Lycopene's Effects on Health and Diseases

A comprehensive review of the literature

By V. Kalai Selvan, MPharm, PhD, A. Vijayakumar, MPharm, PhD, K. Suresh Kumar, MPharm, and Gyanendra Nath Singh, MPharm, PhD

About The Authors

V. Kalai Selvan, MPharm, PhD, is senior scientific officer for the Indian Pharmacopoeia Commission, Government of India (Ministry of Health and Family Welfare), in Ghaziabad. He obtained his bachelor's degree and master's degree in pharmacy from the Tamil Nadu Dr M G R Medical University, Chennai, and his doctorate from Delhi Institute of Pharmaceutical Sciences and Research, University of Delhi. Selvan has published 16 research papers in peer-reviewed national and international journals.

Abstract

Lycopene is present in many fruits and vegetables, with tomatoes and processed tomato products being among the richest sources. This review highlights the scientific documentation of lycopene as a therapeutic agent. Lycopene may alleviate chronic diseases such as cancer and coronary heart disease. Lycopene has also been found effective in the treatment of eye diseases, male infertility, inflammation, and osteoporosis. Experimental, clinical, and epidemiological studies have also established its role in the management of diabetes and hepatoprotection. Uses of lycopene have been studied extensively through epidemiological and biochemical investigations of its properties and its bioavailability from tomato-based diets. No adverse events have been reported in association with the consumption of lycopene-containing foods. The present review article supports the therapeutic efficacy of lycopene; however, more multicenter clinical trials are warranted to confirm its efficacy.

Introduction

Lycopene, a carotenoid without provitamin-A activity, is present in many fruits and vegetables. It is a red, fat-soluble pigment found in certain plants and microorganisms, where it serves as an accessory light-gathering pigment and protects them from ultraviolet B radiation. Gac fruit (Momordica cochinchinensis); tomatoes (Lycopersicon esculentum); and tomato products, including ketchup, tomato juice, and pizza sauce, are the more bioavailable sources of lycopene.1 Gac fruit contains 2,227 mcg/g lycopene; tomato contains 31 mcg/g.2 Lycopene is also found in watermelon, papaya, pink grapefruit, and pink guava. Lycopene is more bioavailable in processed and cooked tomato products than in fresh tomatoes.3,4

Lycopene is synthesized by plants and microorganisms, but not by animals. It is a red open-chain unsaturated carotenoid, acyclic isomer of beta-carotene, and longer than any other carotenoid. This highly unsaturated hydrocarbon contains 11 conjugated and 2 unconjugated double bonds, predisposing lycopene to isomerization and degradation upon exposure to light, excessive heat, and air. This results in color loss and renders tomato extract ineffective as a food or pharmaceutical coloring agent.5,6
Lycopene, also known as psi-carotene, is very sensitive to heat and oxidation and is 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 are found in nature. In a study cis-isomers of lycopene were shown to be more stable, having higher antioxidant potential compared to the all-trans lycopene.

This review summarizes the background information about lycopene and presents the most current knowledge with respect to its role in human health.

Bioavailability and Pharmacokinetics

The mechanism of absorption of lycopene is still being determined. Lycopene ingested in its natural trans form (e.g., in raw tomatoes) is poorly absorbed; heat processing tomatoes and tomato products induces isomerization of lycopene from all-trans to cis configuration, in turn increasing its bioavailability. Also, because lycopene is a fat-soluble compound, absorption into tissues is improved when it is consumed with oil. Its concentration in body tissues is higher than all other carotenoids. In one study, serum concentrations of lycopene increased after consumption of heated tomato juice mixed with oil, with a peak at 24–48 h after ingestion. Heating tomato juice resulted in trans-to-cis isomerization of lycopene, and on ingestion of this juice, the cis isomers of lycopene appeared to predominate in human serum over the all-trans isomers. The exact functions and relative activities of these different isomers are yet to be studied.

