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Role of lycopene in the prevention of oral precancerous lesions. A review

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ABSTRACT

Objectives. To systematically review the methodology and results of clinical trials conducted on oral precancer patients using lycopene. ***Methods.*** An internet search using google search engine including key words - "lycopene, oral submucous fibrosis oral leukoplakia and oral cancer"- was done Full text articles in English language of all the clinical trials that were published in journals from the year 2004 to 2016 were obtained and evaluated. ***Results.*** The data available from the clinical trials were analyzed and presented under broad headings of sample size, duration of study, dosage and results and presented in tabular form. ***Conclusions.*** Lycopene is a promising candidate in reducing cancer and oral diseases in human beings. This review discusses the benefits of lycopene in prevention of different oral diseases.

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Keywords: Lycopene, oral cancer, antioxidants, natural sources

Introduction

Lycopene is one of the most potent antioxidants among all the carotenoids with applications in oral diseases ranging from management of oral pre-cancer to management of periodontal diseases [1]. Studies have indicated that lycopene exhibits anti-artherogenic properties and hence can play a major role in prevention of heart diseases [1]. Besides its role in prevention in of oral cancer recent studies have exhibited that the serum and tissue levels of lycopene are inversely associated with the risk of breast and prostatecancer [2].

Biological properties of lycopene

Lycopene is a bright red carotene found mainly in tomatoes and other red- coloured fruits and vegetable like carrots, water-melons, and papayas [3]. Lycopene exhibits the highest physical quenching rate constant with free radicals like singlet oxygen [4]. Lycopene has a high number of conjugated double bonds; therefore it has a higher singlet oxygen quenching capacity in comparison to beta-carotene or alpha-tocopherol [5]. Lycopene has been found to be three times more effective than beta-carotene in arresting

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cell death by neutralizing of reactive nitrogen species [6]. Lycopene has higher antioxidant capacity than that of α-tocopherol [7]. Stahl *et al.* [8] in 1998 ranked the antioxidants as follows: lycopene > α-tocopherol > α-carotene > ß-cryptoxanthin > zeaxanthin = ß-carotene > lutein. Lycopene protects DNA damage caused by 1-methyl-3 nitro-1-nitrosoguanidine and hydrogen peroxide [9]. Lycopene is believed to promote the expression of a gene encoding a gap junction protein. It is also said that this property is independent of its pro-vitamin A or antioxidant properties [10]. Some in vitro experiments have shown that lycopene inhibits the growth process of human neoplastic cells, by interfering in growth factor receptor signaling and reducing progression of cell cycle [11]. Studies have shown that administration of lycopene suppresses DMBA(7,12-Dimethylbenz[a]anthracene)-induced oral carcinogenesis [12]. In vitro studies have revealed thatlycopene in various doses results causes reduced proliferation of oral cancer cells called KB1 human oral cells. These 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 [13]. Lycopene is believed to act by stimulation of the immune system or a direct action on the tumour cells [14]. Lycopene is said to increase the resistance of lymphocytes to stress associated with oxidative process [13]. Lycopene has been shown to inhibit hepatic fibro genesis in experimental rats prompting views that it may also exert a similar inhibition on the abnormal fibroblastic activity in oral submucous fibrosis [14]. Lycopene has been reported to increase p53 protein levels which has tumor suppressor properties [15]. Recent animal studies have shown that lycopene may prevent smoke exposure-induced changes in p53, p53 phosphorylation, p53 target genes, cell proliferation, and apoptosis in the gastric mucosa of ferrets [16].

Several recent studies revealed the serum and tissue levels of lycopene are inversely associated with the risk of breast cancer, prostate cancer, coronary heart disease and oral premalignant lesions [17-19]. The physiologic mean plasma range of lycopene extends from 0.22 to 1.06 nmol/ml, and it contributes 21-43% of the total carotenoids [20]. Recent years have also witnessed surged in clinical trials involving lycopene in the treatment of oral cancer and precancer.

Bioavailability of lycopene

Researchers have found that in fresh fruits, lycopene is present within the fruit tissue hence only a portion of the lycopene in the fruit is absorbed [5]. Research has revealed that processing fruit into a juice, sauce, paste, or ketchup makes the lycopene more bioavailable by increasing the surface area available for digestion [5].

