-carotene, which is one of the members of carotenoid family. It is a lipid soluble antioxidant which is naturally synthesized by various plants, microorganisms and of certain algae and fungi but not synthesized by animals and humans [1]. It acts as an accessory light-gathering pigment and protects the plants and microorganisms against the toxic effects of oxygen and light. Chemically, lycopene is a highly unsaturated hydrocarbon having 11 conjugated and 2 unconjugated double bonds. As a polyene, it undergoes *cis-trans* isomerization induced by light, thermal energy and chemical reactions (**Fig. 1**) [2, 3].

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Lycopene obtained from plant sources exists predominantly in an all-*trans* configuration, which is the most stable form, thermodynamically [2, 3]. Lycopene is present as an isomeric mixture, with 50% as *cis*isomers, in human plasma [4]. It is one of the most potent antioxidants, [5 - 8] which has a singlet-oxygen-quenching ability twice as high as that of β-carotene and it has 10 times higher ability than that of α-tocopherol [8].

Description of Lycopene:

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

Molecular Weight: 536.85Da

Melting Point: 172-175 ^{O}C

Density: 0.889 gm. /cm^3

Stability: Sensitive to light, oxygen, high temperature, acids, catalysts and metal ions.

Solubility: Synthetic lycopene occurs in form of red to dark violet crystalline powder. It is insoluble in water and nearly insoluble in methanol and

ethanol whereas freely soluble in chloroform and tetra hydrofuran. It is sparingly soluble in solvents like ether, hexane, and vegetable oils [2].

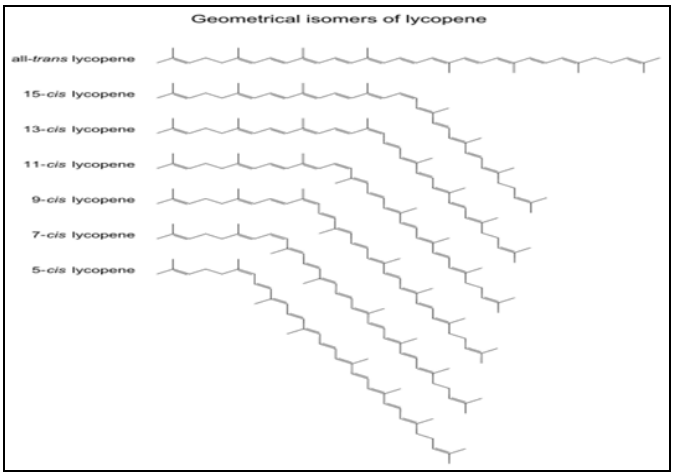

FIG. 1: STRUCTURES OF *TRANS* AND *CIS* ISOMERS OF LYCOPENE

Mechanism of Action: The biological activities of carotenoids like β-carotene are related in general to their ability to form vitamin A within the body [9]. Lycopene doesn't have β-ionone ring structure, so it does not form Vitamin A [10]. Its biological effects in humans have therefore been attributed to mechanisms other than Vitamin A.

Two major hypotheses have been proposed to explain the anticarcinogenic and antiatherogenic activities of lycopene: nonoxidative and oxidative mechanisms. Among the nonoxidative mechanisms, the anticarcinogenic effects of lycopene have been reported to be due to regulation of gap-junction communication in mouse embryo fibroblast cells [11, 12]. Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb anti-oncogenes and stop cell division at the G0-G1 cell cycle phase [13].

Astorg *et al*., [14] demonstrated that lycopene-induced alteration of the liver metabolizing enzyme like cytochrome P4502E1, was initial *in-vitro* evidence also indicated that lycopene was found to reduce cellular proliferation induced by insulin-like growth factors, which are potent mitogens, in various cancer cell lines [15]. Regulating intrathymic T-cell differentiation (immunomodulation) was predicted to be the underlying mechanism for suppression of mammary tumor growth by lycopene treatments in SHN retired mice [16, 17]. It has also been demonstrated that lycopene acts as a hypo-cholesterolemic agent by inhibiting HMG–CoA (3-hydroxy-3-methylglutaryl- coenzyme A) reductase enzyme [18]. It has been hypothesized that lycopene possesses anti-carcinogenesis and anti-atherogenesis by protecting critical cellular biomolecules, like lipids, proteins, lipoproteins and DNA [19, 20, 21].

In healthy volunteers, lycopene or tomato free diets resulted in loss of lycopene and showed increase in lipid oxidation [22], whereas dietary supplementation or dietary consumption with lycopene for 1 week, reported in increased serum lycopene levels and reduced endogenous levels of lipid oxidation, protein oxidation, oxidation of lipoproteins and DNA [19, 20]. Patients having prostate cancer were reported to have low levels of lycopene and high levels of oxidation of serum lipids and proteins [23].