Lycopene is incorporated into lipid micelles in the small intestine. These micelles are formed from dietary fats and bile acids and help to solubilize the hydrophobic form of lycopene and allow it to permeate the intestinal mucosal cells by a passive transport mechanism. In blood plasma, lycopene is eventually distributed into the very low- and low-density lipoprotein fractions. Lycopene is mainly distributed to fatty tissues and organs such as the adrenal glands, liver, and testes. In contrast to other carotenoids, lycopene’s serum values are not regularly reduced by smoking or alcohol consumption, although levels decrease with increasing age.

Effect of Lycopene on Free Radical– and Nitric Oxide–Scavenging Properties

Oxidative stress is an important contributor to the risk of chronic diseases. Antioxidants scavenge free radicals, otherwise known as reactive oxygen species (ROS), and prevent the damage they can cause. Free radicals have been associated with pathogenesis of various disorders and diseases such as cancer, cardiovascular disease, osteoporosis, diabetes, and cataracts. In one study, lycopene significantly restored the antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and glutathione reductase (GR); reduced glutathione (GSH); and decreased levels of the lipid peroxide malondialdehyde (MDA) in hypertensive patients. In another study, lycopene was found to have a favorable effect in reducing MDA levels and increasing GSH levels in coronary artery disease in postmenopausal women.
The protective effect of lycopene on ischemic brain injury in rat brain homogenates has also been established. In one study, lycopene (5 µM and 10 µM) inhibited iron-catalyzed lipid peroxidation and nitric oxide production by about 31% and 61% respectively.17

The generation of nitric oxide gives rise to several other reactive species, including peroxynitrite (ONOO−), which is capable of inflicting tissue damage.18 Lycopene at the concentration of 0.31–10 µM prevented the 3-morpholinosydnonimine stress-induced DNA damage in Chinese hamsters; the protective effect is due to the scavenging of intracellular reactive oxygen and/or nitrogen species, reducing the amounts 47.5% and 42.4% respectively.19,20

**Effect of Lycopene on the Management of Diabetes**

A recent study demonstrated that administration of lycopene (90 mg/kg body weight) to streptozotocin-induced hyperglycemic rats caused a decrease in glucose levels, an increase in insulin concentration, a decrease in H2O2 and thiobarbituric acid reactive substances levels, increased total antioxidant status, and increased antioxidant enzyme activities (ie, catalase, superoxide dismutase, glutathione peroxidase) with improvement in serum lipid profile.21 Kuhad et al reported that lycopene at doses of 1, 2, and 4 mg/kg has significant, dose-dependent antidiabetic action in streptozotocin-induced diabetic rats.22 In a clinical study investigating the role of lycopene in diabetic patients (N=133), lycopene reduced the risk of diabetic retinopathy.23

**Role of Lycopene in Atherogenesis**

Inflammatory mediators such as tumor necrosis factor (TNF-α), interleukin (IL)-1β, and IL-8 enhance binding of low-density lipoprotein to endothelium and up-regulate expression of leukocyte adhesion molecules on endothelium during the process of atherogenesis.24 A study found that lycopene inhibited TNF-α-induced NF-κB activation, ICAM-1 expression, and monocyte-endothelial interaction in human umbilical endothelial cells. A further analysis revealed that lycopene attenuated TNF-α-induced IkB phosphorylation, NF-κB expression, and NF-κB p65 translocation from cytosol to nucleus.25 In a placebo-controlled, double-blind, crossover study on healthy human volunteers, 5.7 mg of lycopene for 26 days significantly restricted TNF-α production.26 In one rodent study, lycopene significantly inhibited paw edema formation and attenuated liver injury induced by ischaemia-reperfusion at doses of 25 and 50 mg/kg.27 It also exhibited antiatherogenic effects by inhibiting the expression of inflammatory mediators in hyperhomocysteinemic rats.28

