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Review Article: An Overview on Novel Antioxidant and Anti-Cancer Properties of Lycopene: A Comprehensive Review

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ABSTRACT

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

Introduction

Lycopene is well known for one fat-soluble red pigment that is synthesized in some plants and microorganisms [1]. Lycopene is extensively found in tomatoes and insignificant amount in other plants such as papaya [2, 3]. Lycopene is one lipophilic acyclic isomer of β-carotene but it did not perform activity of vitamin A [4] and that could be attributed to absence of a β-ionic ring structure. It is widely found in human blood plasma with low-density lipoprotein fractions [5, 6]. As the Lycopene is originated from β-carotene and α-tocopherol,

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it shows significantly higher antioxidant activity and has been extensively interested. [7, 8].

Skin lycopene is known to have sensitive rather than UV light stress. Lycopene present in natural plant sources is broadly found in trans form that have the high thermodynamic stability [9]. However, all the trans, 5-cis, 9-cis, 13-cis and 15-cis are known as the most common isomeric forms in lycopene [9]. The biological importance of the isomers in lycopene has been not still elucidated. It has been accepted that lycopene present in tomatoes, natural trans form, is slowly absorbed. Previous studies have reported that heat processing of tomatoes and tomato products causes to induce the isomerization of lycopene to the cis form which elevates its bioavailability [10]. Some evidences have been reported that isomerization reactions may occur in the cells. For example, increased concentration of cis isomers in serum and prostate tissue implicates the in vivo isomerization of lycopene [9].

Importance of lycopene for 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 known different carotenoids [11], that is as follows lycopene>α-tocopherol>α-carotene>β-cryptoxanthin>zeaxanthin=β-carotene>lutein [12]. Lycopene has ability to decrease oxidative damage through stimulation of enzyme activity of antioxidant [13]. Lycopene also inhibits the oxidative injuries of macromolecules [14]. Lycopene is involved in immune system and induces cellular apoptosis [15]. It has also been suggested to prevent reactive oxygen species formation and reduced phosphorylation of extracellular signal-regulated kinase that helps in prevention of cancer cell growth [16, 17]. This paper aims to investigate the anti-cancer effects of lycopene, especially mechanisms.

Chemistry of lycopene

Lycopene is one non-cyclic carotenoid which is found in tomatoe. Lycopene, one hydrocarbon carotenoid with general formula of C40H56 contains one acyclic open-chain structure that comprises 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.

Antioxidant activity of lycopene

Oxidative stress is known as one of reasons for increased risk of cancer. Lycopene has been reported to have antioxidant properties as shown by in vitro experimental systems [11]. It is found that carotenoids reactivity not only relies on molecular and physical compounds but it also depends on their location or place of action into cells, ability to interact with other antioxidants, 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 have 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 in order to prevention of free radical reactions. Peroxyl radicals are produced in the organism when lipid peroxidation occurs and that could cause damages in lipophilic parts. The carotenoid oxidation products are epoxides placed in the β-ionone ring, as well as those are in the central double bond of the conjugated polyene chain. The most products of reaction are included ketones and aldehydes in the β-ionone ring. Prevention of these radical reactions by lycopene can prevent membranes from lipid peroxidation [23].

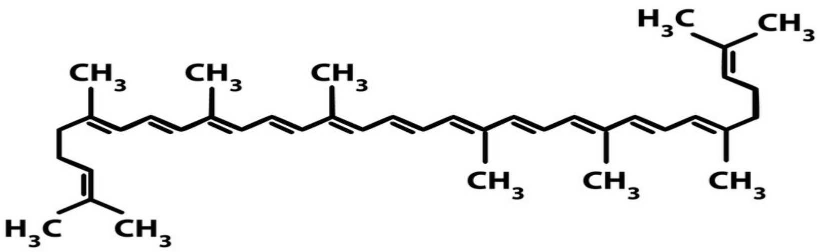

Figure 1. Molecular structure of lycopene

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 Nrf2 nuclear transcription pathway could upregulate ARE system in HepG2 and MCF-7 cells [24] and is also involved in 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]. A damage in DNA was usually induced by H_2O_2. Studies have shown that high levels of H_2O_2 caused to induce the damage in DNA and each cell could protect itself against damage [27]. In a study, subjects consuming tomato for 2 weeks showed a strong inverse association between plasma lycopene content and lymphocyte DNA damage. Bast et al. has shown that lycopene may increase the cellular antioxidant defense system through increasing non-enzymatic antioxidants [28].

