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Review

Oral Medicine and Radiology /Dentistry

# LYCOPENE-A BIOLOGICAL TERPENOID

Biju B Joseph

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# ABSTRACT

Healthy diet forms the verry base of a good health of a human. Diet should include various nutrients, cereals, so as to keep the system going smoothly and avoiding the unnecessary accumulation from varus diseases process. Antioxidants are now a day's added as food supplements so as to keep its level optimal in the system. Antioxidants play a key role in reducing the indirect damage caused to cells. Lycopene is a good and strong such compound, and are discussed widely for various ailments. In this review, various aspects of this food supplements is discussed under various headings.

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# INTRODUCTION

Health and nutrition are the contributing factors for human development and well-being. Adequate food and regular exercise are the major contributing factors for the maintenance of health .Fruits and vegetables form a major constituent in the diet regime. 1 However consumption of fruits and vegetables are not in a satisfactory level nowadays. This can be attributed to the change in food pattern and economic status of the population. There was a shift from high fibre to ones, that are high in sugar, animal products, processed foods which paved the way for different systemic ailments from diabetes to cancer .2,3,4 In Indian population too these foods are consumed less frequently. So, a regular intake of these foods are necessary to avoid aliments, as recognized by different health promoters, which also reduces the prevalence of even cardiovascular disease and obesity significantly .1According to article by WHO, the goal of Health 2020: is to significantly improve the health and well-being of populations, reduce health inequalities, strengthen public health and ensure people-centred health systems that are universal, equitable, sustainable and of high quality.5 Nowadays India is undergoing an impressive economic growth accompanied by a very slow decline, almost stagnation, in malnutrition levels. In developing countries, studies on dietary patterns and their relationship with nutritional status are scarce. Various studies show that most Indians are vegetarians, consumed less food containing micronutrients., which may promote inadequate nutrition intake causing, oxidative stress accumulation .Oxidative stress occurs in diabetes, various cancers, liver diseases, stroke, rheumatoid arthritis, chronic inflammation, and are related other degenerative diseases related to the nervous system. An imbalance between food intake and

energy expenditure is an important health determinant, causally linked to the incidence of lifestyle diseases such as obesity, diabetes, cancer and cardiovascular diseases1, 2, 6.

Fruits, nuts, and vegetables play a significant role in human nutrition, especially as sources of vitamins, minerals. These foods included in the daily diet regime have been strongly proved to reduce the risk for some forms of cancer, heart disease, stroke, and other chronic diseases. Certain chemical agents present in fruits and vegetables (Phytochemicals) are having strong antioxidant property. These chemical components are shown to modify the metabolic activation and detoxification/disposition of carcinogens, or even influence during the tumour cell during their activity in the body .Although the antioxidant property varies greatly among these fruits and vegetables, it is better to consume a variety of commodities rather than limiting consumption to a few with the highest antioxidant capacity7,8 Due to insufficient intake of fruits and vegetables, and need for additional supplements as an external source for all these components were extracted from available natural fruits , so the chemical compound extracted from these has nutraceutical activity and these are put under the group of functional foods which the, International Food Information Council (IFIC) defines as, foods that provide health benefits beyond basic nutrition.9

