ANTI-OXIDATIVE AND ANTI-CARCINOGENIC ROLE OF LYPHEPENE IN HUMAN HEALTH – A REVIEW

Avneet Rajoria, Jitendra Kumar² and A.K. Chauhan³

Dept. of Dairy Science & Technology, J.V. College,
Baraut, Uttar Pradesh – 250611 India

ABSTRACT

Lycopene is principally responsible for the characteristic deep-red colour of ripe tomato and tomato products. Lycopene is a lipophilic compound and an acyclic isomer of α-carotene. The food matrix as well as the processing methods determine the extent of release of lycopene and its bioavailability. In fresh tomatoes, about 95% of lycopene is in the trans and about 5% in the cis form. Thermal processing of tomatoes leads to isomer transformation. Lycopene acts as a natural antioxidant in human blood to protect the oxidative damage of lipids, proteins, and DNA. Absorption of lycopene in the body is improved by heat processing and presence of â-carotene whereas presence of dietary fiber may reduce its absorption. Lycopene has been found to be a potent and specific inhibitor of epithelial cancer cell proliferation. Tissues that take up lycopene include the skin, human mammary gland, prostate and buccal mucosa cells. Based on the numerous epidemiological and clinical studies, strong evidence exists that associates high serum or plasma lycopene with decreased risks of some chronic diseases such as cancers of the lung, stomach, gastrointestinal tract, prostate and colorectum and also skin diseases, age related degeneration, osteoporosis and atherosclerosis. Use of tomato and tomato products in daily diet and their application in the formulation of new foods with enhanced antioxidative property is recommended to alleviate human suffering inflicted by major chronic diseases around the world.

Key words: Lycopene, Anti oxidative, Anti carcinogenic, Cardio-vascular health.

INTRODUCTION

Lycopene is a phytochemical nutrient that is found in many fruits and vegetables but abundantly in tomatoes and tomato products contributing about 80-90% of total pigments. The amount of lycopene in tomato juice varies from 4.0 to 11.6 mg per 100 g. Other sources of lycopene are: watermelon (2.3 – 7.4 mg), papaya (2.0 – 5.3 mg), grapefruit (0.2 – 3.4 mg) and guava (4.5 – 5.5 mg) per 100 g on fresh weight basis (Pohar et al., 2003). Lycopene has been classified as one of the pigments in the carotenoids family, which is responsible for natural red color. Lycopene is a 40 carbon (C₆₀H₉₆) acyclic carotenoid with 11 linearly arranged conjugated double bonds, making it soluble in fats and oils and insoluble in water. Because of the abundance of double bonds in its structure, there are potentially 1,056 different isomers of lycopene, but only a fraction of them found in nature (Britton, 1995).

¹Corresponding author address: 154, Sector 7, Urban Estate, Karnal 132 001 Email: arajoria123@rediffmail.com
²Dept. of Horticulture, C.C.S. University, Meerut 200005
³Centre of Food Science & Technology, Banaras Hindu University, Varanasi 221005
Lycopene exhibits the characteristic red color and a specific UV-visible spectrum because of its chromophores which are very sensitive to oxygen and light under various conditions of process operations. The most established natural roles of carotenoids are to protect cells against photosensitization and to serve as light absorbing pigment during photosynthesis (Demmig-Adams et al., 1996). Carotenoids are strongly bound to intracellular macromolecules in foods, and its absorption may be limited unless released from food matrix (Zhou et al., 1996).

Lycopene is found predominantly in the chromoplast of plant tissues. In tomatoes, lycopene biosynthesis increases dramatically during the ripening process as chloroplasts undergo transformation to chromoplasts (Kirk et al., 1978). Tomato chromoplasts are categorized into two types. Globulous chromoplasts containing mainly â-carotene are found in the jel part of the pericarp, while chromoplasts in the outer part of the pericarp contain voluminous sheets of lycopene (Laval-Martin, 1974). It is of great interest to know that lycopene concentration in tomatoes is affected by many factors such as: genetics, soil type, plant nutrition, cultivation practices, post harvest handling, maturity and seasons (Tawfik, 2001).