It is also believed that the temperature changes involved in processing alters the bound chemical form of lycopene to make it more easily absorbed by the body [5]. Since lycopene is fat-soluble absorption into tissues enhanced when oil is added to the diet [5]. Researchers have found isomerization of all trans-isomers to cis-isomers occur under acidic conditions of the gastric juices [21]. Under experimental conditions incubated lycopene derived from capsules with simulated gastric juice for 1 min showed a 40% cis-lycopene content, whereas the levels did not exceed 20% even after 3-hour incubation with water as a control [22]. This experiment was one of convincing evidence regarding the isomerization of all trans- lycopene to cis-isomers, under acidic conditions of the gastric juice. Thus proving the fact that gastric pH and food matrix influence isomerization further subsequent absorption and increased bioavailability of cis-lycopene [22].

Factors reducing the absorption of lycopene include certain fibers, fat substitutes, plant sterols and cholesterol-lowering drugs [23]. These agents prevent incorporation of lycopene into micelles, thus reducing absorption. Clinical trials using lycopene have been reported recently. Consumption of dietary fat in the form olive oil or sunflower oil has proven to promote lycopene absorption, primarily by stimulating bile production for the formation of bile acid micelles [24]. One study has demonstrated the positive effect of avocado consumption on lycopene absorption. The effect was attributed to high oleic fatty acid present in avocado, which probably facilitated the formation of chylomicrons and facilitated absorption [25].

Review methodology

An internet search using google search engine including key words -"lycopene, oral submucous fibrosis oral leukoplakia and oral cancer"- was done. Full text articles of clinical trials in English language that were published in journals from the year 2004 to 2016 were obtained. Information from case reports and reviews were excluded from the tables.

Lycopene and oral precancer

Recently there has been a surge in the literature

Table 1. Summary of clinical trials involving lycopene in oral precancer cases

Researcher and year	Study subjects	Duration	Dose of lycopene	Disease condition	Results
Singh *et al.* 2004	58	3 months	8 mg and 4 mg	Oral leukoplakia	Significant reduction in the clinical and histological results was seen.
Kumar *et al.* 2007	58	2 months	16 mg	Oral submucous fibrosis	Increase in mouth opening
Gowda *et al.* 2011	12	3 months	2000 µg	Oral submucous fibrosis	Clinical and histological improvement
Karemore *et al.* 2012	92	3 months	4 mg and 8 mg	Oral submucous fibrosis	Significantly efficacious in the amelioration of signs and symptoms of OSMF
Aung *et al.* 2013	72	3 months	10 mg	Oral leukoplakia	Mild improvement in thin leukoplakia cases
Selvam *et al.* 2013	45	3 months	16 mg	Oral submucous fibrosis	There was significant increase in mouth opening
Patel *et al.* 2014	41	3 months	3 mg	Oral leukoplakia	Patients receiving lycopene in combination with vitamin E and selenium havestatistically significant improvements both clinically and histologically as compared to those receiving placebo and with no side effects.
Patil *et al.* 2015	60	3 months	8 mg	Oral submucous fibrosis	Clinical improvements in mouth opening and tongue protrusion were significant

regarding lycopene in oral precancer. [Table 1]. One of the foremost clinical trials using lycopene in oral precancer was done by Singh *et al.* [12] in 2004. The study involved fifty-eight clinically and histologically diagnosed patients of oral leukoplakia randomly divided into three groups. Two study groups were administered 8 mg and 4 mg lycopene, respectively. The third group was administered placebo. When the outcome was assessed clinically, the patients in the three groups had a mean response of 80%, 66.25% and 12.5%, respectively. Histological evaluation yielded similar results. Based on these results, the researchers suggested that lycopene can be effectively and safely used for the management of oral leukoplakia. Kumar *et al.* [26] in 2007 evaluated the efficacy of oral lycopene therapy in patients with oral submucous fibrosis. Fifty-eight patients with oral submucous fibrosis were recruited for the study and were randomly divided into 3 groups. First group received 16 mg of lycopene whereas the second group received 16 mg of lycopene along with biweekly intralesional steroid injections. The third group was administered placebo. The researchers observed an average increase of 3.4 mm, 4.6 mm, and 0.0 mm in the mouth opening values of the first second and third groups.Based on these results the researchers suggested that lycopene should be used as a first line of therapy in the initial management of oral submucous fibrosis.

Gowda *et al.* [14] in 2011evaluated the clinical and histopathological response of oral submucous fibrosis to Lycopene in 12 adult patients picked from the regular outpatient of dental department. The study subjects were administered 2000 µgof lycopene and the responses were assessed clinically and histopathologically after 3 months. They observed clinical parameters such as mouth opening of the oral submucous patients [14].