All vegetables are having different type of antioxidant components which provide protection against harmful-free radicals formed in the body and have associated with lower incidence and mortality rates of cancer and heart diseases in addition to a number of other health benefits which improves the quality of life Carotenoids are an important group of antioxidants in human diets which in addition to their vitamin activity, has several other biological activities including antioxidant capacity4.In 1831, Wackenroder , isolated an orange pigment from the carrot and coined the term "Carotene "from the Latin word carotacarota. The main carotenoids are  $\beta$ -carotene, lute in and lycopene. The antioxidant property of lycopene and this pigment and lime juices were studied in detail 9,10The most efficient carotenoid antioxidant is lycopene which was first isolated in 1910 and are present as coloured natural pigments .4Naturalpigments from plant products have drawn great attention worldwide. These pigments display various colours and are made up of different phytochemicals commonly found in the food matrix such as orange (β-carotene), yellowish-green (lutein), green (chlorophyll), and blue-purple(anthocyanin) 11 Tomato is one of the most popular and abundant fruits available ,although it is categorized as a vegetable, but in botanical terms, the tomato is the fruit born on a vineyard .The solid matter content of tomato ranges from 5.5-9.5% of which about 1% is seed and skin (on fresh weight basis).Tomato contains more fructose than glucose, various polysaccharides like xylan, pectin, cellulose, arabinoxylan and arabinogalactan. These polysaccharides are about 0.7% of tomato juice. Lycopene is one of the most important carotenoids present in red tomato. Lycopene formation occurs at the last stage of tomato ripening. It is also seen in other fruits like papaya insignificant amount. A fat-soluble, red pigment, is one lipophilic acyclic isomer of  $\beta$ -carotene, and found in human blood plasma with low-density lipoprotein fractions. It has strong antioxidant activity and exhibits the highest physical quenching rate constant with singlet oxygen.12Lycopene produced by plants to protect them from photo oxidation, is an important intermediate in biosynthesis of vitamin A precursor carotenoids like β-carotene and β-cryptoxanthin. As said, prolycopene (7Z, 9Z, 7'Z, 9'Z-lycopene) is formed by successive dehydrogenations of phytoene and  $\zeta$ -carotene catalyzed by phytoene desaturase (PDS) and ζ-carotene desaturase (ZDS), respectively. Subsequently, prolycopene is transformed to all-E-lycopene by a carotene cis- transisomerase.4

The biological importance of the isomers in lycopene has been not still elucidated. However, the anticancer property of this chemical is verry well established in different articles. The free radical formed during different disease process in the body is curbed by this antioxidant. Lycopene is known to have powerful antioxidant properties compared to other known different carotenoids, that is as follows lycopene> $\alpha$ tocopherol> $\alpha$ -carotene> $\beta$ cryptoxanthin>zeaxanthin= $\beta$ -

carotene>lutein. Lycopene has ability to decrease oxidative damage produce to different cells, through stimulation of enzyme activity of antioxidant.12 Lycopene, one hydrocarbon carotenoid, with general formula of C40H56 contains one acyclic open-chain structure that comprises 13 double-bonds. The double bonds present in lycopene are exposed to isomerization and various cis isomers are observed in plants and blood plasma. Physical variables including heat, light or some chemical reactions could cause isomerization from the trans-isomer into different mono-or poly-cis structures. It is found that carotenoids reactivityrelies on different criteria's notonly on the molecular and physical compound but also on their location or place of action into cells, ability to interact with other antioxidants, concentration and the partial pressure of oxygen. Antioxidant activity of these Chemical is due to polyene structures that are rich in electrons. Lycopene is known to have potent oxygen scavenging reagent between

different carotenoids, and thus it modulates reactions activated by free radicals such as OH- or peroxy radicals. Peroxyl radicals are produced during lipid peroxidations which cause damages in lipophilic parts. The carotenoidoxidation products are epoxides placed in the  $\beta$ -ionone ring, as well as those are in the central double bond of the conjugated polyene chain. The most products of reaction are ketones and aldehydes in the  $\beta$ -ionone ring. Prevention of these radical reactions by lycopene can prevent membranes from lipid peroxidation. It has also shown that this component stimulates the formation of phase II detoxifying antioxidant enzymes that keep the cells safe from reactive species. Studies suggest the reversal of DNA damage caused by free radicals by consumption of tomatoes by the subject.12Carotenoids have direct role in some redox-sensitive signaling pathways. Lycopene inhibits cancer through induction of apoptosis and have reported that lycopene and its auto-oxidant products could induce apoptosis in HL-60 cells. Lycopene also inhibits carcinogenesis by rescuing essential biomolecules such as lipids, LDL, proteins, and DNA. It has ability to quench singlet oxygen that could be credited to its conjugated double bonds. The biochemical changes occurring in the intestine are well documented. Lycopeneis internalized into the lipid droplets and released into the small intestine, where enzymes and bile acidscontinue the breakdown of the food matrix which can then be incorporated into the lipid micelles and be taken up by enterocytes. lycopene is absorbed by passive diffusion and by the action of scavenger receptorclass B type 1 (SR-B1), which is known to mediate the absorption of other carotenoids suchas ß-carotene and lutein. The majority of lycopene is packed into chylomicrons in its intact form and transported to the lymphatic system. This process could be mediated by themicrosomal triglyceride transfer protein (MTTP), an enzyme that delivers triglyceridesand other lipids into nascent chylomicrons. The enterocytes release chylomicronsinto the lymph and then into the portal circulation, where extrahepatic lipoprotein lipasescan partially degrade them into chylomicron remnants. The liver clears chylomicron remnants present in the portal system, and lycopeneand perhaps some of its metabolites are packaged into very-low-density-lipoproteins tobe transported into the bloodstream. Tissuestake up lycopene from lipoproteins by interacting with certain membrane proteins suchas SR-B1 and CD36. Lycopene preferentially accumulates in the liver, but it can befound in other organs, including the adipose tissue, adrenal glands, testes, ovaries, kidneys, lungs, skin, and the prostate.4, 10

