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LYCOPENE - ROLE IN CANCER PREVENTION

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ABSTRACT

Lycopene belongs to a group of naturally-occurring pigments known as carotenoids. Carotenoids are colored compounds found in the photosynthetic pigments of fruits and vegetables which provide them their bright colors and benefit human health by playing an important role in cell function. Red fruits and vegetables, including tomato-based products are the major sources of lycopene. Oxidative stress is recognized as one of the major contributors to the increased risk of cancer and lycopene being a potent antioxidant has been found to inhibit proliferation of several types of human cancer cells, including endometrial, prostate, breast, upper aero digestive tract and lung and lycopene to have tumor suppressor activity. This review summarizes the background information about lycopene and presents the most current knowledge with respect to its role in cancer prevention.

KEY WORDS: Cancer, Lycopene, Oxidative stress, Prevention

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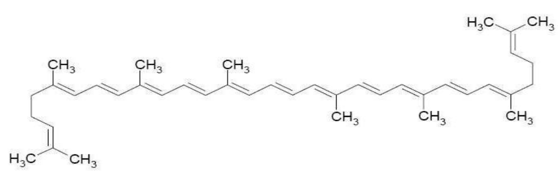
INTRODUCTION

"The art of medicine consist in amusing the patient, while nature cures the disease." Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi. Tomatoes and tomato-based products are the major sources of lycopene in the human diet (Nguyen and Schwartz, 1999). Carotenoids are colored compounds found in the photosynthetic pigments of fruits and vegetables which provide them their bright colors and benefit human health by playing an important role in cell function (Sanjiv Agarwal et al., 2000). Lycopene is a fat soluble carotenoid. Lycopene is one of the most potent antioxidants among dietary carotenoids. Serum and tissue lycopene levels have also been inversely related with the chronic disease risk. Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties, evidence is accumulating to suggest other mechanisms such as modulation of intercellular gap junction communication, hormonal and immune system and metabolic pathways may also be involved (Schierle et al., 1997).

DISCUSSION

Lycopene

Lycopene is an acyclic isomer of ß-carotene and has no vitamin A activity. 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*-carotene, and (all-E)-lycopene. The chemical formula is C40H56. The structural formula of all-*trans*-lycopene is shown below:



The molecular weight of lycopene is 536.9 and the Chemical Abstract Service (CAS) number is 502-65-8. It is a highly unsaturated, straight chain hydrocarbon containing 11 conjugated and two non-conjugated double bonds (Nguyen and Schwartz, 1999). Lycopene from natural plant sources exists predominantly in *trans* configuration, the most thermodynamically stable form. In human plasma, lycopene is an isomeric mixture containing 50% of the total lycopene as *cis* isomers. All *trans*, 5-*cis*, 9-*cis*, 13-*cis* and 15-*cis* are most commonly identified isomeric forms of lycopene. Lycopene, ingested in its natural *trans*form found in tomatoes, is poorly absorbed. Recent studies have shown that heat processing of tomatoes and tomato products induces isomerization of lycopene to the *cis* form which in turn increases its bioavailability. However, there is some indication that isomerization reactions may be taking place in the body. High concentration of *cis* isomers were also observed in human serum and prostate tissue, suggesting that tissue isomerases might be involved in *vivo* isomerization of lycopene from all *trans* to *cis* form. The mean plasma level of lycopene ranges from 0.22-1.06nmol/ml and it contributes to about 21%-43% of the total carotenoids. Lycopene accumulates in human tissues (Schierle et al., 1997). 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. In liver metabolism, lycopene is incorporated into chylomicrons and released into the lymphatic system. In blood plasma, lycopene is eventually distributed into the very low and low density lipoprotein fractions. Lycopene is mainly distributed to fatty tissues and organs such as the adrenal glands, liver, and testes (Nguyen and Schwartz, 1999).

Table 1
Distribution of lycopene in tissues

Tissues	(nmol/g wet weight)
Liver	1.28–5.72
Kidney	0.15–0.62
Adrenal	1.9–21.6
Testes	4.34–21.4
Ovary	0.25–0.28
Adipose	0.2–1.3
Lung	0.22–0.57
Colon	0.31
Breast	0.78
Skin	0.42

Dietary sources of Lycopene

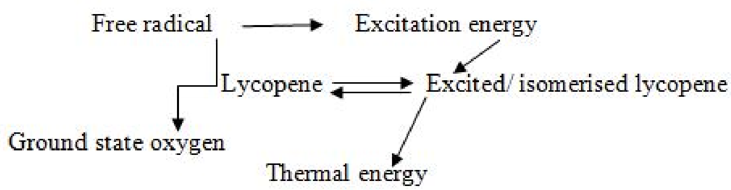
Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots and pink guavas, contain lycopene. Processed tomato products, such as juice, ketchup, paste, sauce and soup, all are good dietary sources of lycopene (Gärtner et al., 1997). A average daily dietary intake of lycopene (Table 2), assessed by means of a food-frequency questionnaire, was estimated to be 25 mg/d with processed tomato products, accounting for 50% of the total daily intake (Nir and Hartal, 2000).