One of the most important properties of lycopene is its lipophilicity and complete insolubility in water. It cannot be optimally absorbed from the intestines unless fat is consumed at the same meal. Factors affecting fat absorption directly and indirectly also influence the bioavailability of lycopene. Although, the relevance of carotenoids in human health has historically been confirmed by many researchers who have experimented on provitamin A activity of â-carotene and º-carotene, other carotenoids have also emerged as important dietary phytochemicals. Among the carotenoids with potentially beneficial biological activities beyond their traditional role as a vitamin A precursor, lycopene is reported to be most promising in human nutrition and health. Various epidemiological and clinical studies have proved that lycopene because of antioxidative property is helpful in reducing the risk of occurrence of certain types of cancer and other diseases (Giovannucci, 1999; Nguyen et al., 1999). The latest findings on this subject have been reviewed in the various sections of this article.

**ANTIOXIDATIVE PROPERTY**: Substances which are capable of quenching or stabilizing free radicals are called antioxidants, since they prevent the oxidation of organic entities caused by free radicals. Several carotenoids, such as â-carotene, lycopene, lutein, and zeaxanthin are known to exhibit varying degree of antioxidant properties. It has been estimated that there are more than 4,000 compounds in foods that act as antioxidants. Beside â-carotene, ascorbic acid, tocopherol and selenium are most studied natural antioxidants. The biological activity of carotenoids is related with their ability to form vitamin A within the body. Since lycopene lacks the β-ionone ring structure, it cannot form vitamin A (Stahl and Sies, 1996). Lycopene, however, exhibits a physical quenching rate constant with singlet oxygen almost twice as high as that of â-carotene and 10 times higher than that of β-tocopherol (DiMascio et al., 1989) make its presence in human diet of considerable significance.

Free radicals are unstable molecules that have an unpaired electron, which makes them highly energized and reactive. They seek out other electrons, setting off chain reactions that lead to damage to body cells and DNA until they are quenched and return to a stable state. Free radicals may come from outside and also as a natural consequence of human metabolism. Lycopene provides the mechanism that inhibits the oxidation of low-density lipoproteins (LDL) and LDL cholesterol. Reducing the LDL oxidation, in a long term, could inhibit atherosclerosis that may lower coronary risk (Balch, 2001). It has been confirmed that lycopene quenches singlet oxygen [1O₂] and traps peroxide radicals [ROO·] (Sies et al., 1998; BASF, 2000) that can prevent and repair damaged cells. Therefore, lycopene and other carotenoid components that
make foods rich source of antioxidants must be included in the human diet (Beecher, 1998; Weisburger, 1998).

Increasing clinical evidence supports the role of lycopene as a micronutrient with significant health benefits, because it appears to provide protection against a broad range of epithelial cancers and from warding off heart disease to slowing down the degeneration of brain and eyes. Free radical production is a normal phenomenon in the body and part of the equation of simply breathing in oxygen. Usually, the body’s natural defense systems neutralize free radicals, rendering them harmless. However, environmental assaults on the body such as UV-radiation, pollutants, smoking and alcohol consumption can overpower the body’s ability to neutralize free radicals, allowing them to cause damage to the structure and function of the body’s cells. There is good evidence to support that this damage contributes to aging and leads to a host of illnesses, including cancer, diabetes and heart disease.

**EFFECT OF PROCESSING ON LYCOPENE**

Lycopene in fresh tomato fruits occurs essentially in all-trans configuration. The main causes of tomato lycopene transformation during processing are isomerization and oxidation. Isomerization converts all-trans isomers to cis-isomers due to additional energy input and results in an unstable, energy-rich station. Evidence exists to show that lycopene in tomatoes can be absorbed more efficiently by the body in the form of tomato juice, sauce, paste and ketchup. The bound form of lycopene in tomatoes is unfolded by high temperature treatment to make it more easily absorbed by the body. Determination of the extent of lycopene isomerization during processing would provide a measure of the potential health benefits of tomato-based foods. Degradation of lycopene and colour loss of processed tomato products may be affected by a number of factors such as high temperature, long processing time, exposure to light, oxygen, acids, and presence of some metal ions. In a model experiment, Cole and Kapur (1957) investigated that the rate of degradation of lycopene by oxygen in a solution varies according to temperature. Catalytic effects of traces of copper lead to a marked increase in rate of oxidation of solutions. The rate of break down as measured by colour loss varies according to availability of oxygen, temperature and intensity of illumination. Cooking of tomatoes releases lycopene because heat breaks down cell walls and frees the lycopene from a matrix of proteins and fiber that keep it locked in the raw food (Brody, 1997). Thermal processes such as blanching, pasteurization, retorting and freezing of tomatoes generally would cause some changes in lycopene in tomato-based foods. The cis-isomers increase with temperature and processing time.