## Lycopene and its Metabolites

Initial lycopene catabolism results in the production of lycopenoates. Theaction of additional enzymes is expected to produce a variety of additional metabolites. Most studies are carried out using the various pharmacological doses of lycopene. Various studies reported anti-inflammatory results with tis drug both invitro and in vivo. the current literature suggests that lycopene metabolites (derived from the dietor post-absorption metabolism of lycopene) are present in low levels within human serum, breastmilk, and urine, However the bioavailability in human tissues are not studied in tis full efficacy due to many reasons, like limited numbers of subjects and collection points.13,14

#### Benefits on human health

Oxidative stress occurs as a state of disturbance between free radical produced and the capability of antioxidant system to counteract such. Free radicals are also classified asreactive oxygen species (ROS) (oxygen centered radicals or oxygen centered non-radicals and reactive nitrogen species (RNS) (nitric oxide, nitric dioxide and peroxynitrite). Free radicals cause damage to all essential biocompoundssuch as DNA, proteins, and membrane lipids, thereby causing cause cell death. These are encountered by antioxidant system that exists in two major groups: enzymatic (glutathione peroxidase, myeloperoxidase, superoxide dismutase, and catalase) and non-enzymatic (minerals, vitamins, polyphenols, and thiols). The various life style diseases are associated with oxidative stress similarly many oral lesion are too are associated with this oxidative stress. This affects the oral hygiene. Among all oral diseases, the periodontal disease, progression due to tis stress. Inchronic periodontitis, there was lower serum total antioxidantlevel and salivary capacity when compared to the control individuals. Assessment of blood and gingival tissues of chronic periodontitis patients also revealed mitochondrial DNA deletion. Gingival blood analysis of periodontitis patients also marked high level of 7-8-dihydro-8-ossiguanina (8oxoG), a pre-mutagen base that results from ROS-mediated DNA damage. Similarly, higher level were lipid peroxidation products were noted in the crevicular fluid of gingiva was detected in chronic periodontitis patients compared to those with gingivitis and healthy individuals. Various studies showed that oxidative stress is involved in the pathogenesis of OLP, even though the exact Aetiology is not identified. Significantly higher salivary ROS, lipid peroxidation, nitric oxide, and nitrite levels were found in OLP patients compared to the control subjects. The total antioxidant activity was significantly decreased in OLP patients with increased level of salivary malondialdehyde (MDA) compared to the healthy control group suggesting the possible role of the oxidants to orchestrate the disease via lipid per oxidation mediated pathway. Oxidative stress was also correlated with oral cancer, as increased lipid per oxidation and reduced antioxidants was reported in patients suffering from stage II, III, and IV oral cancer. Nitric oxide-mediated DNA damage was reported in patients with oral leukoplakia. Samples of oral epithelium taken from these patients recorded high levels of 8nitroguanine and 8-oxoG. The deleterious effects of ROS in the event of oxidative stress are through lipid per oxidation and irreversible protein modification that leads to cellular apoptosis or programmed cell death. Numerous pathways mediate oxidative cellular damage and these include as caspase pathway, PERK/NRF2 pathway, NADPH oxidase 4 pathway and JNK/mitogen-activated protein (MAP) kinase pathway. All these paves the way for different system diseases. all the systemic disease are involved with mild or moderate inflammatory changes either initially or as it is inherent in its pathophysiology. The accepted hypothesis is that inflammation can trigger oxidative stress and the oxidation also can induce inflammation. During the onset of inflammation, pro-inflammatory gene expression through activation of numerous cellular pathways finally inducing oxidative stress which activates NOD-like receptor protein 3 (NRLP3) inflammasome (Shimada et al., 2012) which are responsible for maturation of pro-inflammatory proteins such as interleukin . Lipid peroxidation (LPO) is the oxidative