Pharmacological Activities: It has been reported from various studies that a tomato rich diet and products containing tomatoes rich in lycopene have protective effects against number of chronic diseases by removing or reducing oxidative stress. Dietary lycopene protected lipids, DNA and proteins against oxidation. Such oxidized products are considered to possess key role in cancer and various chronic diseases and also have been reported to increase in the chronic disease condition significantly. In addition, dietary intake or consumption of lycopene reduces the risk of various chronic diseases and the serum and tissue levels are inversely related to the risk of these diseases. Various studies have been reported which show an inverse correlation with tomatoes and lycopene-rich diets and the incidence of several cancers and CHD. The beneficial effects are attributed duet o the anti-oxidant properties but several other mechanisms like alteration or modulation of intercellular gap junction, communi-cation, hormonal and immune system, metabolic pathways may also be involved [22, 24, 25, 26].

Role of Lycopene in Cancer: The affirmation in support of lycopene in prevention of various chronic diseases comes from epidemiological studies [27 - 31], studies using human cancer cell lines [31 - 33] pre-clinical studies [34, 35] and also human clinical trial [36]. From all the different types of cancer, the key role of lycopene for prevention of prostate cancer has been widely studied.

Prostate cancer is one of the most common malignancy and leading causes of death occurring in male, worldwide. Although, age and genetic factors are also the leading and important risk factors, environmental exposures, like diet are increasingly being associated with the development of disease. A follow up met analysis of 72 various studies reported that intake of lycopene as well as level of serum lycopene were inversely related to various cancers like breast cancer, prostate cancer, cervical cancer, ovarian cancer, liver cancers and other organ sites. Since then, various studies reported that with increased lycopene intake and serum levels of lycopene the risk of cancers were reported to reduce significantly [36 - 38].

Rao *et al*., [39] demonstrated the level of oxidative stress and antioxidants in the patients of prostate cancer. The results reported the notable differences in the level of prostate specific antigen (PSA), serum carotenoids levels and biomarkers of oxidation. Although there were no significant alterations in the levels of lutein, β-carotene, Vitamin A and E, cryptoxanthin, between the subjects with cancer and their controls, lycopene levels were noted reduced significantly in cancer patients. The PSA levels were significantly increased in the patients with cancer, along with elevated levels of proteins and lipid oxidation reporting the increased levels of oxidative stress in the patients with cancer.

Furthermore, lycopene is utilized to reduce the lipid oxidation suggesting that reduced lycopene levels in cancer cases were caused due to the disease rather than the cause of the disease [39]. Lycopene was reported to reduce the PSA levels and also the development of prostate cancer in the patients newly diagnosed with cancer, who were receiving 15 mg of lycopene for 3 weeks daily, prior to radical prostactomy [36, 40].

Studies indicated that daily consumption of food rich in lycopene has been reported to be associated with 30 to 40 % reduction in the risk of prostate cancer [28]. According to other study it was demonstrated that consuming tomato sauce, providing 30 mg lycopene for 3 weeks daily prior to prostatectomy in male diagnosed with prostate cancer showed significant elevation in serum and prostate levels of lycopene [41]. Oxidative damage to DNA was reduced and serum PSA declined significantly by 20 % with lycopene treatment.

In pilot studies with the patients having prostate cancer, it was illustrated that daily ingestion of lycopene obtained from tomato sauce or extract of tomato inhibited tumor growth and invasiveness and reduced the growth of prostate cancer probably by up regulation of connexin 43 (Cx43) (tumor suppressor protein [42].

Similarly, Heber and Lu [43] demonstrated that a gene, connexin 43, whose expression was up regulated by lycopene and allowed direct intercellular gap junctional communication (GJC) was identified from preclinical and clinical studies. It was also found that there is deficiency of GJC in many tumors of humans and its restoration or up regulation is associated with decreased proliferation. In the same manner it is confirmed from various preclinical studies that there is the inverse association between lycopene obtained from diet and growth of both spontaneous and transplanted tumors [44]. It has also been reported to inhibit the proliferation of various cancer cells like lungs, breast, and endometrium and also suppress insulin like growth factor I stimulated growth. Moreover, it inhibits growth and development of KB-I human oral tumor cells [45] and C-6glioma cells transplanted into rats [46].

