Multifaceted Effects of Lycopene

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Lycopene is a pigment belonging to the group of carotenoids and it is among the most carefully studied antioxidants found especially in fruit and vegetables. As a carotenoid, lycopene exerts beneficial effects on human health by protecting lipids, proteins, and DNA from damage by oxidation. Lycopene is a powerful oxygen inactivator in the singlet state.

Keywords: antioxidants ; antitumor ; carotenoids ; lycopene

1. Introduction

Lycopene is an acyclic linear carotenoid characterized by eleven conjugated double bonds. Unlike β-carotene, it is not transformed into vitamin A in the body. Lycopene exists in several stereoisomeric forms. Double bonds are subject to isomerization. In nature, lycopene is found in the structural form of “trans”-type isomers; however, exposure to heat sources or even light irradiation involves a modification of its structure in cis isomers (mainly in positions 5, 9, 13, and 15), which are more assimilable by the human body, showing, therefore, a greater bioavailability. Quite possibly this might also occur in vivo. Various lycopene forms are slightly soluble in water. For example, lycopene is found either in crystalline form in the chromoplast or it is available in the form of a carotenoid-protein complex in chloroplasts. Thermal processing enhances the bioavailability of lycopene as it disrupts cellular membranes, which leads to the escape of lycopene from the tissue matrix. Therefore, processed food that involves the concentration procedure, which is associated with water loss, certainly contributes to making cooked tomatoes a great reservoir of lycopene compared to the raw product. Likewise, cooked carrots serve as a great source of carotene [1].

Lycopene is a thermo-stable carotenoid and cooking does not damage it; on the contrary, heat can make the molecule even more bioavailable, i.e., more assimilable by the body. Thus, cooking food can increase lycopene bioavailability and this could be credited to the dissociation of lycopene containing complex proteins [1]. Another reason could be the dispersion of carotenoid aggregates due to the cooking, which are usually crystalline.

Numerous studies suggest that a high consumption of tomatoes decreases the contraction rates of cancer. Given that the tomato is one of the most consumed vegetable products in the world, it is extremely interesting to note these results. Based on several investigations, lycopene seems to exert a preventive action, among other things, against prostate cancer [1][2].

2. The Antioxidant Properties of Lycopene

2.1. Molecular Mechanisms

Oxidative stress is due to an increased production of reactive oxygen and nitrogen species (ROS, RNS), which are not sufficiently balanced by antioxidant cellular systems. These species include the hydroxyl radical (OH), the radical superoxide (O_2), peroxynitrite (ONOO), peroxyl (ROO), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and ozone (O_3) [3].

A myriad of cellular processes, such as inflammation, ischemia or reperfusion, metabolic activities, and mitochondrial respiration, generate these chemical species [4]. The uncontrolled production of these chemical species may cause significant cellular damage due to the oxidation of cellular biomolecules such as DNA, proteins, and lipids. Consequently, this might augment processes related, for example, to carcinogenesis, cell transformations, resistance to apoptosis, proliferation, metastasis, angiogenesis, DNA damage, and therefore mutations, as well as genetic instability [5].

Lycopene possesses consistent antioxidant activity, which is exerted through various mechanisms [6]. Lycopene is an alluring biological target for electrophilic reagents, credited to its electron-rich structure. Further, the electron-rich reservoir bestows a remarkable oxygen as well as free radical reactivity upon lycopene. Quite aptly, lycopene tops the list of

carotenoids in terms of oxygen quenching ability and also offers the possibility to interfere in free-radical-initiated reactions, such as ROS [7]. It is speculated that the antioxidant properties of lycopene are responsible for its cancer inhibitory roles and prevention of various chronic ailments [8].

Lycopene and other carotenoids act as antioxidants via different mechanisms. The reactive oxygen species (for example, “singlet oxygen” ($^1O_2$) (highly reactive), which can oxidize nucleic acids, unsaturated fatty acids, or amino acids) can be neutralized by carotenoids/lycopene by carrying out the following reaction:

$$^1O_2 + LYC \rightarrow {}^3O_2 + {}^3LYC$$

$$^3LYC \rightarrow LYC + heat$$

The higher amount of energy that lycopene has obtained in this reaction, reaching the triplet state, is then delivered through vibrational as well as rotational interactions with solvents, and with the consequent liberation of thermal energy. Again, the extended conjugated polyene lycopene structure is accountable for the above reaction. Once the molecule reaches its ground state, another $^1O_2$ can be neutralized, thus providing the ability for each carotenoid molecule to extinguish approximately one thousand molecules of $^1O_2$ [8].