deterioration of lipids caused by ROS. LPO is a chain reaction that mostly affects polyunsaturated fatty acids due to the presence of methylene bridges (-CH2-) that possess reactive hydrogen atoms. LPO has been implicated in numerous noncommunicable diseases and aging-related disorders such as cataract. rheumatoid arthritis, atherosclerosis, and neurodegenerative diseases. Oral health is an important aspect of overall well-being of an organism. Numerous systemic conditions and diseases are related to the realhygiene aspects. Saliva actas the first line of defense against free radicals through antioxidants suchas catalase, superoxide dismutase, and glutathione peroxidase. In the event of an infection, increased generation of free radicals outnumber antioxidants to initiateoxidative stress.15 To keep the system going smoothly here must be adequate supply of multivitamins, minerals, and other associated nutrients . Polyphenols are naturally occurring compounds that are found in vegetables, fruits, beverages, herbs and spices. Recent advances in research focusing on the anti-inflammatory and antioxidant effects of the polyphenolshave shed light on the mechanisms of the phenolic compounds n scavenging free radicals, regulation of cytokine activities, and the maintenance of antioxidant enzyme system.16 The effectiveness of any antioxidant depends on which free radical is involved in the process, how and where it is generated, and the target of damage. Hence an antioxidant in one particular system may protect against free radicals, while in another it makes no effect. The various therapeutic use of antioxidants for oral lesions include

- 1. Prevention of lesions in high-risk individuals with mucosa that clinically appears normal with no history of either premalignant or malignant lesion
- 2. The treatment of premalignant oral lesions
- 3. In patients who have had either premalignant or malignant oral lesions that have been successfully treated, in order to prevent recurrence of the treated initial lesion or to prevent the development of a second or a separate primary.17

#### Role of Lycopene in Prevention of Oral Diseases

Lycopene has some beneficial effects in the treatmentof certain diseases of oral cavity including oral cancerand precancerous lesions; lycopene does not have thepro-vitamin A activity and its various benefits are

- AO activity
- Inhibition of cancer cell proliferation
- Interference with growth factor stimulation
- Inducing phase II enzymes
- Regulation of transcription and
- Restoration of gap junctions.

Lycopene exerts its AO activity by physical and chemical quenching of free radicals and is the most efficient singlet oxygen quenching carotenoid. The stereo chemical properties of lycopene are quite different from those of other carotenoids, making it the most efficient quencher of singlet oxygentherebyprotecting cellular components against specific types of damage from highly reactive oxygen species.16 As oxidative stress plays a major role in pathogenesis of PMD lesions, use of antioxidants plays a vital role in the treatment. Lycopene is widely and successfully used in the treatment of oral PMD's and oral cancer 18

### Antioxidant Action of Lycopene

Lycopene is one of the most potent antioxidant, The physical quenching capability of lycopene is two times higher than  $\beta$ -carotene and ten times higher than  $\alpha$ -tocopherol. Lycopene scavenges singlet oxygen (1O2), nitrogen dioxide (NO2.), thiyl (RS.), hydrogen peroxide (H2O2.) and sulphonyl (RSO2.) radicals. Moreover, lycopene protects biological molecules including lipids, proteins and DNA.Due to its excellent antioxidant properties and anticancer activities, lycopene is successfully and safely. Used in the treatment of oral precancerous lesions and precancerous conditions.19