Diet is believed to play a major role in the development of cardiovascular diseases.29 Ingestion of oxidizable lipids and iron catalysts for peroxide decomposition can lead to extensive formation of potentially toxic lipid peroxides, which are implicated in the process of atherosclerosis. Research is focused on preventing cardiovascular diseases through dietary changes. Primarily epidemiological studies, as well as some in vitro and limited in vivo experiments, support the hypothesis that carotenoids, including beta-carotene and lycopene, may protect lipoproteins and vascular cells from oxidation. In particular, lycopene is known to be an efficient scavenger of ROS, including singlet oxygen and other excited species.30,31 Lycopene has demonstrated reduction in oxidative DNA damage in cell culture.
and in rodent models. In addition, clinical studies demonstrate that a lycopene-rich diet (including tomato sauce-based pasta dishes for 3 weeks) protects against oxidative DNA damage in human leukocytes in vitro and prostate tissue in vivo. In another rodent study, the efficacy of lycopene on myocardial injury after ischemia and reperfusion was explored. In histopathological examinations, myocardial damage was significantly reduced in the lycopene-treated group. Lycopene treatment resulted in preservation of the myocardial antioxidant status and altered hemodynamic parameters as compared to control.

“Clinical studies demonstrate that a lycopene-rich diet (including tomato sauce-based pasta dishes for 3 weeks) protects against oxidative DNA damage.”

A single-blind placebo controlled clinical trial found tomato extract (250 mg per day) for 4 weeks reduced blood pressure in patients with grade-1 hypertension. The hypcholesterolemic effect of lycopene was also demonstrated in an in vitro study in which it inhibited the activity of 3-hydroxy-3-methyl-glutaryl-CoA reductase—the rate-limiting enzyme in cholesterol biosynthesis.

Effect of Lycopene on Hepatoprotection

Liver damage is associated with cellular necrosis, increase in tissue lipid peroxidation, and depletion of tissue GSH levels. In addition, serum levels of many biochemical markers like serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, triglycerides, cholesterol, bilirubin, and alkaline phosphatase are elevated when liver damage is present. The hepatoprotective effect of lycopene was evaluated against galactosamine/lipopolysaccharide (D-GalN/LPS)-induced hepatitis in rats. Lycopene at a dose of 10 mg/kg (intraperitoneal) significantly reduced the levels of cholesterol, triglycerides, and free fatty acids, followed by a decrease in the levels of phospholipids in the serum and the liver. Another study demonstrated lycopene significantly restored antioxidant liver enzymes, such as glutathione peroxidase, glutathione-S-transferase, against N-methyl-N′-nitro-N-nitrosoguanidine, and saturated sodium chloride (S-NaCl)-induced gastric carcinogenesis.

Role of Lycopene in the Treatment of Hepatitis C

Hepatitis C virus infection and hepatocellular carcinoma are growing health problems around the globe. In vitro, animal, and clinical studies suggest that lycopene may attenuate liver injury and possibly prevent the development of hepatocellular carcinoma.

Role of Lycopene in the Prevention of Cancer

There have been a few experimental studies on the role of lycopene in preventing or treating cancer. Some evidence suggests that cancers of the pancreas, colon and rectum, esophagus, oral cavity, breast, and cervix could be reduced with increased lycopene intake.
Lycopene supplementation in mice reduces experimental tumor metastasis in vivo induced by the human hepatoma cell line SK-Hep-1; the same study suggests that such an action is associated with attenuation of tumor invasion, proliferation, and angiogenesis.\textsuperscript{46} An in vitro cell culture study showed that lycopene inhibited the growth of human colon cancer HT-29 cells even at low concentration. The inhibitory effects of lycopene on cell proliferation of human colon cancer HT-29 cells were, in part, associated with the down-regulation of the PI-3K/Akt/mTOR signaling pathway.\textsuperscript{47} Lycopene inhibited platelet-derived growth factor-BB-induced signaling and cell migration in human cultured skin fibroblasts through a direct binding to platelet-derived growth factor-BB.\textsuperscript{48}

The antiproliferative and apoptotic effect of lycopene on various cell lines, such as human colon carcinoma (HuCC), B chronic lymphocytic leukemia (EHEB), human erythroleukemia (K562), and Raji, a prototype of Burkitt lymphoma cell line, was evaluated. Lycopene 4 \mu M/ml reduced the proliferation capacity.\textsuperscript{49}

