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LYCOPENE: POTENT ANTIOXIDANT FOR ORAL PREMALIGNANCY AND ORAL CANCER

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ABSTRACT

Lycopene is a red coloured carotinoid an acyclic isomer of beta carotene predominantly accumulated in tomatoes as well as other fruits & vegetables. Humans are unable to synthesize it & can only be obtain it from diet. It is the most common carotinoid in human plasma. Epidemiological data proved that lycopene acts as an antioxidant & has significant role in prevention & treatment of oral premalignant lesions, also prevents further progression of oral cancer by various means. The purpose of this article is to highlight the role & importance of lycopene in prevention & treatment of oral premalignant lesions, also prevents further progression of oral cancer by various means.

KEYWORDS: Antioxidant, Leukoplakia, Lycopene, Oral cancer, OSMF.

INTRODUCTION

Lycopene has attracted attention for nearly 50 years for its biochemical and physiochemical properties. Various epidemiological studies, in vitro, and in vivo animal and human experiments have provided support for lycopene's antioxidant health benefits.[1]

Lycopene is red colored carotinoid pigment, a member of the carotenoid family of phytochemicals. It is responsible for deep red color of tomato, strawberry, watermelon, pink grapefruit, apricots, pink guava etc. Humans are not able to synthesize hence can only be obtain from diet. Lycopene have some unique feature like it is most potent anti oxidant found in food, it is most predominant carotinoid in human plasma. It is lipophilic, insoluble in water. Heated and processed foods are rich sources. Lipid rich diets show more bioavailability than from raw food.[2]

Chemically, Lycopene is 40 carbon acyclic carotinoid, isomer of b-carotene, but does not have provitamin A activity. Lycopene is an acyclic, highly unsaturated straight chain hydrocarbon containing 11 conjugated & 2 unconjugated double bonds (at position c-12, 15). It is present in cis & trans isomer, cis isomers are more bioavilable, due to its increase uptake by intestinal cells.[3]

Lycopene is a highly stable molecule. Its stability depends on its chemical structure and cis , trnas isomeric forms. However, it can undergo oxidative, thermal, and photodegredation.[4] Studies have shown lycopene to be stable under the conditions of thermal processing and storage.[5] A recent publication showed 5-cis lycopene to be most stable isomer followed by the all-trans, 9-cis, 13-cis, 15-cis, 7-cis and 11-cis. 5-cis lycopene was also shown to have the highest antioxidant properties followed by 9-cis, 7-cis, 13-cis, 11-cis and the all-trans isomers.[6]

It is evident that the average intake levels of Lycopene are lower than required to provide its beneficial effects. In general it ranges from 3.7 to 16.2 mg. Although the beneficial effects of Lycopene in the prevention of human diseases have been well documented it is not yet recognized as an essential nutrient. As a result there is no official recommended nutrient intake (RNI) level set by health professionals and government regulatory agencies.[7] However, based on reported studies a daily intake level of 5–7 mg in normal healthy human beings may be sufficient to maintain circulating levels of lycopene at levels sufficient to combat oxidative stress and prevent chronic diseases.[8] Under the condition of disease such as cancer and cardiovascular diseases, higher levels of lycopene ranging from 35 to 75 mg per day may be required.[9]

Tomatoes and tomato-based foods account for more than85% of all the dietary sources of Lycopene. Lycopene content of some common tomato-based foods is shown in Table 1.

Absorption of Lycopene

Absorption of lycopene is similar to other lipid soluble compounds and is absorbed across the gastrointestinal tract via a chylomicron mediated mechanism.[10] Lycopene is absorbed into the gastrointestinal mucosal cells & appear unchanged in circulation & tissue. In intestine carotinoid are absorbed by passive diffusion after being incorporated into the micelles, micelles are formed by dietary fat & bile acids.[11]

In general, 10–30% of the dietary lycopene is absorbed by humans. It is absorbed equally efficiently from different sources of lycopene including tomato sauce, tomato juice. Lycopene absorption from dietary sources is influenced by several factors including the breakup of the food matrix containing lycopene, cooking temperatures and the presence of lipids and other lipid soluble compounds including other carotenoids.[10] Other studies have shown that Lycopene is absorbed more efficiently from processed tomato products compared to raw tomatoes. The increased absorption of lycopene from processed tomato products is attributed to the presence of cis-isomers of Lycopene.[12]

Distribution of Lycopene

Absorbed lycopene is distributed throughout the body via the circulatory system. Lycopene is the most predominant carotinoid in human plasma with a half life of about 2–3 days.[12] In serum mostly cis form of Lycopene is exist. As the micellular carotinoids i.e. absorbed form of Lycopene incorporated into chylomicrons & released into lymphatic system. Then Incorporated into the lipoprotein at the site of liver & released into blood stream. The major site of storage of carotinoids are adipose tissue.

