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An Overview of Novel Antioxidant and Anti-Cancer Properties of Lycopene

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ABSTRACT

Introduction Lycopene, a non-provitamin A carotenoid, is the reason for redness in tomatoes and some other vegetables. Lycopene is one fat-soluble red pigment produced by plants and some microorganisms. Nowadays, the effects of lycopene on health have recently been significantly interesting. Antioxidant properties of lycopene have been received attention as an anticancer. Different studies have investigated the effects of lycopene in relation to different cancer types.
Conclusion Lycopene significantly shows powerful anticancer activity against prostate cancer, even in progressed and aggressive conditions. This review article aims to introduce lycopene and possible mechanisms for the treatment of cancer.

Keywords Antioxidant; Cancers; Lycopene

CITATION LINKS

[1] A carotenogenic gene cluster from Brevibacterium linens with novel lycopene cyclase genes involved in the synthesis ... [2] Carotenoid content and in vitro bioaccessibility of lycopene from guava (Psidium guajava) and watermelon (Citrullus lanatus) by high-performance liquid chromatography ... [3] Carotenoids: Actual knowledge on food sources, intakes, stability and bioavailability and their ... [4] Role of antioxidant lycopene in cancer ... [5] Lycopene: Chemistry, biology, and implications for human ... [6] Absorption and transport of ... [7] Lycopene as the most efficient biological carotenoid ... [8] Antioxidant activities of carotenes ... [9] Cis-trans lycopene isomers, carotenoids and retinol in ... [10] Uptake of lycopene and its geometrical isomers is greater from heat-processed than unprocessed tomato ... [11] Lycopene suppresses the lipopolysaccharide-induced phenotypic and functional maturation of murine dendritic cells through inhibition of mitogen-activated protein kinases ... [12] Overview of mechanisms of action ... [13] Prevention of N-methyl-N'-nitro-N-nitrosoguanidine and saturated sodium chloride-induced gastric carcinogenesis in Wistar ... [14] Lycopene prevents 7-ketocholesterol-induced oxidative stress, cell cycle arrest and apoptosis ... [15] Lycopene [16] Lycopene consumption decreases oxidative stress and bone resorption markers ... [17] Lycopene inhibits cell growth by altering the mevalonate pathway and Ras signaling ... [18] The tomato as a functional ... [19] Lycopene in tomatoes: Chemical and physical properties affected ... [20] Enhancing the health-promoting effects of tomato fruit ... [21] Antioxidant functions of ... [22] Antioxidant nutritional quality of ... [23] Antioxidant activity of ... [24] Carotenoids activate the antioxidant response ... [25] Systematic investigation of lycopene effects in LNCaP cells by use of novel large-scale ... [26] Structure activity relationship of carotenoid derivatives in activation of the electrophile/ antioxidant response ... [27] Antioxidant supplementation decreases oxidative DNA damage ... [28] Antioxidant effects of ... [29] Lycopene content of tomato products: Its stability, bioavailability and ... [30] Tomato lycopene and inflammatory cascade: Basic interactions ... [31] A dose-response study on the effects of purified lycopene supplementation on biomarkers ... [32] Physiological dose of lycopene suppressed oxidative stress and enhanced serum levels of immunoglobulin M in patients with Type 2 diabetes mellitus: A possible role in the prevention ... [33] Lycopene interferes with cell cycle progression and insuline-growth factor I signalling ... [34] Tomato lycopene and low density lipoprotein oxidation: A human ... [35] Modulation of apoptotic signalling by carotenoids ... [36] Lycopene is a more potent inhibitor of human cancer cell proliferation than either ... [37] Lycopene inhibition of cell cycle progression in breast and endometrial cancer cells is associated with reduction in cyclin D levels and retention of p27(Kip1) in the ... [38] Lycopene inhibition of IGF-induced cancer cell growth depends on the ... [39] Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning ... [40] Lycopene differentially induces quiescence and apoptosis in androgen-responsive and -independent prostate ...

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Introduction

Lycopene is well known as one fat-soluble red pigment synthesized in some plants and microorganisms [1]. Lycopene is extensively found in tomatoes and insignificant amounts in other plants such as papaya [2, 3]. Lycopene is one lipophilic acyclic isomer of β-carotene. Still, it did not perform the vitamin A activity [4], which could be attributed to the absence of a β-ionic ring structure. It is widely found in human blood plasma with low-density lipoprotein fractions [5, 6]. As Lycopene originated from β-carotene and α-tocopherol, it shows significantly higher antioxidant activity and has been extensively interesting [7, 8]. Skin lycopene is known to be sensitive to UV light stress. Lycopene in natural plant sources is broadly found in a transform with high thermodynamic stability [9]. However, all the trans, 5-cis, 9-cis, 13-cis, and 15-cis are lycopene's most common isomeric forms [9]. The biological importance of the isomers in lycopene has still not been elucidated. It has been accepted that lycopene in tomatoes, in natural trans form, is slowly absorbed. Previous studies have reported that heat processing of tomatoes and tomato products induces the isomerization of lycopene to the cis form, which elevates its bioavailability [10]. Some evidence has been reported that isomerization reactions may occur in the cells. For example, increased cis isomers in serum and prostate tissue implicate the in vivo isomerization of lycopene [9].