Prostate cancer is the most common male cancer in developed countries and is increasing in the developing world. One study of 404 patients in China, 130 of whom had prostate cancer, suggested that those who had the highest intakes of green tea or lycopene, independently, had an inverse association with developing prostate cancer. In addition, those ingesting both green tea and lycopene had an even greater inverse association (P<0.01), suggesting there may be synergistic effects.\textsuperscript{50} In vitro studies with lycopene have shown induction of apoptosis and inhibition of cell growth in androgen-sensitive (LNCaP) and androgen-independent (PC3 and VeCaP) prostate cancer cell lines.\textsuperscript{51} The data also suggest that lycopene and soy isoflavones may delay progression of both hormone-refractory and hormone-sensitive prostate cancer.\textsuperscript{51} In a clinical investigation of elderly men, lycopene (15 mg/day) inhibited progression of benign prostate hyperplasia.\textsuperscript{52} At less than 1 \mu M concentration, lycopene was shown to inhibit human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression, specifically in prostate cancer cells, without evidence of toxic effects or apoptosis of cells. Studies using human and animal cells have identified a gene, connexin 43, whose expression is up-regulated by lycopene, allowing direct intercellular gap junction communication (GJC). GJC is deficient in many human tumors, and its restoration or up-regulation is associated with decreased proliferation.\textsuperscript{53} A recent analysis of the evidence to date stated that there is insufficient evidence to conclude lycopene reduces tumor progression or improves overall survival in patients with existing prostate cancer.\textsuperscript{54}

In cell cultures, lycopene has been found to inhibit breast cancer tumors more efficiently when compared to alpha- and beta-carotene.\textsuperscript{55,56} In one study, samples taken from the Breast Cancer Serum Bank in Columbia, Mo., were analyzed to evaluate the relationship of types of carotenoids, lycopene, selenium, and retinol with breast cancer. Only lycopene was found to be associated with a reduced risk for developing breast cancer.\textsuperscript{57}

**Effect on Eye Diseases**

Cataracts are a multifactorial disease. Osmotic stress, together with weakened antioxidant defense mechanisms, is attributed to the changes observed in human diabetic cataract (Figure 4). Epidemiological studies provide evidence that nutritional antioxidants slow down the progression of cataracts and age-related macular degeneration.\textsuperscript{58} An experimental study
found lycopene can protect the human retinal pigment epithelium cell line ARPE-19. ARPE-19 protects against H2O2-induced oxidative stress in vitro.59 Lycopene decreases the serum and lipoproteins in age-related macular degeneration patients.60 The potential role of lycopene in the prevention of cataracts is also established. It prevents sugar-induced morphological changes and modulates antioxidant status of human lens epithelial cells in vitro; 200 mg/kg significantly delayed the onset and progression of 30% galactose-induced cataract on rats; the protective effect was found to be due to the antioxidant potential.61,62

**Lycopene and Bone Health**

Among the many factors involved in bone health, oxidative stress induced by ROS is one that is associated with osteoporosis.63 Lycopene has an effect on proliferation and differentiation of osteoblasts (human osteoblast-like osteosarcoma SaOS-2 cells), the cells responsible for bone formation.64 In a cross-sectional study, 33 postmenopausal women aged 50–60 years were administered lycopene for 7 days. Serum samples were used to measure serum lycopene, lipid peroxidation, protein thiols, bone alkaline phosphatase, and cross-linked N-telopeptides of type-I collagen (NTx). Higher intake of lycopene decreased the level of NTx and also protein oxidation (P<0.05). Similarly, groups with higher serum lycopene had lower protein oxidation (P<0.05).65 Carbonyl levels, which are the product of protein oxidation, lead to oxidative stress and osteoporosis.66 Hence the possible mechanism of action of lycopene for the treatment of osteoporosis may be by reducing carbonyl levels.