Stahl and Sies (1992) found that heating tomato juice resulted in a trans-to-cis isomerization of lycopene, and on ingestion the cis-isomers of lycopene appeared to predominate in human serum over the trans isomers. Cis-isomers of lycopene have distinct physical characteristics and chemical behaviors different from their all-trans counterpart. Some of the differences observed as a result of trans to cis isomerization reaction include decreased colour intensity, lowering melting points, smaller extinction coefficients, a shift in the lambda maximum, and the appearance of a new maxima in the ultraviolet spectrum.

Gartner et al. (1997) showed that more than half of total lycopene in human serum is in the cis form. The bioavailability of lycopene was significantly higher when it was ingested along with ß-carotene than when ingested alone. It may be postulated that only certain ethylenic groups of a lycopene molecule can participate in cis-trans isomerization because of steric hindrance. Lessin et al. (1997) reported that canning fresh tomatoes increases the ß-carotene cis-isomer content from 12.9 to 31.2%. However, Khachik et al. (1992) indicated that common heat treatments during food preparation such as microwaving, boiling,
steaming, and stewing did not significantly alter the carotenoid distribution in green vegetables and tomatoes.

Lycopene is more stable in native tomato fruit tissues and matrices than in isolated or purified form (Simpson et al., 1976). Tomato paste has more bioavailable lycopene than fresh tomatoes when both are consumed in conjunction with corn oil (Gartner et al., 1997). Lycopene content of tomatoes remained unchanged during the multiple processing operations for the production of juice or paste and remained stable for up to 12 months of storage at ambient temperature. Moreover, subjecting tomato juice to cooking temperatures in the presence of corn oil resulted in the formation of the cis isomeric form as measured spectrophotometrically and by high performance liquid chromatography (Agarwal, 2001). In an earlier experiment also, lycopene remained relatively resistant to heat-induced geometrical conversion during typical food processing of tomatoes in contrast to â-carotene (Beecher, 1998).

The processed tomato products according to Agarwal and Rao (2000) contain significantly higher levels of cis-lycopene compared to raw tomatoes (tomato juice – 33% higher, tomato ketchup – 84% higher and tomato soup – 143% higher). Boskovik (1979) and Cano et al. (1996) observed that processing and extending storage of dehydrated tomato products resulted in a loss of all-trans lycopene content up to 20%. Khachik et al. (1992) reported that carotenoids such as lycopene, â-carotene and â-carotene in processed fruits and vegetables are fairly heat resistant. Saini and Singh (1993) reported that thermal processing had no effect on total lycopene content in juices made from several high-yield tomato hybrids. Zanori et al. (1998) found that despite oxidative and thermal severity of the drying process, reflected in the changed 5-hydroxymethyl 1-2-furfural and ascorbic acid values, lycopene displayed high stability during drying of tomato halves. Takeoka et al., (1998) reported that in processing of tomatoes to paste (25-30° brix) the lycopene loss ranged from 9 to 28 percent.

Determination of degree of isomerization of lycopene in tomatoes during processing would provide a measure of the potential health benefits to consumers. Dehydration and drying of tomatoes may impact lycopene stability unless the product is promptly placed in a hermetically sealed container flushed with inert gases. Based on the information on lycopene degradation and isomerization as influenced by heat, light, irradiation, oxygen and other physical and chemical treatments, improvement in processing technology may be investigated using lycopene content as a quality index. Such efforts will greatly improve the nutritional quality of tomato products, and enhance their health benefits for consumers. A successful commercialization of lycopene-rich tomato products may improve the competitiveness of food industries in nutraceutical market and offer the advantages of product diversification.