The importance of lycopene in the treatment and prevention of cancer has been accepted. Elevation of oxidative stress plays a significant role in cancer risk. Lycopene is known to have powerful antioxidant properties compared to other carotenoids [11], that is, lycopene > α-tocopherol > α-carotene > β-cryptoxanthin > zeaxanthin=β-carotene > lutein [12].

Lycopene can decrease oxidative damage by stimulating the enzyme activity of antioxidants [13]. It also inhibits the oxidative injuries of macromolecules [14]. Lycopene is involved in the immune system and induces cellular apoptosis [15]. It has also been suggested that it prevents reactive oxygen species formation and reduces the phosphorylation of extracellular signal-regulated kinase, which helps prevent cancer cell growth [16, 17]. This paper aimed to investigate the anti-cancer effects of lycopene, especially its mechanisms.

Chemistry of lycopene

Lycopene is a non-cyclic carotenoid found in tomatoes. It is a hydrocarbon carotenoid with the general formula C40H56 and an acyclic open-chain structure comprising 13 double bonds (Figure 1).

The double bonds present in lycopene are exposed to isomerization, and various cis isomers (mainly 5, 9, 13, or 15) are observed in plants and blood plasma [18]. Physical variables, including heat, light, or some chemical reactions, could cause isomerization from the trans-isomer into different mono-or poly-cis structures [11]. There are non-conjugated (2 bonds) and conjugated double bonds (11 cases) that are known to have antioxidant properties in lycopene [19]. Since the body cannot produce carotenoids, it is essential to have lycopene by diet.

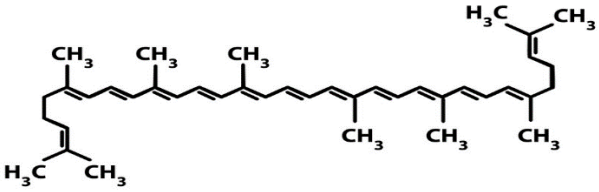

Figure 1. Molecular structure of lycopene

Antioxidant activity of lycopene

Oxidative stress is known as one of the reasons for the increased risk of cancer. Lycopene has been reported to have antioxidant properties, as shown by *in vitro* experimental systems [11]. It is found that carotenoid reactivity relies on molecular and physical compounds and depends on their location or place of action in cells, their ability to interact with other antioxidants, their concentration, and the partial pressure of oxygen [20-22]. Antioxidant activity could be attributed to polyene structures that are rich in electrons. Lycopene has been known to be a potent oxygen-scavenging reagent between carotenoids, and thus, it modulates reactions activated by free radicals such as OH^- or peroxy radicals [23]. Lycopene and other carotenoids have been suggested for their antioxidant properties to prevent free radical reactions. Peroxyl radicals are produced in the organism when lipid peroxidation occurs, and that could cause damage to lipophilic parts. The carotenoid oxidation products are epoxides placed in the β-ionone ring and those in the central double bond of the conjugated polyene chain. Most products of the reaction include ketones and aldehydes in the β-ionone ring. Preventing these radical reactions by lycopene can protect membranes from lipid peroxidation [23]. Some studies have shown that lycopene could upregulate the antioxidant electrophile/antioxidant response element (EpRE/ARE) and the nuclear factor E2-related factor 2 (Nrf2). It stimulates the formation of phase II detoxifying antioxidant enzymes that keep the cells safe from reactive species [24]. It is shown that the Nrf2 nuclear transcription pathway could upregulate the ARE system in HepG2 and MCF-7 cells [24] and is also involved in the expression of ARE-regulated proteins such as epoxide hydrolase 1 (EPHX1), superoxide dismutase-1 (SOD-1), catalase (CAT), and the metal binding protein transferrin (TF), in prostate cells [25]. Enzymatic activity by lycopene induces Nrf2-mediated expression of phase II detoxifying/antioxidant enzymes [26].

Damage in DNA was usually induced by H_2O_2. Studies have shown that high levels of H_2O_2 induce damage in DNA, and each cell could protect itself against damage [27]. In a study, subjects consuming tomatoes for two weeks showed a strong inverse association between plasma lycopene content and lymphocyte DNA damage. Bast *et al.* [28] have shown that lycopene may increase the cellular antioxidant defense system through increasing non-enzymatic antioxidants. Vitamins E and C, from their radicals, also reduce δ -tocopheryl radicals. Agarwal *et al.* [29] have shown a significant decrease in serum lipid and LDL oxidation when subjects consumed tomatoes. In addition, some studies have shown the role of ROS for the Ras superfamily of small GTPase in redox regulation, and ROSs have been known to have significant downstream effects for Ras protein. It has been found that lycopene can rescue Ras activation by reducing its farnesylation and translocating it from the membrane to the cytoplasm in cells of patients with cancer [14] and patients with stimulated macrophages [17]. Changed in Ras activation were severely associated with the prevention of the expression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase through the carotenoid and were associated with reduced ROS formation and activation of MAPK/NF-κB.

