



## Role of lycopene in oral potentially malignant disorders

Dr. Kanupriya Gupta

MDS, Oral and Maxillofacial Pathology, Senior Research Fellow, Faculty of Dental Sciences, IMS, BHU, Varanasi, Uttar Pradesh, India

### Abstract

Oral potentially malignant disorders are commonly encountered and frequently neglected lesions. High rate of malignant transformation necessitates the early diagnosis and prompt treatment of these lesions. Many medical and surgical modalities are widely used and studied for treatment of oral PMD's. As oxidative stress plays a major role in pathogenesis of these lesions, use of antioxidants plays a vital role in the treatment. Lycopene, a naturally available red pigment, is proved to have powerful antioxidant properties. Lycopene is widely and successfully used in the treatment of oral PMD's. The aim of this article is to review the pharmacological actions, therapeutic effects and adverse drug reactions of lycopene in the treatment of oral potentially malignant disorders.

**Keywords:** lycopene, oral potentially malignant disorders

### 1. Introduction

Cancer is the most formidable health problem faced by mankind in today's world. Cancer of the oral cavity is the eighth most common cancer and accounts for 2% cancer deaths worldwide [1]. Unlike the other cancers, oral cancer shows signs and symptoms before developing. These signs and symptoms are broadly termed as potentially malignant disorders (PMD's) of oral cavity [2]. Where premalignant lesions are said to be localized, premalignant conditions are generalized states, both having increased potential for malignant transformation as compared to their normal counterparts [3]. Oral submucous fibrosis, oral leukoplakia, oral lichen planus are most commonly encountered oral PMD's in day to day practice. 8-10% of these lesions undergo malignant transformation [4].

Early diagnosis and prompt treatment of oral PMD's prevent their malignant transformation [5]. Although the vast literature is available describing various aspects of oral PMD's, there is no universally established treatment protocol for management of these entities [6]. Many medical and surgical modalities are available for treatment of these lesions and they are widely used and studied [7]. Use of antioxidants is an important aspect of medical management of these conditions [8]. Lycopene is one of the important antioxidant useful for prevention and treatment of oral precancer and oral cancer [9].

### 2. Lycopene

Lycopene is a red colored, fat soluble pigment synthesized by plants and micro-organisms. It was first discovered by Millardet in 1876. The name Lycopene was given by Schunck [10]. It is a carotenoid mainly present in red fruits and vegetables. The greatest known dietary source of lycopene is tomato. Lycopene can also be derived from other red fruits and vegetables e.g. pink grapefruits, watermelons, pink guavas, apricots etc [11]. Other than these, it is present in certain fungus and algae [12].

Lycopene, the acyclic isomer of  $\beta$ -carotene, is basically a carotenoid. It is a highly unsaturated hydrocarbon containing

11 conjugated and 2 unconjugated double bonds. Light, thermal energy and chemical reactions induces its cis-trans isomerization. The biological significance of these isomers of lycopene is unclear [13]. Lycopene from natural plant sources exists predominantly in an all-trans configuration. In human plasma, lycopene is present as an isomeric mixture, with 50% as cis isomers [14].

Lycopene has a preventive role in chronic diseases and it helps in decreasing cancer risk and also cardiovascular disease risk. These actions are mainly because of its antioxidant properties [13]. Other mechanisms proposed are modulation of intracellular gap junction communication; hormonal, metabolic and immune system modulation; carcinogen metabolism and gene function regulation [15].

### 3. Antioxidant Action of Lycopene

Lycopene is one of the most potent antioxidant. Unlike the other carotenoids, lycopene does not have provitamine A action. Its antioxidant property is mainly attributed to its molecular and physical structure. Biologically, lycopene has a tendency to scavenge the free radicals. Its highly conjugated double bond structure makes it capable of quenching the free radicals. The physical quenching capability of lycopene is two times higher than  $\beta$ -carotene and ten times higher than  $\alpha$ -tocopherol [16]. Lycopene scavenges singlet oxygen ( $^1O_2$ ), nitrogen dioxide ( $NO_2$ ), thiyl (RS.), hydrogen peroxide ( $H_2O_2$ ) and sulphonyl ( $RSO_2$ ) radicals [17, 18]. Moreover, lycopene protects biological molecules including lipids, proteins and DNA. Along with antioxidant function, this action also adds to its anticancer property [13]. These antioxidants and anticancer activities of lycopene has been demonstrated by several studies [19].

