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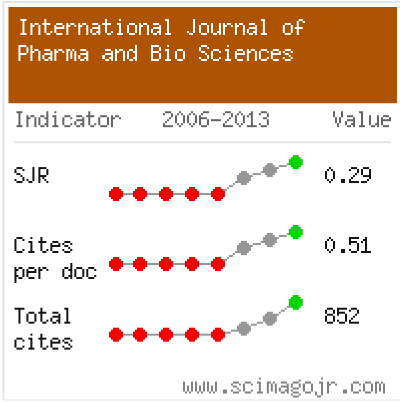


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# LYCOPENE: MOST POTENT ANTIOXIDANT WITH ENDLESS BENEFITS

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## ABSTRACT

Lycopene is the most-potent antioxidant among various common carotenoids. Carotenoids are colored compounds found in the photosynthetic pigments in fruits and vegetables which provide them their bright colors and benefit human health by playing an important role in cell function. Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots and pink guavas contain lycopene. Processed tomato products such as juice, ketchup, paste, sauce and soup all are good dietary sources of lycopene. It is a lipophilic, 40-carbon atom and highly unsaturated, straight open chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds. Many conjugated double bonds of lycopene make it a potentially powerful antioxidant, a characteristic believed to be responsible for its beneficial effects. It is a potent neuroprotective, anti-proliferative, anticancer, anti-inflammatory, cognition enhancer and hypo-cholesterolemic agent. Lycopene's role has also been found to be positive in the management of cataract, malaria, immune modulation, Alzheimer's disease, perclampsia, infertility, aging, osteoporosis, and even male infertility.

**KEYWORDS: lycopene, antioxidant, neuroprotective, anticancer, anti-inflammatory, aging**

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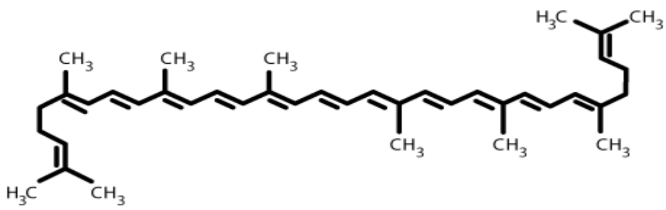
# INTRODUCTION

"Let food be thy medicine and medicine be thy food". Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi. Red fruits and vegetables, including tomatoes and tomato-based products are the major sources of lycopene in the diet[1]. Lycopene belongs to a group of naturally occurring pigments known as carotenoids. Carotenoids are colored compounds found in the photosynthetic pigments in fruits and vegetables which provide them their bright colors and benefit human health by playing an important role in cell function[2]. Lycopene is a fat soluble carotenoid and is one of the most potent antioxidants among dietary carotenoids. Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties, evidence is accumulating to suggest other mechanisms such as modulation of intercellular gap junction communication, hormonal and immune system and metabolic pathways may also be involved [3]. Lycopene is an acyclic isomer of β-carotene and has no vitamin A activity. The chemical name of lycopene is 2,6,10,14,19,23,27,31-octamethyl-2,6,8,10,12,14,16,18,20,22,24,26,30-dotriacontatridecaene. Common names include Ψ, Ψ-carotene, all-trans-carotene, and (all-E)-lycopene. The chemical formula is $C_{40}H_{56}$. The structural formula of all-trans-lycopene is shown below:

:



The molecular weight of lycopene is 536.9 and the Chemical Abstract Service (CAS) number is 502-65-8. It is highly unsaturated, straight chain hydrocarbon containing 11 conjugated and two non-conjugated double bonds[1]. Lycopene from natural plant sources exists predominantly in trans configuration, the most thermodynamically stable form. In human plasma, lycopene is an isomeric mixture containing 50% of the total lycopene as cis isomers. All trans, 5-cis, 9-cis, 13-cis, and 15-cis are most commonly identified isomeric forms of lycopene. Lycopene, ingested in its natural transform found in tomatoes, is poorly absorbed [4]. Recent studies have shown that heat processing of tomatoes and tomato products induces isomerization of lycopene to the cis form which in turn increases its bioavailability. However, there is some indication that isomerization reactions may be taking place in the body. High concentration of cis isomers was also observed in human serum and prostate tissue, suggesting that tissue isomerases might be involved in vivo isomerization of lycopene from all trans to cis form [4]. The mean plasma level of lycopene ranges from 0.22-1.06 nmol/ml and it contributes to about 21%-43% of the total carotenoids. Lycopene accumulates in human tissues [3]. After ingestion, lycopene is incorporated into lipid micelles in the small intestines. These micelles are formed from dietary fats and bile acids, and help to solubilize the hydrophobic lycopene and allow it to permeate the intestinal mucosal cells by a passive transport mechanism. In liver metabolism, lycopene is incorporated into chylomicrons and released into the lymphatic system. 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 [1, 4]. Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots and pink guavas, contain lycopene. Processed tomato products, such as juice, ketchup, paste, sauce and soup, all are good dietary sources of lycopene [5]. An average daily dietary intake of lycopene, assessed by means of a food-frequency questionnaire, was estimated to be 25mg/d with processed tomato products, accounting for 50% of the total daily intake [6].

## *MECHANISM OF ACTION*

Antioxidants are protective agents that inactivate reactive oxygen species and therefore significantly delay or prevent oxidative stress. Oxidative stress induced by reactive oxygen species is one of the main foci of recent research related to cancer and cardiovascular disease. Reactive oxygen species are highly reactive oxidant molecules that are generated endogenously through regular metabolic activity, lifestyle activity and diet. There is strong evidence that this damage may play a significant role in the causation of several chronic diseases [7]. Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins and DNA [8]. Carotenoids like lycopene are important pigments found in photosynthetic pigment-protein complexes in plants, photosynthetic bacteria, fungi and algae [9]. They are responsible for the bright colors of fruits and vegetables, perform various functions in photosynthesis, and protect photosynthetic organisms from excessive light damage [6]. Lycopene has the capacity to prevent free radical damage to cells caused by reactive oxygen species. Studies have shown that it reduces the susceptibility of lymphocyte DNA to oxidative damage, inactivates $H_2O_2$ and NO and protects cells from NO induced membrane damage and cell death. Lycopene exerts its antioxidant properties by two mechanisms physical and chemical. The efficacy of physical quenching exceeds that of chemical [10]. Physical quenching involves transfer of excitation energy from free radicals to lycopene, resulting in ground state oxygen and excited/isomerized lycopene. This energy is dissipated through the rotational and vibrational interactions of the excited carotenoid with surrounding solvent to yield ground state carotenoid and thermal energy. In this process, the lycopene remains intact and can be utilized in further quenching, thus it acts as a catalyst. Chemical quenching contributes less than 0.05% of total quenching results in final decomposition of lycopene. Lycopene with its 11 unconjugated and 2 conjugated double bonds is the most efficient singlet oxygen quencher and this efficiency is mainly attributed to presence of 2 non-conjugated double bonds [11]. It brings about a decrease in cellular cyclin $D_1$, is a key regulator of this process and is also known as an oncogene [4]. In prevention by induction of phase II enzymes conjugate with reactive electrophiles and act as an indirect antioxidant thus eliminating carcinogens and toxins from the body. Lycopene induces the phase II enzymes [4]. Lycopene modulates the process of transcription either directly or through its derivatives by producing changes in the expression of many proteins participating in the transcription process eg. connexins, cyclins, etc. Lycopene induces the formation of protein connexin-3, one of the major building blocks of gap junction, thus restores gap junctions and prevents malignant transformation of cells [12].

