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Lycopene- Nature's Red Shield for Health -A Review

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Abstract

Without pigments, life would lack vibrancy. The natural world presents us with a kaleidoscope of colours from the lush green grass of home to the warm, ruddy hues of an autumn forest. These colours, with few exceptions, arise from natural pigments found in living organisms. Beyond providing visual appeal, pigments fulfil essential biological functions. Among the various classes of natural pigments, carotenoids stand out for their wide distribution and diverse roles in biological systems. Lycopene a red carotenoid pigment, is abundant in tomatoes, apricots, guavas, watermelons, papayas, and pink grapefruits, with tomatoes serving as the primary source in the human diet. Notably, lycopene demonstrates a strong ability to quench singlet oxygen, making it a powerful antioxidant. Its vivid colour and lack of toxicity also make it a valuable natural food colorant. In addition to its antioxidant properties and use as a natural colorant, lycopene demonstrates considerable potential in both medical and dental fields. It has been recognized as an effective adjunctive, non-invasive therapeutic agent in the management of several oral diseases, including leukoplakia, oral submucous fibrosis, lichen planus, and oral squamous cell carcinoma. Furthermore, lycopene contributes to the preservation of periodontal health by preventing the breakdown of supporting tissues. This review highlights the mechanism of action, multifaceted role of lycopene, particularly emphasizing its preventative and therapeutic potential in managing a range of oral health conditions.

Keywords: Lycopene, oral lichen planus, leukoplakia.

INTRODUCTION

Lycopene is a naturally occurring carotenoid pigment. Today, carotenoid pigments number in the hundreds, with carotene being the most well-known. Carotene plays an important role in health and medicine as a precursor to Vitamin A. Historical records reveal that its discovery was a byproduct of the search for a medicinal agent of a different kind, an anthelmintic used to expel parasitic worms from the intestine. German pharmacist Heinrich Wilhelm Ferdinand Wackenroder who first isolated it in 1873 begs the credit for this discovery. Richard Martin Willstätter (1872–1942), working at the Swiss Polytechnikum in Zürich, identified the pigment lycopene in tomatoes. Through comparisons with purified carotene, including analyses of crystal structure and other physical properties, he demonstrated that lycopene is an isomer of carotene. The findings from these studies were published between 1907 and 1913. Lycopene, derived from the Neo-Latin *Lycopersicon* the former genus name of the tomato is a bright red carotenoid hydrocarbon found in tomatoes and other red fruits and vegetables [1].

Lycopene is a naturally occurring pigment synthesized by plants and certain microorganisms, but not by animals. It is an acyclic isomer of β-carotene and a member of the carotenoid family. Structurally, lycopene is a highly unsaturated hydrocarbon, consisting of 11 conjugated and 2 unconjugated double bonds. As a polyene, it readily undergoes cis-trans isomerization when exposed to light, heat, or chemical agents. In natural plant sources, lycopene predominantly exists in the all-trans configuration, which is the most thermodynamically stable form. In human plasma, however, lycopene exists as a mixture of isomers, with nearly 50% present in the cis configuration.[2]

Lycopene is one of the most potent antioxidants, possessing a singlet-oxygen-quenching ability that is twice as high as β-carotene and 10 times greater than α-tocopherol. It is the predominant carotenoid in human plasma, with its levels influenced by various biological and lifestyle factors. Due to their lipophilic nature, lycopene and other carotenoids are primarily concentrated in the low-density and very-low-density lipoprotein fractions of the serum. In human blood at approximately 0.5 µmol/L plasma, with tissue levels ranging from 1 nmol/g wet weight in adipose tissue to as high as 20 nmol/g wet weight in the adrenal glands and testes. Additionally, lycopene accumulates in specific organs, including the liver, and prostate gland, where it is the most abundant carotenoid. The tissue-specific distribution of lycopene may play a crucial role in its antioxidant function. However, unlike other carotenoids, lycopene levels in serum and tissues do not consistently correlate with overall fruit and vegetable intake.[2]