Nkondjock *et al*., [47] demonstrated that tomato rich diet and consumption of tomato based products with increased lycopene content may help to decrease the risk of cancer of pancreas. From various studies it has been investigated that dietary lycopene (10ppm) showed significant reduction in the lipid and protein oxidation and illustrated that it had an apparent protective effect against azoxy-methane induced colonic preneoplastic lesions in rats [26].

Overall epidemiological analysis, *in-vitro* tissue culture studies, preclinical studies and some clinical studies involving human intervention demonstrated that increased consumption of lycopene would indicate increased circulatory and tissue lycopene levels. From *in-vivo* studies it was reported, that lycopene can play a key role as a anti-oxidant potentially and protect cells against oxidative damage and thereby reduces or prevents

the risk of development of various cancers. Further investigations are required for detailed understanding of the underlying mechanisms.

Role of Lycopene in Cardiovascular Disease: The normal function of the cardiovascular system involving heart and blood vessels is remarkably affected by cardiovascular disease (CVD), which is the major and leading cause of deaths in western world and an important contributor of morbidity and mortality in developing countries.

As per reports of the World Health Organization (WHO) [48], it was found that CVD is the world's largest killer, claiming 17.1 million lives a year. Tobacco use, unhealthy diet, physical inactivity and high intake of alcohol are the known risk factors leading to CVD. Plasma low density lipoprotein (LDL) is the major risk factor of CVD. Elevation in oxidation of LDL has been proposed to be associated with elevating risk of atherosclerosis and coronary heart disease. Cumulative evidences in literature support the role of lycopene for the prevention of cardiovascular diseases (CVD) [49 - 52].

Arab and Steck [52] reported that it has a protective effect against intimal wall thickness and myocardial infarction. It was proposed that the protective effect may be due to some other mechanism beside its antioxidant effect. Similarly, Rissanen *et al*., [53] concluded that low plasma lycopene concentration is associated with early atherosclerosis and increased intima media thickness of common carotidartery wall (CCA-IMT). Serum cholesterol levels have been used as a biomarker for the risk of CHD traditionally. Oxidation of the circulating low density lipoprotein (LDL), which is carrying cholesterol into the blood stream, to oxidized LDL (LDLox) is also thought to play a key role in the pathogenesis of arteriosclerosis which is the main disorder leading to heart attack and ischemic strokes [54 - 56].

Owing to its lipophilic nature, lycopene concentrates in LDL and VLDL fractions and not in HDL fractions [57] It has been reported to significantly reduce the levels of oxidized LDL and lipid peroxidation in the subjects who consume tomato sauce, tomato juice and lycopene oleo-resin capsules and also protects LDL from oxidation *in-vitro*.[58] The *in-vivo* and *in-vitro* studies, demonstrated that lycopene can suppress cholesterol synthesis by inhibiting 3-hydroxy-3-methyl glutaryl coenzyme A (HMG Co A) [52, 59].

Ahuja *et al*., [60] reported that the diet high in olive oil and rich in lycopene decreased the risk of CHD by improving the serum lipid profile as compared to high carbohydrate and low fat diet. Although from the epidemiological studies, convincing evidence in support of the lycopene's protective role in CVD has been provided. Well controlled human intervention studies are required to be conducted for validation of these observations in future.

Role of Lycopene in Other Diseases: Researchers have started to investigate role of lycopene in various human diseases, because of its recognition as a potent antioxidant and its preventive role in oxidative stress mediated chronic diseases.

Osteoporosis: Oxidative stress may be one of the contributing factors involved in the pathogenesis of skeletal system like development of osteoporosis, which is the most common metabolic bone disease. Lycopene has a stimulatory effect on cell proliferation and the differentiation marker alkaline phosphatase of osteoblasts as well as inhibitory effects on osteoclasts formation and resorption. There have been results of a possible decrease in bone turnover and oxidative stress markers and an increase in antioxidant status in postmenopausal women taking tomato juice or lycopene capsules. Thus lycopene plays a key role in maintaining bone health and provides dietary alternative to drug therapy especially for women with the risk of this disease [61-65].

Male Infertility: It is the most common male reproductive disorder is now being associated with oxidative damage of the sperm which leads to the loss of its quality and functionality. Significant levels of ROS are detectable in the semen of up to 25 % of infertile men whereas fertile men do not produce detectable levels of ROS in their semen [66, 67]. Researchers are beginning to investigate the role of lycopene in protecting sperm from oxidative damage leading to infertility. Studies show that men with antibody mediated infertility were found to have lower serum lycopene levels than their fertile controls [68]. According to other study, a significant increase in serum lycopene concentration

and improvement in sperm motility, sperm motility index, sperm morphology and functional sperm concentration was reported in infertile men when administered with 8 mg lycopene for 12 months. Furthermore, it was found lycopene treatment resulted in 36 % successful pregnancies.