## *LYCOPENE AS A POTENT ANTIOXIDANT*

Lycopene is an antioxidant, neuroprotective [13], anti-proliferative, anticancer [14], anti-inflammatory, cognition enhancer [15] and hyper-cholesterolemic agent [16]. It is the most-potent antioxidant among various common carotenoids [17]. In case of free radical attack on DNA, it has been noted that, the high-energy highly reactive free electron on DNA is transformed to a much less reactive more stable (with a lower ground-state energy) free electron (radical) after it is dissipated (delocalized) along the conjugated 13 double bonds of the lycopene molecule [18]. The antioxidant activity of lycopene is highlighted by its singlet oxygen quenching property and its ability to trap peroxyl radicals [19]. This singlet quenching ability of lycopene is twice as high as that of β-carotene and 10 times higher than that of α-tocopherol and butylated hydroxyl toluene (BHT) [2, 20]. Furthermore, lycopene may be useful in preventing heart disease. Lycopene apparently inhibits cholesterol synthesis and enhances low-density lipoprotein degradation [21]. Available data suggest that the risks of myocardial infarction are reduced in persons with higher adipose tissue concentrations of lycopene [29]. Accumulating evidences favour the role of oxidative stress in the pathogenesis of various cardiovascular diseases [22]. Lycopene due to its antioxidant properties reduces lipids by inhibiting enzymes involved in cholesterol synthesis and by enhancing LDL regulation. Lycopene act as a hypo-cholesterolemic agent by inhibiting HMG-CoA (3-hydroxy-3methylglutaryl-coenzyme A) reductase [23]. Recent epidemiological studies have shown a reverse relationship between tissue and serum levels of lycopene and mortality of CHD, MI and cerebrovascular diseases. Serum lycopene is inversely related to fasting serum insulin level, suggesting a possible role for lycopene deficiency in pathogenesis of insulin resistance and diabetes. Intake of fruits and vegetables rich in carotenoids including lycopene might be a protective factor against hyper-glycemia [24]. Several studies have reported reduced concentrations of micronutrients including lycopene in patients with human deficiency virus infection despite adequate dietary intake, particularly in those with human immunodeficiency virus infection [25]. Lycopene role has been found to be positive in the management of cataract, malaria, immune modulation, Alzheimers disease, perclampsia, infertility, aging, osteoporosis, and even male infertility [7].

## *LYCOPENE AS AN ANTI-CANCEROUS AGENT*

The public and the biomedical community are increasingly aware of associations between tomato products, lycopene and health outcomes. Scientists from many disciplines ranging from epidemiology, clinical medicine, nutrition, agriculture, and molecular and cell biology have published peer-reviewed studies providing intriguing data suggesting that tomato products and the carotenoid lycopene may be involved in cancer prevention, reducing the risk of cardiovascular disease, and limiting the morbidity or mortality of the other chronic diseases. Lycopene is a potent antioxidant, neuroprotective [13], anti-proliferative, anticancer [14], anti-inflammatory, cognition enhancer [15] and hypo-cholesterolemic agent [16].Oxidative stress is recognized as one of the major contributors to the increased risk of cancer, and lycopene being a potent antioxidant has been found to inhibit proliferation of several types of human cancer cells, including endometrial, prostate, breast, upper aerodigestive tract and lung, and in vivo studies have shown lycopene to have tumor suppressor activity [26]. The anti-carcinogenic effects of lycopene have been suggested to be due to regulation of gap-junction communication in mouse embryo fibroblast cells. Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb anti-oncogenes and stop cell division at the $G_0$-$G_1$ cell cycle phase. Lycopene induced modulation of liver metabolizing enzyme, cytochrome P450 2E1, was the underlying mechanism of protection against carcinogen-induced pre-neoplastic lesions. Preliminary in vitro evidence also indicates that lycopene reduces cellular proliferation induced by insulin-like growth factors, which are potent mitogens, in various cancer cell lines. Regulation of intra-thymic T-cell differentiation (immunomodulation) was suggested to be the mechanism for suppression of mammary tumor growth by lycopene treatments [27].Studies have found lycopene has been found to inhibit breast cancer tumors more efficiently. Intake of dietary lycopene has been reported to play a role in prevention of ovarian and cervical cancer. Serum lycopene is also associated with decreased risk of bladder and upper aero-digestive tract cancer [28]. Several chemoprotective properties of lycopene on prostate cancer have been proposed, including potent antioxidant properties, decreased lipid peroxidation, inhibition of cancerous cell proliferation at $G_0$-$G_1$ cell cycle transition, and protection of lipoproteins and DNA [29, 30]. Dietary supplementation of lycopene leading to high serum lycopene levels protected men from development of prostate cancer [31]. The health benefits of lycopene might extend beyond fighting prostate cancer since accumulating evidence suggests that the anti-proliferative properties of lycopene may extend to other types of cancer [32].