MECHANISM OF ACTION

- Carotenoids exhibit strong antioxidant activity by quenching singlet oxygen ($^1O_2$) and trapping peroxyl radicals. Singlet oxygen quenching occurs via physical or chemical mechanisms, with physical quenching being more efficient. In this process, excitation energy from ($^1O_2$) is transferred to the carotenoid, producing ground-state oxygen and an excited triplet carotenoid, which dissipates energy to the solvent and returns to its ground state. Carotenoids remain intact, enabling repeated quenching and acting as catalysts, though isomerization may occur. Their quenching rate 10^9 M^{-1} s^{-1} is near diffusion-controlled, and efficiency mainly depends on the number of conjugated double bonds, with minor effects from end-group structure and substituents.
- Lycopene, with 11 conjugated and two nonconjugated double bonds, is one of the most potent natural singlet oxygen ($^1O_2$) quenchers, though its superior reactivity over other C-40 carotenoids remains unclear and may relate to its nonconjugated bonds. While chemical quenching accounts for <0.05% of total ($^1O_2$) quenching, it contributes to carotenoid "bleaching" via decomposition. Upon irradiation with methylene blue and oxygen, lycopene yields products such as 2-methyl-2-hepten-6-one and apo-6'-lycopenal. In vitro, carotenoids protected human lymphoid cells from photodynamic damage, with lycopene showing the highest protection, followed by astaxanthin and β-carotene.
- Lycopene is a highly effective peroxyl radical scavenger, particularly at low oxygen levels. Using ABTS radicals, it showed the greatest scavenging activity—three times that of Trolox—followed by lutein, zeaxanthin, cryptoxanthin, and β-carotene. In carotene–oxygen radical studies, β-carotene's reduction potential favors superoxide (O_2^-) formation, while lycopene is less efficient, with bidirectional electron transfer and a rate constant one-tenth that of β-carotene, indicating distinct reactivity patterns. [2,3]
- The NF-κB pathway regulates inflammation, immune responses, and cell survival, remaining inactive in the cytoplasm via IκB binding. Pro-inflammatory stimuli (e.g., TNF-α, IL-6, IL-1β), oxidative stress, or LPS trigger IκB phosphorylation and degradation, freeing NF-κB to activate inflammatory genes.[4] Lycopene inhibits NF-κB activation by preventing IκB degradation and reducing NF-κB DNA-binding, thereby lowering pro-inflammatory cytokine production.[5] It also neutralizes ROS, which activate NF-κB, and activates the Nrf2-ARE pathway, upregulating antioxidant enzymes like HO-1. In endothelial cells, lycopene increases glutathione (GSH) levels within 6–12 hours, enhancing redox balance [6]. These actions underpin lycopene's potent anti-inflammatory and antioxidant effects, supporting its role in preventing inflammation-related diseases. [7,8]

ROLE OF LYCOPENE

Osteoporosis and Bone disease

Osteoporosis is a skeletal disorder marked by reduced bone mass and microarchitectural deterioration, increasing fracture risk, particularly in the elderly. Lycopene directly influences osteoblast and osteoclast activity,[9] with epidemiological and clinical evidence supporting its benefits in postmenopausal women. Rao *et al.,* found that higher dietary and serum lycopene levels correlated with lower NTX ($p<0.005$) and reduced protein oxidation ($p<0.05$), indicating antioxidant-mediated bone protection.[10] Umani S. Walallawita *et al.,* reported that ≥30 mg/day lycopene significantly reduced bone resorption markers, while May Nasser Bin-Jumah *et al.,* showed 50 mg/kg/day for 10 weeks improved metabolism, upregulated osteoblasts, and regulated osteoclast differentiation.[11,12] Gasparo I demonstrated that lycopene inhibited hydrogen peroxide–induced oxidative stress, and Fansurina Yuli Erdayanti et al. found 2–20 mg/day reduced oxidative stress from low estrogen, supporting bone health. Lycopene-rich foods like tomatoes enhance intake.[13] Cristina Russo *et al.,* showed lycopene activates WNT/β-catenin and ERK1/2 pathways, upregulating RUNX2, alkaline phosphatase, and COL1A while suppressing RANKL, helping prevent bone loss in postmenopausal women. [14]

INFLAMMATORY DISEASE

(a) Asthma and Chronic Obstructive Pulmonary Diseases

Asthma is a heterogeneous condition characterized by chronic inflammation of the airways. Chronic obstructive pulmonary disease (COPD) is a progressive condition with high morbidity and mortality, characterized by persistent airflow limitation and an

abnormal inflammatory response to harmful stimuli. (figure 3) The inflammation in COPD is systemic, extending beyond the airways to affect multiple organs and systems. Campos *et al.,* conducted a study and found that lycopene inhibits tumor necrosis factor (TNF)-induced activation of the NF-κB signaling pathway, thereby suppressing the expression of pro-inflammatory cytokines and chemokines.[15] Shaista Sumayya *et al.,* conducted study and concluded that lycopene may offer benefits in respiratory conditions. and an intervention study in asthma reported that lycopene supplementation can suppress neutrophilic airway inflammation thus proving beneficial in asthma and COPD.[16] Janani Manochkumar *et al.,* in their study found that lycopene shows significant effect against chronic lung diseases (asthma, COPD, emphysema and lung cancer). They also stated that the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) reported that consuming a carotenoid-rich diet may reduce the risk of lung and breast cancer.[17]