**BIOAVAILABILITY OF LYCOPENE:** It is important to make a clear distinction between the total lycopene content and its bioavailability. On one hand, lycopene is very stable, but not reactive, if it remains in an aqueous environment (particularly in an undamaged cell structure): in such circumstances, it has a very low bioavailability and virtually no effect as an antioxidant. On the other hand, its high solubility in the lipidic environment (such as in certain oil-rich sauces) makes it highly reactive and bioavailable: carotenoid uptake is greatly improved when the food product is cooked and homogenized in conditions that are likely to break down the cell structure, particularly when they include the presence of oily substances. These benefits seem to be the result of thermal weakening and disruption of lycopene-protein complexes, rupturing of cell walls, and/or dispersion of crystalline carotenoid aggregates (Hadley et al., 2002). Like wise, various food processing operations such as chopping and pureeing, which result in a reduction in physical size of the food
particle, will also enhance lycopene bioavailability (Erdman et al., 1988; Rock et al., 1998).

A significant increase in the cis-isomers with a simultaneous decrease in the all-trans isomers can be observed in the dehydrated tomato products depending upon the different dehydration methods. Frozen foods and heat-sterilized foods exhibit excellent lycopene stability throughout their storage at normal temperature. Food processing improves lycopene bioavailability by breaking down cell walls, which weakens the bonding forces between lycopene and tissue matrix, thus making lycopene more accessible to digestive functions and enhancing its cis-isomerization. The bioavailability of lycopene is also affected by the dosage and the presence of other carotenoids, such as ß-carotene and bioavailability was found to be higher with ß-carotene than when ingested alone (Johnson et al., 1997). Lycopene is extremely hydrophobic and most commonly located within cell membranes. Therefore, the interaction of lycopene with reactive oxygen molecules may be most profound in the hydrophobic inner core of the cellular membranes unless the lycopene is associated with specific transmembrane proteins extending to the surface and interacting with the aqueous environment (Hadley et al., 2002).

**BIOLICAL IMPLICATIONS** : Laboratory tests have shown that lycopene is twice as powerful as ß-carotene in neutralizing free radicals. Lycopene is carried in plasma entirely by lipoproteins, and no other lycopene-specific binding or carrier proteins have been identified thus far (Parker, 1996). It is hypothesized that lipophilic carotenoids, such as lycopene, are present within the hydrophobic core of the lipoprotein particle. Once ingested, lycopene appears in plasma, initially in the chylomicrons (microscopic emulsified fat particles found in the blood serum and lymph that result from fat digestion) and VLDL fractions and later in low-density lipoprotein (LDL) and high-density lipoprotein (HDL), the highest levels are found in LDL (Levy and Sharma, 2004). Levy et al. (1995) showed lycopene to be more potent inhibitor of human cancer cell proliferation than either ß-carotene or ß-carotene.

The study conducted by Agarwal and Rao (1998) showed that daily consumption of tomato products providing at least 40 mg of lycopene was enough to substantially reduce LDL oxidation. Allen et al. (2002) presented data on a clinical trial of lactating women showing greater concentration of lycopene in human milk in those mothers consuming tomato sauces compared to fresh tomatoes. Several studies (Bendich and Olsen, 1989; Di Mascio et al., 1989, Miller et al., 1996) have reported that lycopene may have an important role in the antioxidant defense system of human beings. Studies on the distribution of lycopene in the body indicate that it is present at relatively high concentrations in plasma and in selected organs (testes, adrenal glands, liver and kidney) where it may have specialized functions (Stahl et al., 1996).

Few controlled studies in human subject exposed to ultra violet radiation have shown that lycopene supplementation mitigates oxidative damage to the skin thus contributing, along with sunscreens, to the defense against UV light-mediated skin damage (BASF, 2000).

**CLINICAL STUDIES ON Lycopene** : Rapid and uncontrolled cell division causes formation of cancer tissue anywhere in the human body. Recent studies have identified oxidative stress as an important causative agent in the etiology of cancer, cardiovascular disease, diabetes and osteoporosis. Giovannucci (1999) made a comprehensive review based on 72 studies that looked for a link between cancer risk and food made with tomatoes. In 57 studies tomato intake or blood lycopene level was linked with a reduced risk, and in 35 cases, the association was strong enough to be considered statistically meaningful and recommended to increase the consumption of tomato products, fruits and vegetables as a preventive measure in people having carcinogenic manifestations.
Agarwal and Rao (2000) have proposed a mechanism of action of lycopene in the prevention of cancer. Lycopene needs to be bioavailable to act as an antioxidant and thus lower oxidative damage to DNA, lipids and proteins. Lycopene is also involved in gene regulation and stimulates gap-junctional communication which is involved in the control of precancerous cells.

