Review Article

Lycopene in oral health

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ABSTRACT

Functional components of food are potentially valuable substances found naturally in foods or added to them as useful ingredients and include carotenoids, dietary fibers, fatty acids, flavanoids, phenolic acids, etc. Carotenoids are among the most widespread and important ones due to their varied functions. They are fat-soluble pigments mostly found in plants, fruits, algae, photosynthetic bacteria, and also occur in yeasts and molds. The most abundant naturally occurring carotenoids are β-carotene, α-carotene, γ-carotene, lycopene, lutein, β-cryptoxanthin, zeaxanthin, and astaxanthin. Lycopene, one of the most important carotenoids, structurally determines the potential biological function and plays an equally important role in oral health. Lycopene is a red plant pigment found in tomatoes, apricots, guavas, watermelons, papayas, and pink grapefruits, with tomatoes being the largest contributor to the dietary intake of humans. Lycopene exhibits higher singlet oxygen quenching ability. Due to its strong color and non-toxicity, it is a useful food coloring agent. Moreover, it plays a multifunctional role in the body by protecting the body from the oral pre-cancers like leukoplakia and also prevents the destruction of periodontal tissues. This review article focuses mainly on the role of lycopene in the prevention of periodontal disease and oral cancers.

Key words: Antioxidants, free radicals, lycopene, periodontal disease, reactive oxygen species

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Introduction

Periodontal disease is an inflammatory disease process resulting from the interaction of a bacterial attack and host inflammatory response. Arrays of molecules are considered to mediate the inflammatory response at one time or another. Among these are free radicals and reactive oxygen species (ROS). Periodontal pathogens can induce ROS overproduction and, thus, may cause collagen and periodontal cell breakdown. When ROS are scavenged by antioxidants, there can be a reduction of collagen degradation.[1]

The periodontal tissues also provide an ideal medium to study the mechanisms of ROS-mediated tissue damage and antioxidant defense in response to bacterial colonization, through the non-invasive collection of gingival crevicular fluid (GCF).[2] ROS cause tissue damage by a variety of different mechanisms, which include DNA damage, lipid peroxidation (through activation of cyclooxygenases and lipooxygenases), protein damage, including gingival hyaluronic acid and proteoglycans, oxidation of important enzymes, e.g. anti-proteases, and stimulation of pro-inflammatory cytokine release by monocytes and macrophages. While most ROS have extremely short half-lives, they can cause substantial tissue damage by initiating free radical chain reactions. It is, therefore, not surprising that the body contains a number of protective antioxidant (AO) mechanisms whose specific role is to remove harmful oxidants or ROS as soon as they form, or to repair the damage caused by ROS *in vivo*. Carotenoids are powerful antioxidant agents which are important in the maintenance of overall health of an individual and have a protective role against cancer, heart diseases, and oral malignancies and diseases. Among the carotenoids, lycopene is the most potent antioxidant. It also enhances the effect of other carotenoids. It possesses anti-carcinogenic property and can be effective in cancer therapy. Lycopene shows promising effect in the treatment of gingivitis.

Structure of lycopene

Lycopene is an important intermediary product in the biosynthesis of many carotenoids, which include β-carotene, responsible for yellow, orange, or red pigmentation, photosynthesis, and photo-protection. Like all carotenoids, lycopene is a polyunsaturated hydrocarbon (an unsubstituted alkene). Structurally, it is a tetraterpene assembled from eight isoprene units, composed entirely of carbon and hydrogen, and is insoluble in water. Lycopene's 11 conjugated double bonds give it a deep red color and are responsible for its antioxidant activity.

Bioavailability of lycopene

Although comparative bioavailability values for lycopene from different tomato products are unknown, lycopene from processed tomato products appears to be more bioavailable than that obtained from raw tomatoes. The release of lycopene from the food matrix due to processing, the presence of dietary lipids, and heat-induced isomerization from all-*trans* to a *cis* conformation enhance lycopene bioavailability. The bioavailability of lycopene is also affected by the dosage and the presence of other carotenoids such as β-carotene. Bioavailability of lycopene was significantly higher when it was ingested along with β-carotene than when ingested alone.[3]

Biological properties of lycopene

In non-photosynthetic organisms, carotenoids have been linked to oxidation-preventing mechanisms.[4] Humans are incapable of synthesizing carotenoids and must obtain them through their diet. Among the 600 known carotenoids in nature, only about 20 are found in human plasma and tissues. Lycopene is the most important carotenoid found in human blood and tissues, and is found primarily in the testis, prostate, breast, adrenal glands, liver, colon, and lung. It has a half-life of about 48-72 h and was found to be transported in plasma by lipoproteins, primarily low density lipoproteins (LDL) and very low density lipoprotein (VLDL) but not high density lipoproteins (HDL). The role of lycopene in preventing human pathologies is simply illustrated in Figure 1. Gap junction communication (GJC) involves cell-to-cell channels that enable the concerned cells to exchange low-molecular-weight compounds like nutrients and signaling molecules. One feature of carcinogenesis is the loss of GJC. Lycopene increase GJC between cells and enhances the expression of connexin 43, a gene encoding major gap junction protein, and thereby up-regulates GJC and acts as an anti-carcinogen.[5]