## 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. tobacco usage has been warranted as the etiological factor beyond doubt or this type of oral lesions, which induce the oxidative stress further paving the way or malignancy. Treatment for OL, includes assessing the degree of epithelial dysplasia which can help in the treatment strategy.16

Lycopene is a promising treatment modality for oral leukoplakia. First description for the use of chemo preventive agents for leukoplakia dates back around 25 years ago. Various study show relapse with the use of topical agents hence the development of an invitro agent t was tried.19 In a systematic review of antioxidants in treatment of oral leukoplakia, lycopene was demonstrated to be a potential treatment option. Study that improvement of micronutrient levels of lycopene and other antioxidants may protect against the relative risk of OLP can protect cells against cell damage and play a protective role against progression of dysplasia by inhibiting tumor cell proliferation.16 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. Lycopene has also been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins and DNA.lycopene reduces cellular proliferation induced by insulin-like growth factors, which are potent mitogens, in various cancer cell lines. It can protect cells against cell damage and play a protective role against progression of dysplasia by inhibiting tumor cell proliferation. Various other study showed the significance lycopene either alone or in combination with other micronutrients for the treatment of oral leukoplakia20. Oral submucous fibrosis: 6, 20, 21

Oral submucous fibrosis (OSMF) is a chronic, progressive, scarring, disease , found to be of multifactorial etiology including excessive chili consumption, genetic susceptibility, autoimmunity, iron and vitamin deficiency. The malignant transformation rate of OSMF to oral squamous cell carcinoma (OSCC) accounts for 7%-13%. Fibrosis and hyalinization of sub epithelial tissue are the most crucial clinic pathological features of OSMF, which greatly affect the patients' quality of life. The appearance of my fibroblasts and the consistent expression of  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) are considered to be signs of progressive fibrosis and are thought to cause the change of OSMF microenvironment, leading to tumorigenesis.

Fibrosis, results from the effects of areca nut, stimulated by are choline, which increases collagen production and decreases collagen degradation. Thus, OSF is now considered collagen metabolic disorder.OSF causes atrophy in the epithelium, increasing carcinogen penetration.20

Many treatments have been tried to relieve-related symptoms and for enhanced function status in OSF patients ranging from conservative treatments such as steroids, hyaluronidase, placental extracts, collagens and nutrients supplements to surgical excision of fibrotic bands, and grafting and bilateral cricoidectomy Lycopene inhibits carcinogen, induces angiogenesis, and favors cell cycle growth. Micronutrients are the carotenoids, like lycopenehave shown to be good enough for the treatment of some. Its mode of action may involve stimulation of the immune system or a direct action on the tumor cells. Lycopene also up regulates the lymphocyte resistance to stress and suppresses the inflammatory response. These properties of lycopenemake it helpful in the treatment of OSMF.16, 19 Vinay kumar et al in their study showed that Lycopene appears to be a very promising antioxidant in the management of oral sub mucous fibrosis, both in clinical and symptomatic improvement. They had done the study with lycopene and vitamin E, which give them the good results.22, 23, 24 the conservative drug treatment that is currently available for OSF is clearly inadequate. No single drug has provided complete relief of symptoms of OSF 2; this has lead to the use of combination of drugs to treat the condition. The antioxidant potential has been ranked as follows: lycopene >  $\alpha$ -tocopherol >  $\alpha$ -carotene >  $\beta$ -cryptoxanthin > zeaxanthin =  $\beta$ carotene > lutein.

Selvam *et al* in their study showed that lycopene when combined with intralesional steroids offer more benefit than when used alone, that Lycopene in combination with intralesional steroids and Hyaluronidase, is highly efficacious in improving the mouth opening and reducing other symptoms in patients with Oral Submucous Fibrosis.25 Kareemore etal also sowed the same benevolent result of lycopene when studied for the osmf group of patients. With no or minimal side effects.26 Gowda *et al* STUDIED the effect of lycopene in osmf subjects and found that the drug was giving a good repose,.