Table 2
Dietary sources of lycopene from Vegitables

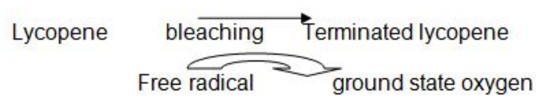
Source	(µg/g wet weight)
Raw tomato	8.8–42
Tomato juice	86–100
Tomato sauce	63–131
Tomato ketchup	124
Watermelon	23–72
Pink grapefruit	3.6–34
Pink guava	54
Papaya	20–53
Rosehip puree	7.8
Apricot	< 0.1

Mechanism of action

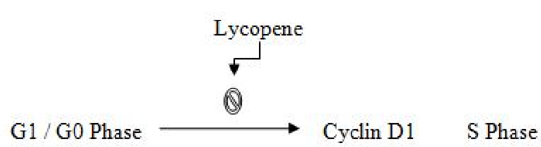
Antioxidants are protective agents that inactivate reactive oxygen species and therefore significantly delay or prevent oxidative damage. Oxidative stress induced by reactive oxygen species is one of the main foci of recent research related to cancer and cardiovascular disease. Reactive oxygen species are highly reactive oxidant molecules that are generated endogenously through regular metabolic activity, lifestyle activity and diet. There is strong evidence that this damage may play a significant role in the causation of several chronic diseases (Halliwell, 1994). Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins and DNA (Witztum, 1994). Carotenoids like lycopene are important pigments found in photosynthetic pigment-protein complexes in plants, photosynthetic bacteria, fungi, and algae (Cunningham et al., 2007). They are responsible for the bright colors of fruits and vegetables, perform various functions in photosynthesis, and protect photosynthetic organisms from excessive light damage (Nir and Hartal, 2000). Lycopene has the capacity to prevent free radical damage to cells caused by reactive oxygen species. Studied have shown that it reduces the susceptibility of lymphocyte DNA to oxidative damage, inactivates H_2O_2 and NO and protects cells from NO induced membrane damage and cell death. Lycopene exerts its antioxidant properties by two mechanisms physical and chemical. The efficacy of physical quenching exceeds that of chemical (Pincemail, 1995). Physical quenching involves, transfer of excitation energy from free radicals to lycopene, resulting in ground state oxygen and excited / isomerised lycopene. This energy is dissipated through the rotational and vibrational interactions of the excited carotenoid with surrounding solvent to yield ground state carotenoid and thermal energy.



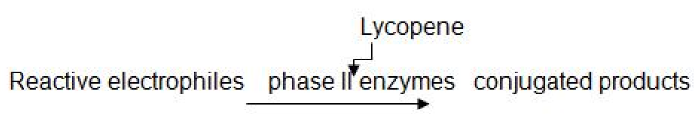
In this process the lycopene remains intact and can be utilized in further quenching, thus it acts as a catalyst. Chemical quenching, contributes less than 0.05% of total quenching results in final decomposition of lycopene.



Lycopene with its 11 conjugated and 2 conjugated double bonds is the most efficient singlet oxygen quencher and this efficiency is mainly attributed to presence of 2 non conjugated double bonds (Ernst , 2002). It brings about a decrease in cellular cyclin D_1 is a key regulator of this process and is also known as an oncogene



In Prevention by Induction of Phase II enzymes conjugate with reactive electrophiles and act as an indirect antioxidant thus eliminating carcinogens and toxins from the body. Lycopene induces the phase II enzymes.



Lycopene modulates the process of transcription either directly or through its derivatives by producing changes in the expression of many proteins participating in the transcription process. E.g. connexins, cyclins etc. Lycopene induces the formation of protein connexin-43, one of the major building blocks of gap junction and thus restores gap junctions and prevents malignant transformation of cells (Ames et al., 1992).

Lycopene an antioxidant in cancer prevention

The public and the biomedical community are increasingly aware of associations between tomato products, lycopene, and health outcomes. Scientists from many disciplines ranging from epidemiology, clinical medicine, nutrition, agriculture, and molecular and cell biology have published peer-reviewed studies providing intriguing data suggesting that tomato products and the carotenoid lycopene may be involved in cancer prevention, reducing the risk of cardiovascular disease, and limiting the morbidity or mortality of other chronic diseases. Lycopene is a potent antioxidant, neuroprotective (Hisao et al., 2004), antiproliferative, anticancer (Gunasekera et al., 2007), antiflammatory, cogntion enhancer (Akboraly et al., 2007) and hypocholesterolemic agent (Amany et al., 2009). Accumulating evidences favor the role of oxidative stress in the pathogenesis of various cardiovascular diseases (Venket Rao et al., 2000). Lycopene due to its antioxidant properties reduces lipids by inhibiting enzymes involved in cholesterol synthesis and by enhancing LDL regulation. Lycopene act as a hypocholesterolemic agent by inhibiting HMG-CoA (3-hydroxy-3-methylglutaryl- coenzyme A) reductase (Witztum, 1994). Recent epidemiological studies have shown a reverse relationship between tissue and serum levels of lycopene and mortality of CHD, MI & cerebrovascular diseases. Serum lycopene to be inversely related to fasting serum insulin level, suggesting a possible role for lycopene deficiency in pathogenesis of insulin resistance and diabetes. Intake of fruits and vegetables rich in carotenoids including lycopene might be a protective factor against hyperglycaemia (Rao and Rao, 2007).