(b) Rheumatic Diseases

Rheumatoid arthritis is a common, systemic, and chronic inflammatory disorder characterized by symmetrical joint inflammation and arthritis. Vivian Meira Moia *et al.,* in their study formulated nanodrug in nano emulsion of lycopene and used in rheumatoid arthritis and concluded that lycopene shows promise as a potential therapeutic agent in the management of rheumatoid arthritis.[18]

(c) Pancreatitis

Suyun Choi *et al.,* in their study concluded that Lycopene reduces cell death by activating 5′-AMP-activated protein kinase (AMPK)-dependent autophagy in certain cell types. Consequently, it may help ameliorate pancreatitis by preventing oxidative stress-induced autophagy impairment and/or by directly promoting autophagy in pancreatic acinar cells (PACs).[19] In another study conducted by Yoonseon Jeong et al concluded that supplementation of lycopene can significantly reduce the risk of developing pancreatic cancer.[20]

(d) Inflammatory Bowel Diseases

Dominika Glabska *et al.,* conducted the study and concluded that Fecal blood, mucus, and pus tend to decrease with higher lycopene intake and is a promising nutrient for alleviating symptom of ulcerative colitis.[21] In another study conducted by Mustafa Cengiz *et al.,* and concluded that a daily dose of 5mg per kg body weight lycopene has been shown to protect against colitis-induced liver damage, primarily through its potent antioxidant properties, which help mitigate oxidative stress.[22]

Cardiovascular diseases

May Nasser Bin-Jumah *et al.,* in their study found that dose of 2 miligram per day for 12-20 weeks reduces atherosclerotic plaques thus reducing the chances of cardiovascular diseases.[11] Ming-Ju Hsieh *et al.,* in their article showed that in patients with cardiovascular disease a dosage of 7 mg per day for 2 months showed improvement in arterial vasodilation. Another study demonstrated that increasing lycopene intake through diet or supplementation over a period of 12 weeks led to a reduction in HDL3 levels and serum amyloid A content.[23] Zhihong Xie *et al.,* in their study found that lycopene when administered in doses of more than 15 mg per day for 12 weeks showed significant benefits in management of patients with cardiac disorder.[24] In another study conducted by A.V Rao *et al.,* concluded that dietary consumption of tomatoes and tomato-based products rich in lycopene has been associated with a reduced risk of chronic conditions, including various forms of cancer and cardiovascular diseases.[25]

Periodontitis

In a randomised study conducted to access the efficacy of systemic lycopene supplementation combined with scaling and root planing (SRP) in patients with moderate periodontitis, the results demonstrated a significant improvement in clinical attachment levels (CAL), along with notable reductions in plaque index (PI) and probing pocket depth (PPD) in the short term, emphasizing the potential benefits of lycopene in periodontal therapy [26]. Kaur *et al.,* in their study found that lycopene in a dose of 10 mg twice daily for 3 weeks showed better resolution of inflammation when used as an adjunct to scaling and root planning Lycopene's anti-inflammatory properties may contribute to relieving pain and reducing inflammation associated with temporomandibular disorders (TMD) [27]. Shilpa Kamra *et al.,* lycopene, due to its potent antioxidant properties, serves as a promising adjunctive treatment to full-mouth scaling. It helps modulate oxidative stress within the periodontium during periodontitis and contributes to the maintenance of overall periodontal health.[28] (figure 4)

Oral Premalignant Diseases

Lycopene has shown efficacy in the treatment of various oral premalignant conditions, including oral submucous fibrosis and oral leukoplakia, and may be used alongside other medications for the prevention and management of oral cancer. May Nasser Bin-Jumah *et al.,* in their study found that a daily dose of 5mg per kilo gram for 16 weeks enhance ROS scavenging.[11]

(a) Oral Leukoplakia

Oral leukoplakia (OL) is a premalignant lesion described as “a predominant white lesion of the oral mucosa which cannot be defined as any other known lesion.” S Gupta *et al.,* conducted a study explaining that lycopene is a highly promising antioxidant (AO) for the treatment of oral leukoplakia (OL), offering protection against cell damage and playing a crucial role in preventing dysplasia progression by inhibiting tumor cell proliferation. The first reported evidence of lycopene's efficacy against human oral cancer cells highlighting its

significant therapeutic potential.[29] Singh M *et al.,* conducted a study on 58 patients clinically and histopathologically diagnosed of leukoplakia to compare the efficacy of different dosage of lycopene and found that it can be used effectively in management of Oral leukoplakia with most effective dosage of 8 mg per day for 3 months.[30] Nagao *et al.,* investigated the relationship between serum micronutrient levels and OL, finding that men with OL had significantly lower serum lycopene levels compared to controls. Gupta *et al.,* investigated the relationship between nutrient intake and the prevalence of oral leukoplakia (OL), observing that tomato consumption the primary source of lycopene had the most protective effect among all dietary factors.