Patil *et al* studied on subjects with omf by using two drugs as lycopene and aloe vera and found significant t improvement in various parameters. Like clinical improvements in mouth opening and tongue.27 Oral Lichen Planus. 18

Oral lichen planus is a chronic inflammatory mucocutaneous disease with unknown etiology. Although the exact etiology of the disease is unknown, the role of free radicals and oxidative stress has been implicated in its pathogenesis.

Sander n his study demonstrated increased oxidative stress and decreased antioxidant enzyme production in tissues of vulval erosive lichen planus. A study of Nagao et al 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. various study conducted elucidate this factor of lycopene, suggesting its use in these kind of oral lesions. By virtue of its AO and anticancer properties, it may be useful in the prevention of malignant

transformation in the OLP. However an affirmative treatment remains, and a vast array of empirical treatments reported in the literature indicates the continuing search for the solution. D 6The Role of Lycopene in Preventing Oral Diseases as a Nonsurgical Aid of Treatment is discussed widely nowadays with utmost importance, its role in treating various other oral diseases are also thought about. The common one among them being the periodontal diseases, the mechanism of periodontal is based on the ROS-mediated tissue damage and AO defense in response to bacterial colonization, through the noninvasive collection of gingival crevicular fluid. ROS cause tissue damage by a variety of different mechanisms, which include DNA damage, lipid peroxidation, protein damage, including gingival hyaluronic acid and proteoglycans, and stimulation of pro-inflammatory cytokine release by monocytes and macrophages. Though most ROS have extremely shorthalf-lives, they can cause substantial tissue damage by initiating free radical chain reactions. Among other antioxidants lycopene is the most potent one .along with other drugs it act as an adjuvant. Lycopene exerts potent antifungal activity against Candida albicans by causing significant damage to the cell membrane16

Another study done by Jyoti etal showed that Oral lycopene and green tea extract supplementation is positively associated with salivary uric acid levels and plays an important role in the management of gingivitis.28 Chronic pain from or facial pathologies is correlated to a state of neuronal hypersensitivity known as central sensitization. Increased reactive intermediates from oxidative stress were found to mediate sensitization mechanisms. Elevated levels of both reactive species and products of the oxidative damage along with lowered levels of markers of the antioxidant defense were noted in different or facial diseases and disorders. Antioxidants are considered safe and reliable therapeutic options that modulate the pain pathway beside their wideranging benefits in human health and disease. 29

In RAS the inflammatory and immune response triggers the production of free radicals. Uses of Herbal topical applications like curcumin and ocmium sanctum are found to be effective against RAS since they possess anti-ulcerogenic properties. Antioxidant properties of the essential oil of Ocimum Sanctum (holy basil, Tulsi) and its two main components i.e. eugenol and linalool have shown promising results against C.albicans. Recent studies have demonstrated that antioxidants like propolis, Pelargonium grave lens (olive oil), Equisetum giganteum (horsetail plant extract), Punicagranatum (pomegranate), and Melaleuca alternifolia (tea tree oil) are ideal for the treatment of denture stomatitis due to their in vitro inhibitory actions on the colonization and development of Candida biofilm.30

# CONCLUSION

The antioxidant system and oxidative stress balance in humans depend upon numerous factors like diet, immune function, altered inflammatory response, obesity, smoking, alcohol, chemicals, and radiation. For the past several years, antioxidants are widely used in the treatment of oral mucosal diseases.Lycopene has been recognized as a safe product for daily dietary intake, no adverse effects were observed at the highest intake level provided (3 g/kg/day) of dietary or formulated lycopene.However studies have to initiatedto identify the anti-inflammatory, anti-ulcerogenic, antitumorigenic, immunomodulatory, antimicrobial activities in various naturally-derived antioxidants with stress on areas like dose factors, biocompatibility, drug interactions and combination therapy.

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