## *LYCOPENE AS A NEUROPROTECTIVE AGENT*

Lycopene has also been found in cultured rat cortical neurons to protect against the neurotoxicity of amyloid beta, believed to be causative agent in Alzheimer's disease, by inhibiting the increased expression by amyloid β of Bax (a pro-apoptotic factor) and increasing the expression of anti-apoptotic Bcl2 [33]. Interestingly, lycopene is able to cross blood-brain barrier, unlike many other supplements and drugs. Another study describes neuroprotection by lycopene against microglia activation and focal cerebral ischemia in rats [13, 33]. Previous studies may indicate that the neuronal degeneration in certain cases, such as transient occlusion of bilateral carotid arteries, achieved by stopping the blood supply to the forebrain, involves oxidative stress in the pathophysiological outcome of cerebral ischemia [34, 35]. These studies also indicated that increased levels of reactive oxygen species (ROS) are major cause of tissue injury after ischemia [36]. Elevated ROS levels and subsequent inactivation of antioxidant defenses and depletion of existing antioxidants may result in massive breakdown of endogenous antioxidant defense systems, resulting in failure to protect cerebral neurons from oxidative damage. Recent studies have shown that oxidative molecules formed in the mitochondria may also play a role as mediators of molecular signaling in mitochondria dependent apoptotic pathways, which involve anti-apoptotic protein binding and subsequent release of cytochrome c [37].B cell leukemia (bcl) -2 family proteins possess one or more bcl-2 homology domains and play a crucial role in intracellular apoptotic signal transduction by regulating mitochondrial membrane permeability. Bcl-2, an apoptosis suppressing protein, is expressed in neurons that survive ischemia/reperfusion treatment. Conversely, members of Bax family of pro-apoptotic proteins, links the upstream and downstream portions of the cell survival signaling pathway by inactivating anti-apoptotic bcl-2 family proteins [34]. Cysteinyl-aspartate-specific protease-3 (caspase-3), a cysteine protease, is also involved in ischemia-induced neuronal death through the apoptotic pathway [38], and is located downstream of the bcl-2 family in the serial cascade of apoptosis. This enzyme may cause DNA fragmentation thus, increasing TUNEL staining of nuclei, which is a characteristic feature of apoptosis.Because of their interwining roles in cell death and survival, it is important to clarify possible functional relationships between bcl-2, Bax and caspase-3 that are relevant to ischemia-induced apoptosis during the progression of neuronal degeneration. Superoxide dismutase (SOD) is normally found in various animal tissues and acts to eliminate or delay the influence of oxidative damage.Lycopene from plant sources exhibits activity in animal tissues [39, 40] and can penetrate blood-brain barrier [41, 42]. Antioxidants such as lycopene may act directly on neurons and reduce peripheral markers of oxidative stress [43].Lycopene also has a strong potential to scavange free radicals. The observation provide an evidence for beneficial effect of lycopene supplementation in neurological disorder patients including Parkinson's disease and suggest therapeutic potential in neurodegenerative diseases involving accentuated oxidative stress [56.]