**Lycopene Therapy in Male Infertility**

Excessive ROS-containing free-oxygen radicals have been identified as one of the causes of male infertility.67 Lycopene is a component of the human redox defense mechanism against free radicals. It is found in high concentrations in the testes and seminal plasma (Figure 3), and decreased levels have been demonstrated in men suffering from infertility.67 Oral administration of lycopene (2 mg twice a day for 3 months) to men with infertility significantly improved the sperm concentration in 66% of cases and motility in 73% of cases.67

<table>
<thead>
<tr>
<th>S. No</th>
<th>Pharmacological action</th>
<th>Experimental study</th>
<th>Effective doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nitric oxide scavenging</td>
<td>In vitro</td>
<td>5 and 10 µM</td>
</tr>
<tr>
<td>2</td>
<td>TNF-α inhibition26</td>
<td>Clinical</td>
<td>5.7 mg/kg</td>
</tr>
<tr>
<td>3</td>
<td>Anti-inflammatory27</td>
<td>In vivo</td>
<td>25 and 50 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>Anti-diabetic21</td>
<td>Animal</td>
<td>90 mg/kg</td>
</tr>
<tr>
<td>5</td>
<td>Hepatoprotection40</td>
<td>In vivo</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Anti-apoptotic</td>
<td>In vitro</td>
<td>4 µM</td>
</tr>
<tr>
<td>---</td>
<td>---------------</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>7</td>
<td>Anti-cataract</td>
<td>In vivo</td>
<td>200 mg/kg</td>
</tr>
<tr>
<td>8</td>
<td>Treatment of male infertility</td>
<td>Clinical</td>
<td>2 mg twice/day</td>
</tr>
</tbody>
</table>

### Drug and Food Interactions

Cholesterol-lowering drugs like Probucol decrease the absorption of lycopene. Food substances such as mineral oil, red palm oil, fat substitutes, and pectin may also decrease the absorption of lycopene, whereas beta-carotene, medium-chain triglycerides, and dietary oils such as olive oil may enhance its absorption. Antioxidant effects are increased when lycopene is combined with lutein, and the growth of cancer cells is decreased when it is combined with vitamin D or E.

### Toxicity Profile

A sub-chronic toxicity study on lycopene was conducted by oral administration at dietary concentrations of 0.25, 0.50, and 1.0% to rats for a period of 90 days. The results from this study do not show any evidence of toxicity of lycopene at dietary levels up to 1.0% as demonstrated by the findings of clinical observations, neurobehavioral observations, motor activity assessment, body weight and food consumption measurements, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, or histopathology. Another study also demonstrated that intake of lycopene (75 mg/day) did not cause any adverse events in humans. A phase I clinical trial conducted on healthy adult male subjects found no significant hepatic or renal toxicity attributable to lycopene doses ranging from 10 to 120 mg, though minimal gastrointestinal toxicity was observed.

Scientific evidence for lycopene use in pregnancy is not available; however, no adverse events have been reported in association with the consumption of lycopene-containing foods during pregnancy.

### Recommended Intake Levels of Lycopene

Due to the variation of lycopene content in food sources, it has been difficult to estimate optimal daily intake. Ranges of 3.7 to 16.15 mg have been reported for the United States. Reported values for Finland, the United Kingdom, and Germany have been 0.7, 1.1, and 1.3 mg, respectively. A survey in Canada showed daily intake of lycopene to be 25.2 mg. However, a recent study in which healthy human subjects ingested lycopene from tomato ketchup and supplements at levels of 5, 10 and 20 mg daily for 1 week found that doses of 5–10 mg significantly increased serum lycopene levels (P<0.05) and also significantly reduced lipid and protein oxidation (P<0.05). This level of intake can easily be achieved by ingesting several dietary sources of lycopene.

### Summary and Conclusions
Lycopene, as an antioxidant, reduces oxidative stress. It may play a significant role in many health concerns, including cardiovascular disease, diabetes, cancer, osteoporosis, liver disease, cataracts, and male infertility. The appropriate dose and duration of lycopene supplementation remains to be determined. Some of the studies on lycopene have included other food supplements, making it difficult to discern lycopene’s individual effects.

References