Anti-cancer activity of lycopene

In this section, we discuss the anti-cancer mechanisms of lycopene. Carotenoids have been known to have a direct role in some redox-sensitive signaling pathways, which have changed in cancer [30]. It is also known to have the ability to modify Ras activation through reducing farnesylation and inducing translocation in the membrane into the cytoplasm in cancer cells [31] and stimulating macrophages [32]. It has also been known to have the ability to suppress MAPK phosphorylation and NF-κB activation in prostatic cancer cells [32]. Lycopene prevents AP-1 signaling in mammary cells [33]. Lycopene is believed to inhibit cancer through the induction of apoptosis [34]. Zhang *et al.* [35] have reported that lycopene and its auto-oxidant products could induce apoptosis in HL-60 cells. Lycopene is involved in Bcl-2, which modulates the apoptosis that could be attributed to the antioxidant properties of lycopene [34]. Lycopene also inhibits carcinogenesis by rescuing essential biomolecules such as lipids, LDL, proteins, and DNA [35]. It can quench singlet oxygen, which could be credited to its conjugated double bonds [7]. A study has shown that lycopene prevented the growth of human endometrial, mammary, and lung cancer cells grown in in vitro culture [36]. It keeps cells against microcystinCR-induced mouse hepatocarcinoma through suppression of the phosphorylation of regulatory proteins and arrest of cells in the G0/G1 phase of the cell cycle [36]. Other studies have shown that lycopene decreases cellular proliferation created through IGF-1 in the different cancer cell lines [36]. Previous studies have shown that the use of lycopene prevented cell cycle progression by modulation in the G0/G1 stage by down-regulation of IGF-1R expression and the following decreased cell cycle regulatory proteins, such as cyclin D1, cyclin E, and cyclin-dependent kinases (CDK) 2 and 4 in breast and prostate cancer cell lines [37-39]. Lycopene-induced prevention of DNA formation has been seen in HL-60 promyelocytic leukemia cells by a (3H) thymidine incorporation evaluation and caused cell cycle arrest in the G0/G1 phase [40]. Lycopene has been known to have the ability to attenuate the phenotypic and functional maturation of murine bone marrow-dendritic cells that are present in lipopolysaccharide (LPS)-induced DC maturation through down-regulating the expression of costimulatory molecules (CD80 and CD86) and significant histocompatibility complex type II molecules and through prevention of activation of MAPK and NF-κB [11]. Some papers have been reported to assess the effect of lycopene and/or tomato consumption on the involvement of oxidative stress markers and on changed redox signaling. Some believe that lycopene shows anti-cancer properties by modulation in antioxidant properties. Devaraj *et al.* [31] examined the antioxidant ability of 8 weeks of lycopene consumption (6.5, 15, 30mg/d) after 14 days of washout in healthy individuals. However, their results showed that used doses could not significantly affect LDL oxidation rate, plasma lipid peroxidation markers, and urinary F2-isoprostanes. They also showed that 30mg/d doses could alleviate the lymphocyte DNA damage and urinary 8-OHdG contents compared to baseline levels. Another study has shown that lycopene supplementation could not change total antioxidant capacity or oxidized-LDL antibody levels, but it reduced serum MDA levels compared to baseline levels [32]. A summary of the Anti-cancer of lycopene is shown in Figure 2.

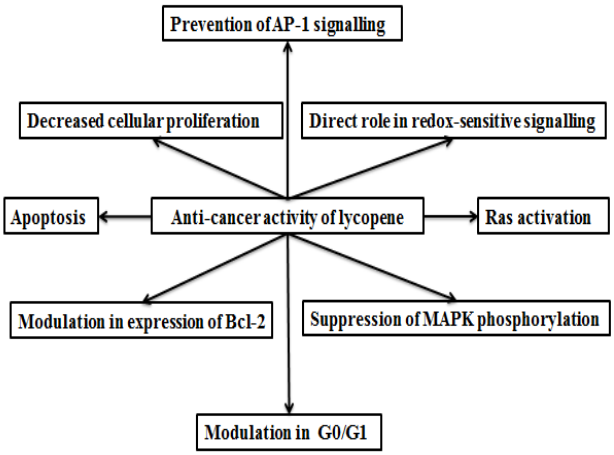

Figure 2. Anti-cancer mechanisms of lycopene

Conclusion

Consumption of lycopene has been relatively related to a decrease in cancer risk. The pharmacokinetic properties of lycopene for preventing and treating cancers have been cleared. We recommend the use of lycopene for the treatment and prevention of cancer.

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