**PROSTATE CANCER**: Initial human data from Kucuk et al. (2001) suggest that lycopene-containing products may serve in the chemoprevention and treatment of prostate cancer. Lycopene has been found to inhibit cancer cell proliferation. The results of a study involving 33 men of Detroit were reported who were randomly assigned to take lycopene or nothing for 30 days before their prostate operations. Before surgery, the volunteers showed no obvious signs that their cancer had spread. After surgery, the doctors found that cancer tissue was less likely to extend clear to the lycopene users’ prostate glands and pre-cancerous cells in their prostates were less abnormal-looking. In another study, Chen et al. (2001) used tomato sauce as a lycopene source in 32 men diagnosed with prostate cancer and scheduled for radical prostatectomy. The study was designed to assess lycopene uptake by the prostate and, to determine if lycopene supplementation can reduce oxidative DNA damage to leukocytes and prostate tissue and its effects on serum Prostate Specific Antigen (PSA) level. The supplement (tomato sauce equivalent to 30 mg/day lycopene for three weeks) significantly increased serum and prostate lycopene and reduced oxidative damage to DNA. In addition serum PSA level declined by 20%. It has recently been shown that lycopene effectively inhibits growth of normal prostate cells in an experimental cell structure system. It may be hypothesized that lycopene can beneficially affect the age-related enlargement of the prostate in man (ObermullerJevic et al. 2003).

Many studies (Lu et al., 2001; Gann et al., 1999; Norrish et al., 2000; Giovannucci et al., 2002) have demonstrated an inverse correlation between dietary lycopene intake and both serum insulin-like growth factor-1 (IGF-1) levels and risk of prostate cancer (Mucci et al., 2001). IGF-1 has shown to play a role in the pathogenesis of prostate cancer. Therefore, if as proposed, increased serum IGF-1 levels do raise the risk of prostate cancer, lycopene may exert protection against the disease, particularly in its early stages, by decreasing serum IGF-1 levels (Willis and Wians, 2003). Tomatoes are also rich in several nutrients including potassium, vitamin A, vitamin C, calcium and iron, in addition to lycopene. It is also possible that complex interactions among multiple components present in tomatoes contribute to its anticancer properties.

**LUNG CANCER**: The human lungs are permanently exposed to oxidative and ozone stress making them particularly vulnerable to oxidative damage. Antioxidants in the respiratory epithelia and the lining fluid may provide protection against such damage. In a clinical trial with humans exposed to 0.4 ppm ozone for 2 hours after two weeks of antioxidant supplementation (lycopene rich vegetable juice) or placebo, lycopene concentration in the lung increased by 12% and lung epithelial cell DNA decreased by 20% in supplemented subjects (Arab et al., 2002).

Liu et al. (2003) used cigarette smoke-exposed ferrets that were fed lycopene (LycoVit 10%) at low or high dietary inclusion rates equivalent to a dose of 15 or 60 mg per day in humans. Both low and high dose lycopene substantially inhibited smoke-induced squamous metaplasia and prevented down-regulation of apoptosis induced by smoke. Lycopene, therefore, mediates its protective effects against smoke-induced lung carcinogenesis by promoting apoptosis and inhibiting cell proliferation.

**CARDIOVASCULAR HEALTH**: The degenerative effect of free radicals, also known as ‘oxidative stress’, is considered as one of the main culprits in the heart disease. Free radicals can also oxidize low density lipoproteins and promote blockages in the arteries. Studies have shown that
consuming tomatoes and tomato products containing lycopene, reduces the risk of cardiovascular disease (CVD). As lycopene levels in the blood go up, the levels of oxidized lipoproteins, protein and DNA compounds go down which help in lowering the risk of CVD.