Karemore *et al.* [27] in 2012 evaluated the efficacy of lycopene in conjunction with the cessation of causative habit in the treatment of OSMF. Of the 92 study subjects, 46 patients were given lycopene and remaining 46 were on placebo drug. Lycopene group

patients received 8 mg Lycored TM per day in two divided doses of 4 mg each, while placebo group patients received placebo tablet twice a day. Patients were examined for changes in mouth opening and other clinical symptoms of OSMF during three months and were followed up two months. They found that lycopene significantly effective in reduction of signs and symptoms of OSMF. A significantimprovement in the maximal mouth opening was observed in the study subjects administered lycopene [27].

Although most of the clinical trials were carried out in India, one study was carried out in Burma by Aung *et al.* [28] in 2013 also suggested improvement in oral leukoplakia cases when treated with lycopene. Selvam *et al.* [29] in 2013 evaluated the efficacy of oral lycopene therapy when used in combination with conventional intralesional steroid therapy in the management of oral submucous fibrosis. Forty five patients with oral submucous fibrosis were included under the study and were randomly divided into 3 groups. First group received 16 mg/day oral lycopene with biweekly intralesional steroids and hyaluronidase. The second group received oral antioxidant capsules with biweekly intralesional steroids and hyaluronidase whereas the third group received biweekly intralesional steroids and hyaluronidase alone. After 6 weeks there was significant increase in mouth opening among all the 3 groups but the group receiving lycopene in combination with intralesional steroids and Hyaluronidase showed the maximum improvement in mouth opening when compared to other groups.

Patel *et al.* [30] in 2014 studied the efficacy of lycopene in combination with vitamin E and selenium in the treatment of oral leukoplakia. Forty-one patients of leukoplakia were randomly categorized in two groups. First group was administered a combination of lycopene (3 mg), vitamin E (200 I.U.) and selenium (100 mcg) twice daily whereas the second group was given placebo capsules once daily for a period of 3 months. Post-treatment clinical and histopathological evaluation showed that the patients receiving lycopene in combination with vitamin E and selenium have statistically significant improvements compared to those receiving placebo and with no evidence of any side effects.

Patil *et al.* [31] in 2015 compared the efficacy of two antioxidants, lycopene and aloe vera in the management of OSMF. One hundred and twenty clinic-pathologically diagnosed OSMF cases were divided equally into two groups. First group was administered 8 mg lycopene in two divided doses of 4 mg daily whereas second group was given 5 mg aloe vera gel to be applied topically thrice daily for 3 months over the lesion. The researchers observed clinical improvements in mouth opening and tongue protrusion were significant in lycopene group. Although subjective symptoms of burning sensation pain associated with the lesion, and difficulty in swallowing and speech improved in both the groups, but the improvement was not statisticallysignificant. The researchers concluded that lycopene can bring about significant clinical improvements in the symptoms like mouth opening and tongue protrusion when compared to aloe vera [31].

In almost all the studies subjects were counseled and evaluated for cessation of tobacco and alcohol [12, 27, 28, 30]. Study subjects with oral submucous fibrosis were counseled to stop the habit of using areca nut and a complete oral prophylaxis was done to improve the oral hygiene and simultaneously to motivate the patient to cease the habit [28].

Besides it has a positive effect on controlling periodontal diseases through its action in response to periodontopathic bacterial colonization. A strong relationship exists between periodontitis and risk of congestive heart failure, and high monthly total consumption of lycopene appears to affect this relationship in a positive direction in periodontitis subjects has been recorded.The results of a recent clinical study suggested that modulation of the free radical production is important for the inhibition of tissue destruction, and hence treatment with most potent antioxidant like lycopene, will block the production of free radicals and therapeutically effective [32].

Adverse effects of lycopene

According to the available literature a dose of 3 g/kg/d of dietary or formulated lycopene did not show any adverse effects [1]. There are reports yellow-orange discoloration of skin accompanied by elevated lycopene levels in serum due to prolonged, excessive, consumption of tomato juice. However after 3 weeks of lycopene free diet the skin discoloration reduced completely [33].

Conclusion

In conclusion it can be stated that carotenoids, have a powerful antioxidant agent with a various

activities inside the human body as they act as precursors for vitamin A. Lycopene is a fat-soluble carotenoid natural constituent of red fruits, vegetables, fungi and of certain algae. Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. The anticancer activity of lycopene has been demonstrated both in vitro and in vivo tumor models [34]. The mechanisms of actions could involve reactive oxygen species scavenging, up-regulation of detoxification systems, interference with cell proliferation, induction of gap-junctional communication, inhibition of cell cycle progression. Based on the data available from the studies it can be concluded that lycopene has biological properties with promising role in oral cancer chemo-prevention. It has also to be taken into consideration that lycopene is a naturally occurring substance in comparison to other chemically synthesized chemo-preventive agents with substantive antioxidant properties.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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