Hypertension: Hypertension, a 'silent killer,' is a disorder which is asymptomatic until a more advanced and a fatal stage is reached. Lycopene's antioxidant property has attracted scientific research into its protective role in hypertension. As per recent study it was demonstrated that lycopene supplementation of 15 mg/ day for 8 weeks remarkably decreased systolic blood pressures from baseline values to 144 mm Hg to 134 mm Hg in mildly hypertensive subjects.

In another study a significant reduction in plasma lycopene was observed in the hypertensive patients compared to normal subjects. As the antioxidants are important in the management of hypertension, a 'dietary approach for controlling hypertension (DASH)', diet containing substantially higher levels of lycopene along with other carotenoids, polyphenols, flavanols, flavanones and flavan-3-ols is recommended [69-72].

Neurodegenerative Diseases: Rao and Balachandran [73] suggested that lycopene plays important role in neurodegenerative diseases like Alzheimer's disease. It was reported that lycopene was able to cross the blood brain barrier and be present in central nervous system (CNS) in low concentration. Significant reduction in the levels of lycopene was reported in patients suffering from Parkinson's disease and vascular dementia [74]. Similarly, Suganuma *et al*., [75] reported that tomato ingestion might serve as a preventive therapy against neurodegenerative diseases such as Parkinson's disease caused by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and other environmental toxins. Moreover, it was also suggested to provide protection against amyotrophic lateral sclerosis (ALS) disorder in humans [76].

Respiratory Infections: Intake of tomatoes was also inversely and significantly associated with respiratory infections [77]. A study demonstrated that lycopene has a protective role for prevention of emphysema in a mouse model. At a conference held to deliberate on the role of processed tomatoes in human health, data was provided for the lycopene's protective role for emphysema's prevention in Japanese population [78].

Cataract: It was reported that persons with a high intake of carotene showed reduced incidence of risk of cataract [79] and the relationship between nuclear cataract and intakes of α- carotene, β-carotene, lutein, lycopene and cryptoxanthin stratifying by gender and by regular multivitamin use [80]. It has been confirmed that lycopene prevents cataract genesis *in-vivo* and *in-vitro* due to its antioxidant potentials [81]. In previous studies, it was found that lycopene prevented sugar induced diabetic cataract [82].

Erythema: Lycopene plays an important role in the protection against photoxidative processes. It acts as singlet molecular oxygen and peroxyl radicals scavengers. It can also interact synergistically with other antioxidants. Administration of tomato paste daily for 10 weeks, protected against UV light induced erythema on the dorsal skin [83]. However, it is completely depleted from skin upon exposure to solar radiation [84] and undergoes oxidative or enzymatic cleavage to form apocarotenoids [85].

Diarrhea: In a prospective study, Fawazi *et al*., [86] found that an intake of tomatoes for 2-3 days compared with zero days has been associated with significant reduction in mortality (48%) and with a decreased risk of death associated with diarrhea.

HIV: Several studies indicate that lycopene plays important role in the human organism's natural defense mechanism which gives protection from the harmful oxidizing agents. Lower serum lycopene levels were also reported in human immuno deficiency virus (HIV) positive women and children [87, 88]. Further investigations can explore lycopene's role in various human diseases like diabetes, rheumatoid arthritis, periodontal diseases and inflammatory disorders [38]. Antioxidant potential of lycopene are opening up new applications in pharmaceutical; nutraceutical and cosmeceutical products and can inhibit the progression or development of many human diseases at an initial stage and may improve the quality of life [89].

Diabetes: Treatment of lycopene (1, 2 and 4 mg/kg; p.o.) in streptozotocin-induced diabetic rats

has significantly attenuated cognitive deficit, increased acetyl cholinesterase activity, oxidative nitrosative stress and inflammation [90].

Memory and Cognitive Behavior: The treatment of lycopene using 3-nitropropionic acid-induced rats has significantly improved the memory and restored glutathione system functioning [91]. Akbaraly *et al*., [92] also suggested that low plasma lycopene levels could contribute to cognitive impairment.

CONCLUSION: Lycopene is a naturally occurring substance found in many fruits and vegetables including tomatoes. Atleast 85% of lycopene comes from consumption of tomatoes and tomato based products like soups, sauces, juice, ketchups, salad etc. Carotenoids in general have undergone a number of research studies as to their possible benefits against diseases, among other health issues. Owing to the numerous pharmacological actions of tomato lycopene as discussed in above section, and associated health benefits, tomato consumption should be promoted in daily diet.

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