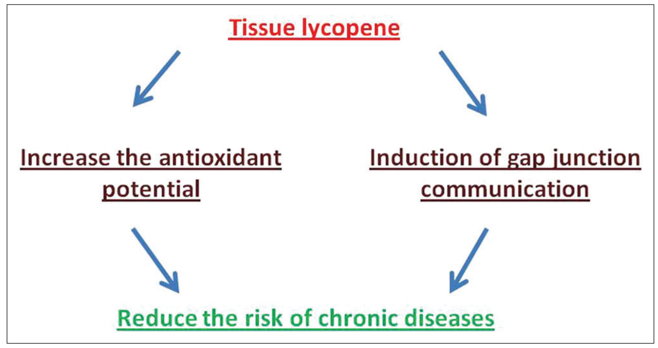

Figure 1: Cellular process of lycopene

In addition, the capability of lycopene to act as a biological antioxidant and a scavenger of free radicals is one mechanism by which it exerts its beneficial effects on human health. It may also impede the oxidative damage to DNA and lipoproteins and inhibit the oxidation of LDL cholesterol.[6] So far, no adverse effects of lycopene use have been reported and it is considered to be safe.[7] However, since lycopene is a lipid-soluble antioxidant, it has been reported that concomitant intake of some cholesterol-lowering drugs such as probucol and cholestyramine significantly decreases the serum concentration of lycopene due to impairment of gastrointestinal absorption.[8]

Lycopene in general health

The ideal intake of lycopene is currently indefinite; however, one study suggested that at least 5-10 g of fat in a meal is required for lycopene absorption and 6 mg/day of lycopene is beneficial for prostate cancer prevention.[6] Many epidemiological studies implicated lycopene in the prevention of cardiovascular disease and cancer.[6] Recently, lycopene has been found to inhibit proliferation of several types of cancer, including those of breast, prostate, lung, and endometrium.

It has been reported that lycopene initiates cell cycle arrest and induction of apoptosis in lymph node cells of prostate cancer (LNCaP), i.e. human prostate cancer cells.[8] The mechanism of action in affecting prostate cells is still unknown, but the most widely accepted theory involves lycopene's antioxidant effect on scavenging of singlet oxygen, which is theorized to damage DNA and cause cancer. Lycopene, therefore, may be used as a potential chemopreventive/chemotherapeutic agent in some chronic diseases, particularly coronary heart disease and prostate cancer.

In a study conducted by Kumar *et al.*, 45 eligible male patients with clinically localized prostate cancer were supplemented with 15, 30, or 45 mg of lycopene or no supplement from biopsy to prostatectomy. Compliance to study agent, toxicity, changes in plasma lycopene, serum steroid hormones, prostate-specific antigen (PSA), and tissue Ki-67 antigen were analyzed from baseline to the completion of intervention. It was seen that 42 of 45 subjects completed the intervention for approximately 30 days from the time of biopsy until prostatectomy. Plasma lycopene increased from baseline to post treatment in all treatment groups, with the greatest increase observed in the 45-mg lycopene-supplemented arm compared to the control arm without producing any toxicity. Overall, subjects with prostate cancer had lower baseline levels of plasma lycopene similar to those observed in previous studies in men with prostate cancer.[9]

The serum lycopene concentrations were significantly lower in women with osteoporosis as compared to the healthy controls. Lycopene, a carotenoid phytonutrient, is the most potent antioxidant naturally present in many fruits and vegetables. In the presence of Vitamin-C (Vit-C), lycopene can repair both itself and other antioxidants to restore their antioxidant qualities. However, tomatoes and processed tomato products constitute the major source of dietary lycopene, accounting for up to 85% of the daily intake.[10]

More recently, the protective effects of carotenoids against serious disorders such as cancer, heart disease, and degenerative eye disease have been recognized and have stimulated intensive research into the role of carotenoids as antioxidants and as regulators of the immune response system.[11]

Rissanen *et al*., in a randomized, double-blind, placebo-controlled population study, showed a direct association between low plasma lycopene concentrations and the onset of early arteriosclerosis, manifested as increased intima–media thickness of the common carotid artery, in middle-aged men living in Eastern Finland.[12]