Testes, adrenal glands, prostate, breast and liver were shown to have the highest levels of lycopene in humans. Lycopene in the tissues undergoes oxidation and metabolism.[13] Hence tissue specific distribution of Lycopene is attributable to site specific antioxidant effect.[14]

Biological effect

Although the epidemiological evidence of the role of lycopene in cancer prevention is persuasive, this mechanism of bioactivity remains to be proven. Two major hypotheses have been proposed to be involved in the bioactivities of lycopene: Antioxidative and Non-oxidative effects.[11] Oxidative stress caused by reactive oxygen species (ROS) can result in damage to macromolecules such as proteins, carbohydrates, lipid, and DNA. The mechanism by which such damage is prevented or damage is revert back. It is called as antioxidative

mechanism. Non-oxidative effects are those by which the cellular structural & functional statuses are improved such that chances of cell damage are reduced. Table 2 represents various mechanisms involved under each heading.

Antioxidative Mechanism

1. Quench reactive oxygen species

As a quench of single oxygen & a scavenger of free radical, lycopene is able to protect against oxidative stress.[15] Potency of such action is related to number of double bonds. Singlet –oxygen quenching capacity is being twice as high as that of b-carotene & ten times as higher than that of vitamin E. Lycopene was most rapidly destroyed carotinoid on reaction with peroxyl radicals, suggesting its role in 1st line of defense against oxidative stress.[16,17]

2. Anti lipid Peroxidation

Free radicals when act on plasma membrane it acts on lipid resulting in lipid peroxidation. Lycopene by inactivation of free radicals prevent lipid peroxidation, thereby preventing tissue damage.[18] and hence basically related to quenching of reactive oxygen species.

3. Anti DNA oxidative damage

Oxygen quenching ability protect against DNA oxidative damage in vitro & in vivo, thereby preventing potential mutation which may be associated with cancerization.[17]

4. Protection against LDL oxidation.

Lycopene is lipophilic present in LDL .thus helps to prevent LDL oxidation.[4]

5. Inhibition of HMG co-A reductase activity.

Lycopene inhibit HMG co-A reductase activity. This help to decrease in native cholesterol and hence help to maintain proper homeostasis and reduce the chances of damage caused by excessive cholesterol.[1]

6. Protection of lymphocytes against membrane damage.[13]

Non- oxidative damage.

1. Increase in gap junction communication

GJC between cells is thought to be one of the protective mechanisms against cancerization. Deficiency of GJC has been observed to be related to many human tumors, while the restoration or upregulation of GJC is associated with decreased proliferation of tumor cells.[18] Studies have identified that lycopene could upregulate the expression of connexin 43

gene, which allowing for a direct formation of intercellular GJC in various human and animal cells.[19] Gene function regulation

2. Hormone & immune modulation

There have been several reports that lycopene can inhibit cell cycle in the G0/G1 phase and induce S phase block in variety of cancer cells, including those of prostate, breast, lung, and edometrium. These effects were accompanied by inhibition of proliferation of different types of cancer cells.[15]

3. Antiproliferation

Apoptosis helps maintain health by eliminating unhealthy, excess, or abnormal cells. Damaged cells those fail to undergo apoptosis may become immortal and can transform to malignant cells. Recently, several in vitro studies with cell lines derived from different human cancer tissues have indicated that lycopene can promote apoptosis in these cells and therefore might have potential as a chemotherapeutic agent. Along with gene function regulation lycopene also inhibit proliferation of different types of cancer cells.[15]

4. Prodifferntiation

Lycopene alone has found to induce cell differentiation as measured by phorbol ester dependent reduction of nitro blue tetrazolium & expression of cell surface antigen CD14.[20] thus appear to be important for inducing differentiation.

5. Carcinogen metabolism

Lycopene significantly induces cytochrome P450-dependent enzyme, phase I enzymes, in a dose-dependent manner and a phase II enzyme hepatic quinone reductase by twofold. This class of enzymes is important for the removal of foreign substances and carcinogens from the body.

Lycopene in the prevention and management of the premalignant lesions of oral cavity

Oral submucous fibrosis

Oral submucous fibrosis (OSF) is a chronic disorder characterized by progressive fibrosis of the oral mucosa, resulting in a series of symptoms. Along with the significant reduced oral function, OSF is a premalignant condition and the potential for malignant transformation in this disorder is considered high.[21]

Kumar et al. carried out a prospective randomized and blinded, placebo-controlled study to investigate the efficacy of lycopene as a conservative strategy in the management of OSF. Patients of experimental group received 16 mg of lycopene with or without biweekly intralesional steroid injections, whereas those of control group were given a placebo. The results showed that lycopene either singly or in combination with intralesional steroid injections was more efficacious in improving the mouth opening and in reducing burning sensation symptoms than the placebo treatment. In addition, there were no reported instances of side effects or intolerance to lycopene. Thus, they concluded that lycopene was seen to be an efficacious, safe, and reliable drug in the management of OSF.[22]