### 4. Lycopene in oral PMD's

Due to its excellent antioxidant properties and anticancer activities, lycopene is successfully and safely [20] used in the

treatment of oral precancerous lesions and precancerous conditions.

### 5. Oral Leukoplakia

Lycopene is a promising treatment modality for oral leukoplakia. In a double-blind, placebo-controlled randomized controlled trial conducted by Singh *et al.* [21] lycopene supplementation in the doses of 4mg and / or 8mg per day showed reduction in hyperkeratosis in 80% of cases in the duration of three months. Complete remission of the lesion was noted in 55% of cases in the doses of 8mg/day and in 25% of cases in the doses of 4mg/day. In a systematic review of antioxidants in treatment of oral leukoplakia, lycopene was demonstrated to be a potential treatment option [22].

A randomized controlled trial conducted by Zakrzewska *et al.* [23] demonstrated clinical as well as improvement in the patients with oral leukoplakia by the treatment with 4 mg and / or 8 mg lycopene per day over a period of 3 months. In patients treated with 8mg lycopene per day, positive histologic changes were also noted. Gupta *et al.* [24], while investigating the relationship of specific nutrients and food items with oral precancerous lesions, noted that consumption of tomato-the main source of lycopene - has protective effect in oral leukoplakia.

Nagao *et al.* [25] varified a relationship of oral leukoplakia and serum levels of antioxidants was verified in 48 patients suffering from oral leukoplakia and also in 192 control patients in his study. Along with other antioxidants, the serum level of lycopene was found to be significantly lower in cases as compared to control group. Authors concluded that improvement of micronutrient levels of lycopene and other antioxidants may protect against the relative risk of oral leukoplakia.

### 6. Oral Submucous Fibrosis

In patients suffering from oral submucous fibrosis, lycopene has shown favorable treatment outcomes either alone or in combination with other treatment modalities. In a study conducted by Kumar A *et al.* [26] statistically significant increase in mouth opening was noted by the treatment with lycopene (16mg / day) alone and also in combination with intralesional steroids as compared to placebo group in the period of two months. Other studies also demonstrated similar results and also reduction in burning sensation by the treatment of lycopene alone [27, 28], or in combination with intralesional steroids and hyaluronidase [29]. Also, lycopene has shown favorable treatment outcomes in combination with Vitamin E [30].

### 7. Oral Lichen Planus

Oral lichen planus is a chronic inflammatory mucocutaneous disease with unknown etiology. Role of oxidative stress has been suggested in its pathogenesis. Sander *et al.* [31] demonstrated increased oxidative stress and decreased antioxidant enzyme production in tissues of vulval erosive lichen planus. Moreover, a study of Nagao *et al.* [32] reported a significant decrease in lycopene levels in cases of atrophic and erosive lichen planus suggestive of a strong co-relation of oxidant-antioxidant status and lichen planus.

Lycopene, being a potent antioxidant, is suggested to have a role in prevention and treatment of oral lichen planus. In a prospective, double blind, placebo controlled randomized controlled study conducted by Saawarn N *et al.* [33] a significant reduction in burning sensation was noted with the lycopene supplements in the doses of 8mg/day for 8 consecutive weeks. In this study all the patients reported to have more than 50% benefit and 73.3% patients showed 70-100% benefit.

### 8. Safety and Adverse Reactions

As lycopene is a naturally derived substance, it has minimal or no adverse effects. Large quantities of dietetic intake do not show any unfavorable effect on individual's health. There is no evidence of side effects or systemic toxicity by the treatment of lycopene noted till date [20]. On the basis of various safety studies, no harmful effects were noted at the highest intake level i.e. 3g/kg/day [34].

### 9. Conclusion

Lycopene is a naturally available, harmless substance with brilliant antioxidant properties. It is a promising tool for treatment of oral PMD's and prevention of oral cancer. Lycopene is useful not only for the oral lesions but it also has a powerful role in maintenance of overall systemic health. However, future research is needed to clarify its potential function in human health in terms of its dietary uptake metabolism, interactions with other carotinoids, role of its cis-trans isomers, its immunologic effects and evidence of its utility in treatment of various human diseases.

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