Role in periodontal health

Lycopene has been found to be more effective with other antioxidants like Vita-C.[10] A relationship exists between periodontitis and risk of congestive heart failure (CHF), and high monthly total consumption of lycopene appears to affect this relationship in a positive direction in periodontitis subjects.[13] Lycopene has also been associated with a decrease in oxidative stress as it is inversely related to malondialdehde (MDA) which is a marker for oxidative stress.[14] Antioxidants may be regarded as "those substances which when present at low concentrations compared to those of an oxidizable substrate, will significantly delay or inhibit oxidation of that substrate."[15] Vita-C has also been shown to reduce oxidative stress during periodontal inflammation.[16] Even the total systemic and local antioxidant capacity can be determined in healthy people and periodontitis patients by means of saliva and GCF.[17]

Chandra *et al*. (2007) conducted a study to compare the effects of systemically administered lycopene as a monotherapy and as an adjunct to scaling and root planing in gingivitis patients. Twenty patients showing the clinical signs of gingivitis were randomly distributed between two treatment groups as follows: Experimental group: 8 mg lycopene per day for 2 weeks and control group: Placebo for 2 weeks. The results of the study suggested that lycopene shows great promise as a treatment modality in gingivitis.[18]

Role of lycopene in oral cancer

Oral malignancy is one of the most common malignancies leading to death worldwide. It ranks 12th among all cancers. Data from Oral Cancer Foundation shows that there are more than 350,000-400,000 new cases of oral cancer each year. Although advancements have been made in diagnosis and therapy, the mortality ratio for patients with oral cancer remains as high as 50% and has not significantly improved in the past 30 years. The etiology of oral cancer is multifactorial. Genetic, environmental, viral infection, social and behavioral effects may all be implicated. Among these factors, the important role of diet and nutrition in prevention of oral malignancy has drawn interest increasingly. Overwhelming evidence from epidemiological studies indicates that diets rich in fruits and vegetables are associated with a lower risk of numerous cancers including oral cancer. Dietary recommendations to increase the intake of citrus fruits, cruciferous vegetables, green and yellow vegetables, as well as fruits and vegetables rich in vitamins A and C to lower the risk of oral cancer have been made by several organizations. Tomato and tomato-based foods account for more than three-fourths of all the dietary sources of lycopene.[3] Although used as food colorant for a long period, it has recently been a subject of intense study with respect to its antioxidant activity and potential role in the prevention and treatment of chronic diseases including cancers, cardiovascular disease, neurodegenerative disease, and bone disorders.

More recently, epidemiologic studies, *in vitro* studies, and animal studies and clinical trials have suggested that lycopene has some beneficial effects in the treatment of certain diseases of oral cavity including oral cancer and precancerous lesions. Oral submucous fibrosis, leukoplakia, and oral lichen planus have been successfully treated by giving lycopene supplements.

Kumar *et al*. conducted a study in which 58 patients with oral submucous fibrosis were randomly divided into three groups and were evaluated weekly over a 2-month period.

Patients of group A received 16 mg of lycopene, those of group B received 16 mg of lycopene along with biweekly intralesional steroid injection, and those of group C were given a placebo. The mouth opening values showed an average increase of 3.4 mm, 4.6 mm, and 0.0 mm for patients in groups A, B, and C, respectively. Thus, lycopene could be used as a first line of treatment for oral submucous fibrosis.[19]

Level of serum lycopene was seen to be significantly reduced in patients with oral leukoplakia.[20]

Resolution of oral leukoplakia was seen to occur on lycopene therapy for 3 months in a study conducted by Singh *et al*. A total of 58 patients received either 8 mg oral lycopene in two doses daily ($n = 20$), 4 mg oral lycopene in two doses daily ($n = 18$), or placebo capsules ($n = 18$), for a 3-month period. Significant reduction in the clinical and histological results was seen.[21]

Relationship between oral leukoplakia and lycopene was studied, and the intake of tomato, which is the richest source of lycopene, was observed to have the most protective role against leukoplakia.[22]

Cell–cell gap junctions are considered to be important in the maintenance of tissue homeostasis. Any alteration in this can give rise to neoplastic phenotype. Studies have shown that the lycopene in various doses results in decrease in the proliferation of oral tumor cells, Killer B-1 (KB-1). KB-1 cells, originating from a human oral cavity tumor, were incubated with different concentrations of lycopene delivered via the cell culture media from stock solutions in tetrahydrofuran. Lycopene strongly and dose dependently inhibited the proliferation of KB-1 human oral tumor cells. Lycopene (3 and 7 μmol/l) significantly up-regulated both transcription and expression of connexin 43, a key protein in the formation of GJC.[23]

Safety of lycopene

Lycopene has been recognized as a safe product for daily dietary intake. Large amounts of dietary intake also do not show any adverse effects on the health of an individual. Based on various safety studies reviewed, no adverse effects were observed at the highest intake level provided, i.e. 3 g/kg/d of dietary or formulated lycopene.[24]

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 disease 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, long-term dietary intervention studies, metabolism and isomerization of lycopene and the biological significance of isomers, interaction with other carotenoids and antioxidants, and mechanism of disease prevention.

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