A study conducted in Belgaum, Karnataka, demonstrated that lycopene is effective in treating OL, with findings indicating that a daily dose of 8 mg was more efficacious than 4 mg. This effectiveness was attributed to lycopene's antioxidant (AO) properties. Similarly Zakrzewska in his study involving 58 patients, concluded that lycopene brought about significant histological changes in individuals with Oral Leukoplakia.[29]

(b) Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is an insidious, chronic, potentially malignant well recognized oral disease condition. It is characterized by inflammation, progressive fibrosis of the connective tissue including lamina propria and deeper tissues. Several studies in humans have confirmed the cancer preventive nature of lycopene. Lycopene's mode of action involves stimulating the immune system or directly targeting tumor cells. Kitade *et al.,* demonstrated that lycopene inhibits hepatic fibrogenesis in liver endothelial cell rats, suggesting it may exert a similar inhibitory effect on abnormal fibroblasts in oral submucous fibrosis (OSMF). Additionally, lycopene enhances lymphocyte resistance to stress and suppresses the inflammatory response, further contributing to its therapeutic potential.[31] Kumar *et al.,* in his study found that there was significant improvement in the mouth opening of OSMF patient after taking lycopene and concluded that it can be considered as first line of therapy in initial management of OSMF.[32] Karemore *et al.,* conducted study in which lycopene was found to be significantly effective in alleviating the signs and symptoms of OSMF. It notably improved objective clinical parameters, as evidenced by the increase in maximal mouth opening.[33] Goel *et al.,* conducted a study with a dose of 2 miligram twice daily for 6 month and found significant improvement in mouth opening.[34] Saran et al. in their study found that a dose of 4 miligram of lycopene twice daily for three months showed significant improvement in burning sensation and mouth opening.[35]

(c) Oral lichen planus

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disorder affecting the oral mucosa, characterized by immune-mediated damage to basal keratinocytes. Motahari P *et al.,* conducted study comparing the effects of lycopene as an herbal intervention and corticosteroids on OLP in clinical trials and found that lycopene was well tolerated, with no reported adverse effects. Findings from a systematic review demonstrated its significant effectiveness in the treatment of oral lichen planus (OLP).[36] Pratibha *et al.,* in their study found that lycopene showed more potent, quick therapeutic effect and substantial reduction in pain and burning sensation.[37] Ramayan Prasad Kushwaha *et al.,* in their study found that 4mg per day for 8 consecutive weeks showed improvement in the clinical sign and symptom in oral lichen planus lesions.[38] Hala H Hazzaa *et al.,* in their study found that oral administration of lycopene offers a promising clinical advantage in the management of symptomatic oral lichen planus (OLP) through its immunomodulatory effect, particularly by influencing salivary malondialdehyde (MDA) levels. Aliaa Eita *et al.,* conducted a study and found that lycopene is a promising and effective therapeutic modality for oral lichen planus.[39]

Adverse Effect

Data on the adverse effects of lycopene in humans are limited. However, excessive intake of lycopene-rich foods has been associated with lycopenemia, a harmless condition marked by orange discoloration of the skin. Due to limited data on adverse effects in animals and healthy humans, the Institute of Medicine (IOM) has not established a tolerable upper intake level for lycopene. However, toxicological studies have shown no observed adverse effects at intake levels as high as 3 grams per kilogram of body weight per day.[41]

CONCLUSION

Lycopene is a fat-soluble red carotenoid pigment synthesized by plants and certain microorganisms. It represents the major carotenoid in tomatoes. The current dietary recommendation to increase the consumption of antioxidant-rich fruits and vegetables has sparked interest in lycopene's potential role in disease prevention. Lycopene is of particular interest due to its exceptional antioxidant activity, which surpasses that of β-carotene and α-tocopherol. Notably, skin lycopene has been reported to be more sensitive to UV light stress than β-carotene. Since carotenoids are depleted during radical quenching, the observed degradation of lycopene may indicate its protective role against oxidative stress. Similar to resveratrol and curcumin, lycopene exhibits a wide range of health benefits, including hypocholesterolaemia, cardioprotective, anti-inflammatory, and anti-mutagenic effects.[29] Since lycopene acts at multiple stages of carcinogenesis without causing adverse effects and has demonstrated anti-metastatic activity, it represents a

highly promising candidate for cancer chemoprevention and treatment.

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