Lycopene has been found to inhibit hepatic fibrosis in rats and human fibroblast activity in vitro, suggesting its potential effect in the treatment of OSF. This curative effect of lycopene may be owing to an inhibition of abnormal fibroblasts, upregulation of lymphocyte resistance to stress, and suppression of the inflammatory response. Further trials in this regard are needed to explain the mechanisms through which lycopene exerts its beneficial effects and to investigate the optimized dosages and treatment periods in usage of this supplementation.[23]

Oral Leukoplakia

Leukoplakia is currently defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease. It is the most common precancerous lesion in the oral cavity with a recognizable risk for malignant transformation.[24]

Tobacco usage also has definite roles in the Etiopathogenesis of oral cancers by generating increased reactive free radicals and active oxygen species, which mediate phenotypic and genotypic alterations and lead mutations to carcinogenesis. A number of studies have suggested that the treatment of premalignant lesions should include antioxidants along with the cessation of tobacco usage. Also, The observed effect of lycopene suggests that it can be effectively used for the management of oral leukoplakia.[25]

Lycopene in the prevention and management of oral cancer

Free radicals such as ROS and reactive nitrogen species (RNS) have been implicated in the development of oral cancer by numerous studies.[26] The increase in ROS and RNS may be the event which lead to the consumption and reduction of antioxidants, explaining the oxidative damage to the DNA, proteins, and lipid of oral cancer patients and possibly the

promotion of oral cancer.[27] Thus, antioxidants should be the necessary part of prevention and therapeutic regiment of oral malignancies.

In a case and control study of 404 case/control pairs in Beijing, China, tomato intake was inversely associated with the risk of oral cancer.[28] A similar finding was observed in another case–control study in north-east Italy, in which reduced risk of cancers of oral cavity and pharynx emerged in subjects reporting more frequent consumption of fresh tomatoes.[29] Another study in Uruguay also revealed that tomato and tomato-rich food intakes and lycopene intake alone were associated with a reduction in risk of cancer of the upper aerodigestive tract including the oral cavity.[28] One study comparing antioxidants like plasma b- and a-carotene, lycopene, lutein/zeaxanthin, total carotenoids, retinol, a-tocopherol, it has been found that only plasma lycopene was significantly inversely associated with total mortality and mortality in non-smoking patients.[30] thus it can be concluded that the consumption of lycopene or lycopene-containing foods might reduce the risk of developing oral cancer.

Recently, in vitro and in vivo experimental data have also demonstrated lycopene's notable anticarcinogenic effect in oral carcinogenesis. Cheng et al. In their study, observed that lycopene-suppressed KB cell proliferation at the G0/G1 phase, with a significant decrease in proliferation cell nuclear antigen (PCNA) expression. Cell–cell interaction via gap-junctional communication (GJC) is considered to be a key factor in tissue homeostasis, and its alteration is associated with the neoplastic phenotype.[31] However, up to today, no clinical trial has evaluated the effect of tomato products or lycopene supplements in the treatment of oral cancer.

Table 1. Lycopene content of common fruits and vegetables

Fruit/Tomato Product	Lycopene Content (ug/g wet weight)
Fresh tomato	8.8±42.0
Watermelon	23.0±72.0
Pink guava	54.0
Pink grapefruit	33.6
Papaya	20.0±53.0
Tomato sauce	62.0
Tomato paste	54.0±1500.0
Tomato juice	50.0±116.0
Tomato ketchup	99.0±134.4
Pizza sauce	127.1

Data taken from: Scott and Hart (1995), Tonucci et al. (1995) and Rao and Agarwal (1999).

Table 2. Various biological mechanisms by which Lycopene acts

I. Antioxidative stress	**Non- oxidative damage.**
1. Quench reactive oxygen species	Increase in gap junction communication
2. Anti lipid peroxidation	Gene function regulation
3. Anti DNA oxidative damage	Hormone & immune modulation
4. Protection against LDL oxidation	Antiproliferation
5. Inhibition of HMG co A reductase activity decrease in native cholesterol	Prodiiferntiation
6. Protection of lymphocytes against membrane damage.	Carcinogen metabolism.

CONCLUSION

Thus Lycopene is promising antioxidant. Considering the biological effect, It act by antioxidant mechanisms and non oxidative mechanisms. Hence present review supports the potential use of lycopene as an adjunct to the management of the oral precancerous lesions and its potential role in decreasing the risk of oral carcinogenesis. Also further studies with use of Lycopene in various premalignant condition & lesion are necessary in particular context.

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