Vitamins E and C from their radicals and also reduces δ -tocopheryl radical. Agarwal et al. have shown a significant decrease of serum lipid and LDL oxidation when subjects consumed tomato [29]. In addition, some studies have shown a 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 is found that lycopene is capable to rescue Ras activation through reducing its pharnesylation and also by conducting its translocation from the membrane to cytoplasm in cells of patients with cancer [14] and also in patients with stimulated macrophages [17]. Changed in Ras activation were severly associated with 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. qqq

Anti-cancer activity of lycopene

In this section, we discuss anti-cancer mechanisms of lycopene. Carotenoids have been known to have direct role in some redox-sensitive signalling pathways, changed in cancer [30]. It is also known to have ability to modify Ras activation through reducing pharnesylation and also inducing translocation in the membrane into the cytoplasm in cancer cells [31] and also stimulating macrophages [32]. It has also been known to have ability for suppression of MAPK phosphorylation and NF-κB activation in prostatic cancer cells [32]. Lycopene prevents AP-1 signalling in mammary cells [33].

It is believed that lycopene inhibits cancer through 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

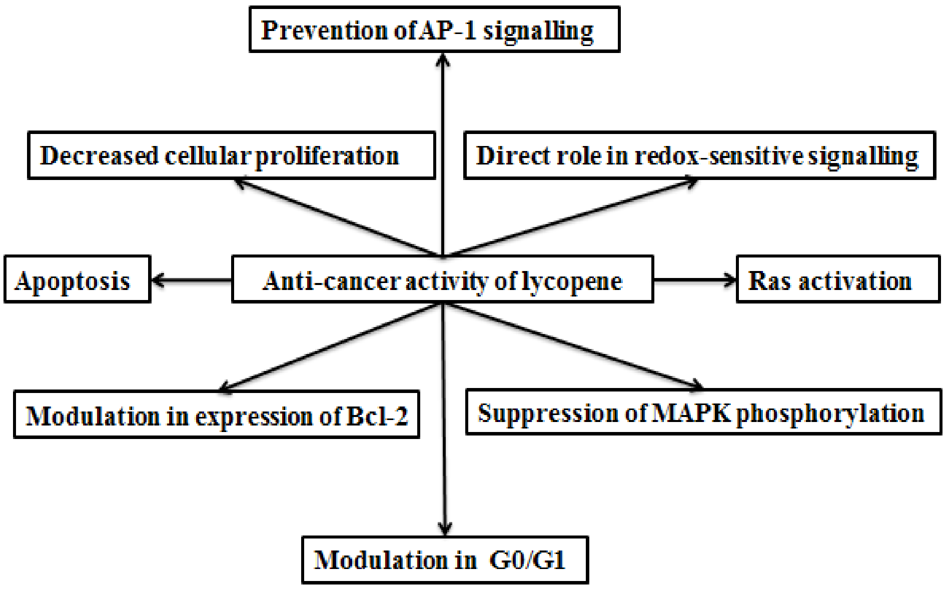

Figure 2. Anti-cancer mechanisms of lycopene

that modulates the apoptosis that could be attributed to antioxidant properties of lycopene [34]. Lycopene also inhibits carcinogenesis by rescuing essential biomolecules such as lipids, LDL, proteins and DNA [35]. It has ability to quench singlet oxygen that could be credited to its conjugated double bonds [7].

A study has been shown that lycopene prevented 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 use of lycopene prevented cell cycle progression by modulation in 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 leukaemia cells by an (3H) thymidine incorporation evaluation and caused cell cycle arrest in the G0/G1 phase [40].

Lycopene has been known to have ability for attenuating 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 [41]. Some papers have been reported the assess the effect of lycopene and/or tomato consumption, in the involvement as the markers of oxidative stress and on changed redox signalling. Some believed that lycopene shows anti-cancer properties by modulation in antioxidant properties.

Devaraj et al. have been examined the antioxidant ability of 8 weeks of lycopene consumption (6.5, 15, 30 mg/d) after 14 days washout period in healthy individuals [42]. However, their results showed that used doses could not have significant effect on LDL oxidation rate, plasma lipid peroxidation markers, and urinary F2-isoprostanes. They also showed that consumption of 30 mg/d dose could alleviate the lymphocyte DNA damage and urinary 8-OHdG contents in comparison to baseline levels. Another study has been shown that lycopene supplementation could not change total antioxidant capacity or oxidized-LDL antibody levels, but it reduced serum MDA levels in comparison to baseline levels [43]. A summary of Anti-cancer of lycopene is shown in Figure 2.

Conclusion

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

Ethical Considerations

Compliance with ethical guidelines

There was no ethical considerations to be noted in this article.

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Authors' contributions

All authors contributed in data analysis, drafting and revising the paper and agreed to be responsible for all aspects of this work.

Conflict of interest

The authors declared no conflict of interest.

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