Sesso et al. (2003) determined whether the intake of lycopene or tomato based foods are associated with the risk of CVD like myocardial infarction, stroke, revascularization, CVD death. Compared with the lowest quintile of dietary lycopene level the highest quintile had a relative risk of 0.90. Based on the consumption of tomato products, women in the highest quintile (greater than 10 servings/week) had a relative risk of CVD of 0.71 compared with the lowest quintile (1.5 servings/week). In a recent clinical trial, 60 healthy individuals (30 men/30 women) were randomized to examine the change in plasma lycopene and resistance of lipoproteins to oxidative stress. Fifteen days of tomato product consumption significantly enhanced the protection of lipoproteins to oxidative stress as measured by a significant increase in the lag period (a measure of antioxidant capacity) after consumption of lycopene (Hadley et al., 2003).

A clinical study by Fuhrman et al. (1997) showed that Lithuanians who suffered a high rate of mortality from CVD had a low blood lycopene levels. Lycopene may reduce lipids by inhibiting the enzyme macrophage 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase (an important step in cholesterol synthesis). In addition, available evidence suggests intimal wall thickness and risk of myocardial infarction are reduced in persons with higher adipose tissue concentration of lycopene. Rissanen et al. (2003) investigated the relationship between plasma concentrations of lycopene and intima-media thickness of the common carotid artery wall (CCA-IMT) in 520 males and females (between ages 45-69). The authors conclude that low plasma lycopene concentrations are associated with early atherosclerosis in men, but not women, as manifested by increased CCA-IMT.

**LYCOPENE IN OTHER DISEASES:**

In some controlled studies, lycopene has been associated with a reduced occurrence of breast cancer (Dorgan et al., 1998). Researchers have observed that lycopene levels may significantly lower the risk in the ovarian and cervical cancer patients. Similarly, a high intake of fruits and vegetables rich in carotenoids and lycopene is expected to provide protection against hyperglycemia in diabetic patients. Inverse relationships between lycopene and cataracts, malaria, digestive tract cancers, immune modulation and longevity are reported.

**ULTRA VIOLET PROTECTION:** à-carotene has been widely used as an oral sun protection agent and has been extensively tested in human studies. Lycopene is also useful in preventing UV-induced skin damage in human volunteers (Stahl et al., 2001). Heinrich et al. (2003) demonstrated that a mixed supplement of lutein, lycopene and à-carotene (8 mg each) was as effective in reducing UV-induced erythema in humans as 24 mg of β-carotene alone.

**SAFETY OF Lycopene:** The Codex Alimentarius Committee has listed lycopene in International Numbering System as a food colour (INS# 160d). Lycopene is nontoxic and considered safe without any side effects. However, cholesterol lowering drugs, fat substitutes and pectin may decrease its bioavailability. Daily intake of lycopene around 60 mg is recommended to reduce the risks of cancers, cholesterol and diabetes to lead a healthy life. Nutritional benefits of lycopene can be obtained by consuming approximately two glasses (500 ml) of tomato juice daily. Other sources of lycopene on 100 gm product weight basis are: tomato paste (42 mg), chili sauce (19.5 mg), spaghetti sauce (22 mg) and tomato ketchup (15.9 mg).

**FUTURE DIRECTIONS:** Consumer demand for healthy food products provides an opportunity to food industries to develop new lycopene-rich foods and nutraceutical products. Optimization of industrial scale, environmentally friendly lycopene extraction and purification process with minimal loss of bioactivities would be highly desirable for
application in the infant foods, cosmetics and pharmaceutical industries. High-quality products that meet food safety and GMP regulations will offer potential benefits to the food industry for formulating lycopene rich new products. Additional research programmes on the bioavailability, pharmacology, biochemistry, and physiology of tomato pigments need to be pursued to reveal the mechanism of its availability in human diet, and also the in-vivo metabolism of lycopene.

It may be recommended that lycopene rich products should be included in daily menu to prevent or delay the onset of certain dreaded diseases. There is a need to have a close look at the mechanism of action and the synergistic relationship of lycopene with other micronutrients. Addition of certain food ingredients such as whey proteins and selected minerals may further enhance the beneficial effects of lycopene in human health which should be investigated.

REFERENCES