Oxidative stress is recognized as one of the major contributors to the increased risk of cancer, and lycopene being a potent antioxidant has been found to inhibit proliferation of several types of human cancer cells, including endometrial, prostate, breast, upper aerodigestive tract and lung, and in vivo studies have shown lycopene to have tumor suppressor activity (Stefani et al., 2000). The anticarcinogenic effects of lycopene have been suggested to be due to regulation of gap-junction communication in mouse embryo fibroblast cells. Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb antioncogenes and stop cell division at the G_0-G_1 cell cycle phase. Lycopene-induced modulation of the liver metabolizing enzyme, cytochrome P450 2E1, was the underlying mechanism of protection against carcinogen-induced preneoplastic lesions. Preliminary in vitro evidence also indicates that lycopene reduces cellular proliferation induced by insulin-like growth factors, which are potent mitogens, in various cancer cell lines. Regulation of intrathymic T-cell differentiation (immunomodulation) was suggested to be the mechanism for suppression of mammary tumor growth by lycopene treatments (Khan et al., 2008).

Studies have found lycopene has been found to inhibit breast cancer tumors more efficiently. Intake of dietary lycopene has been reported to play a role in prevention of ovarian and cervical cancer. Serum lycopene is also associated with decreased risk of bladder and upper aerodigestive tract cancer (Melissa et al., 2012). Several chemoprotective properties of lycopene on prostate cancer have been proposed, including potent antioxidant properties, decreased lipid oxidation, inhibition of cancerous cell proliferation at the G0-G1 cell cycle transition, and protection of lipoproteins and DNA (Elizabeth et al., 2002; Giovannucci et al., 1995). Several studies have reported reduced concentrations of micronutrients including lycopene in patients with human deficiency virus infection, despite adequate dietary intake, particularly in those with human immunodeficiency virus infection (Riso et al., 2006). Lycopene role has been found to be positive in the management of cataract, malaria, immune modulation, alzheimers disease, perclampsia, infertility, aging, osteoporosis, and even in male infertility (Halliwell, 1994).

Lycopene role in oral cancer

Oral leukoplakia (OLP) is a premalignant lesion described as “a predominant white lesion of the oral mucosa which cannot be defined as any other known lesion” (Adriana Spinola Ribeiro et al., 2010). Population based case control study observed a protective effect of tomato consumption in oral leukoplakia (Gupta et al., 1998). A study conducted at Karnataka showed lycopene to be efficacious in the treatment of oral leukoplakia. They also reported that daily dose of 8mg of lycopene was more efficacious than 4mg a day (Mohitpal Singh et al., 2004). This efficiency of lycopene in the managent of leukoplakia was associated to its antioxidant properties (Van der Waal and Ax´ell, 2002). Oral Sub Mucous Fibrosis (OSMF) is a precancerous condition of the oral cavity. Untreated and neglected cases of OSMF might end up as invasive squamous cell carcinoma. Free radicals have more recently emerged as mediators of other phenotypic and genotypic changes that lead from mutation to neoplasia. The role of free radicals in the various oxidation processes in the body has lead to the identification of antioxidants in inhibiting and reversing the disease process (Bhagavan Banige Komary Gowda et al., 2011).

Though the exact role of free radicals in the pathogenesis of OLP is not established, various studies have suggested oxidative stress to play vital role in the same. Lycopene being a potent antioxidant may have an important role in the prevention and management of this disease entity before progressing to cancer. Lycopene supplementation can be used as a therapeutic modality for treatment of atrophic/erosive oral lichen planus patients (Basu and Imrhan, 2007). Researchers discovered lycopene to kill oral cancer cells when added to culture. They believed it to be due to its ability to restore gap junction communication, which is believed to be destroyed in oral malignancies, suggesting its possible role in oral cancer management as an adjuvant therapy (Bertha Schwartz, 2001).

Safety, adverse effects and toxicity

Lycopene is generally considered safe, non toxic and consumption is usually without known side effects. Excessive carotenoid intake have been reported in a middle aged woman who had prolonged and excessive consumption of tomato juice, her skin and liver were colored orange-yellow and she had elevated levels of lycopene in her blood. After three weeks on a lycopene-free diet her skin color returned to normal (McClain and Bausch, 2003).

CONCLUSION

The current dietary recommendation to increase the consumption of fruits and vegetables rich in antioxidants has generated interest in the role of lycopene in cancer prevention. However, the evidence thus far is mainly suggestive and the underlying mechanisms are not clearly understood. Further research is critical to elucidate the role of lycopene and to formulate guidelines for healthy eating and disease prevention. Areas for further study include epidemiological investigations based on serum lycopene levels, bioavailability and effects of dietary factors and also in metabolism and isomerization of lycopene, including biological significance, interaction with other carotenoids, antioxidants and mechanism of disease prevention (Khan et al., 2008).

DISCLOSURE OF INTEREST

The authors declare that they have no conflicts of interest concerning this article.

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