## *LYCOPENE AS A CARDIOVASCULAR PROTECTANT*

There have been a number of studies recognizing that lycopene as well as some other natural products inhibit the mevalonate pathway that requires HMG-CoA reductase enzyme. Statins inhibit HMG-CoA reductase, that is why they reduce LDL cholesterol but may not account for all of their beneficial effects. The anticancer effects of statins may, however, be a result of HMG-CoA reductase activity because rapidly proliferating cancer cells require large quantities of cholesterol for synthesis of cell membranes [44]. Lycopene inhibits HMG-CoA reductase as a result of being a product of mevalonate pathway and, as such downregulates the enzyme as a form of feedback control [45]. This is a very fundamentally different mechanism of inhibiting the enzyme than that of statins and, as a result, lycopene does not prevent the synthesis of $CoQ_{10}$ as do statins nor does it cause the severe liver and/or muscle damage that sometimes occurs with statins. A study says that the effect of lycopene on the synthesis of cholesterol in human macrophages, the inhibition of HMG-CoA reductase by lycopene was accompanied by a reduction in intracellular cholesterol levels [45]. In another study, liver X receptor (LXR) is mentioned as being of great interest as a target for the prevention of cardiovascular diseases because several relevant genes, such as cholesteryl ester transferase protein, ABCA1, and others are LXR regulated [45]. Lycopene also significantly increased caveolin-1 (cav-1) and some studies have found to be associated with an enhancement of cholesterol efflux from cells [45].Despite secondary prevention medication, endothelial function is impaired in patients with cardiovascular disease and this is improved by oral supplementation with 7 mg Lycopene, without any concomitant changes in the traditional risk factors such as bipolar disorders or lipid profiles or measures of inflammation [55].

### *LYCOPENE AS A HEALTH ENHANCER*

In an associational study it was reported that high plasma concentrations of lycopene, cryptoxanthin and α-carotene are associated with decreased carotid atherosclerosis in elderly men. Lycopene supplementation decreases gene expression associated with low grade inflammation that occurs in obesity. The low grade inflammation caused by obesity is a major risk factor for cardiovascular disease and type 2 diabetes, quite likely for many aches and pains, and possibly for some neurological disorders. In a study using Wistar rats, the animals ate a maize oil diet designed to induce obesity or the same maize oil supplemented with lycopene for 6 weeks. Although lycopene supplementation did not affect body weight or adiposity, it significantly decreased pectin, resistin, and IL-6 gene expression in epididymal adipose tissue and plasma concentrations. Also, it significantly reduced the gene expression of MCP-1 in epididymal adipose tissue [46]. Studies have also suggested that circulating molecules of pro-inflammatory molecules reflect excess body fat and predispose an individual to a higher risk of developing metabolic diseases. In addition, the adipose tissue hyper-secretion or pro-inflammatory adipokines, such as IL-6, TNF-alpha, leptin and resistin, may play an important role in the pathophysiology of obesity-related complications. In this study, lycopene has been reported to display anti-inflammatory effects in adipocytes and liver, along with preventing cardiovascular disease [46]. In another associational study an association was found between high lycopene intake and a low waist circumference [47]. The NFkappaB signaling pathway is modulated by lycopene. A study found increased expression of NFkappaB in the hypothalamus to be associated with pro-aging effects and that decreasing the excessive expression of hypothalamic NFkappaB induced anti-aging effects in a rodent model of aging. Lycopene also has anticancer effects that can potentially reactivate silenced antitumor genes.A study found that lycopene reduced ACE (angiotensin-converting enzyme) activity in rats with experimental diabetes. ACE inhibitors are used in the treatment of hypertension, peripheral artery disease, kidney disease, and may have anti-aging effects as well as improving physical performance [48, 49, 50]. In studies of diabetic rats and humans, ACE activity is usually, but not always, increased. Increased ACE level is considered a marker in cardiovascular disease as well as in diabetic nephropathy (kidney damage). ACE activity was highest in the diabetic rats but significantly lower in the diabetic rats treated with lycopene [51]. Another study reported lycopene to ameliorate erectile dysfunction in diabetic rats. Chronic treatment significantly and dose-dependently restored erectile function in diabetic rats, while lowering blood glucose, reducing oxidative stress and up-regulating endothelial nitric oxide synthase (eNOS) expression. The latter changes, particularly the involvement in eNOS function, may account for the effect on erectile function [52].Lastly, if you take lycopene you may notice how much better your skin looks. A study reported that the skin concentration of lycopene was significantly correlated with the roughness of forehead skin in humans aged 40-50 years. The efficacy in neutralizing radicals is much higher in lycopene than for other carotenoids present in the skin [53]. As carotenoids, lycopene and beta carotene are lipophilic (fat loving) molecules, they tend to be concentrated in fatty tissues such as skin. Studies have shown that infra A irradiation from sunlight destroys carotenoids in skin by free radical degradation. Hence, to prevent or reduce photo-damage to the skin, carotenoids such as lycopene can act as important protectants [54].

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