2.1.1. Modulatory Effect on Lipid Peroxidation and DNA Damage

Lycopene along with the carotenoids are well-known for their antioxidant activity aimed at preventing free radical reactions. During the lipid peroxidation process, the peroxyl radicals are fortified in the body. Eventually, this might cause damage to the lipophilic sections. Further, the amelioration of such highly reactive species accentuates the formation of radical adducts. Collectively, these crucial oxidation products of lycopene partake in the membrane repair process via lipid peroxidation [8][9].

Given the above result, the study by Matos et al. [10] reports the ability of lycopene to protect mammalian cells from an iron chelator-induced lipid peroxidation and oxidative DNA damage in vitro chelator. Besides this, the damage to mitochondrial DNA caused by the production of ROS through UV radiation is partially abrogated by lycopene tomato sauce in vivo [11] [12].

2.1.2. Modulation of Antioxidant Responsive Elements (ARE) and Nrf2

Several studies have shown the effects of lycopene on the induction of antioxidant enzymes and detoxifying enzymes of phase II. In vivo studies performed by Bhuvanewari et al. suggested that lycopene (2.5 mg/kg) can potentially suppress gastric cancer by multimodal mechanisms of reduction in lipid peroxidation, elevation in the levels of antioxidants, and enhanced GSH-dependent enzyme activities; for example, glutathione reductase, glutathione peroxidase, and glutathione-s- transferase [13][14].

Nrf2 (nuclear factor E2-related factor 2) is an important ARE (antioxidant response element), which is integral to the reactions involved in detoxification of carcinogens and antioxidant cell defense system modulation. This is because it promotes the upregulation of phase II cytoprotective enzymes induced by stress. Depending on this, Nrf2 also produces anti-inflammatory effects [15].

Several pieces of evidence suggest that lycopene is capable of upregulating electrophilic antioxidants and antioxidant responsive elements (EpRE/ARE) and, again, nuclear factors (Nrf2), generating the production of detoxifying-antioxidant enzymes (phase II). These, in turn, provide protection to the cells against various reactive oxygen species as well as electrophilic molecules [16][17][18]. The upregulated transcription of the genes coding for antioxidant enzymes and detoxifying phase II occurs via DNA sequences present in promoter regions of AREs. Reportedly, lycopene is known to “upregulate” this ARE system via Nrf2 in vitro (HepG2 and MCF-7 cells) [15].

In general, Nrf2 is localized in the cytoplasm, where it specifically binds to the inhibitory protein known as Keap1 and forms a complex. Although this Nrf2 and Keap1 complex is dissociated under the conditions of oxidative stress, the rescue of Nrf2 from proteasome degradation, together with the induction of translocation of Nrf2 itself to the nucleus, enables its binding to the AREs along with various other transcription factors. This allows the regulation of gene expression of detoxifying/antioxidant enzymes, such as Heme oxygenase and NAD(P)H quinone oxidoreductase 1 [19][20][21].

The molecular mechanisms underlying lycopene-mediated induction of Nrf2 nuclear translocation are scarcely known. Lian and Wang [16] hypothesized that the highly reactive aldehyde groups present in lycopene metabolites facilitate Schiff base formation with the group N-terminus of proteins. Specifically, it can cause a direct modification of the cysteine residues in Keap1, then repeal ubiquitination followed by Nrf2 degradation mediated by Keap1. Next, there occurs an

oxidation of covalent modification of thiol groups, which are present in the Keap1 harbored cysteine residues. Finally, these steps allow Nrf2 and Keap1 complex dissociation [22][23].

Quite possibly, these “lycopenoids” influence upstream signaling pathways. Precisely, these lycopenoids target the receptors for epidermal growth factor (known as EGFR), mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase(PI3K) and protein kinase C (PKC). In addition, Nrf2-ARE regulating proteins and those involved in pulmonary epithelial cell signal regulation are targeted by these lycopenoids [24].

2.1.3. Expression Modulation of P450

The cytochrome P450 family is an enzymatic superfamily of proteins present in all domains of living beings and is involved in the detoxification of the organisms, being able to act on a large number of different substrates. It also partakes in the metabolism (usually oxidative) of myriad lipophilic compounds that are of endogenous or exogenous origin. Since the P450 cytochrome catalytic cycle is poorly coupled, there occurs steady and uninterrupted ROS production. Consequently, the pathways for cellular signaling and associated functions are affected [25][26][27].

It is well-documented that carotenoids cause an induction of cytochrome-associated (P450 family) enzymatic activities [28][29]. Notably, Astorg et al. [30] put forward the hypothesis that lycopene exerts its protective effect against preneoplastic lesions by modulating cytochrome P450 2E1 enzymes, when studied in a rat model of a tumor. Furthermore, lycopene administration in rat tumor models induced hepatic cytochromes in a dose-dependent manner. These specifically included cytochromes 1A1/2, 2B1/2 and 3A [31]. The observations that the activity of the P450 was induced by plasma levels of lycopene indicate that carotenoid-mediated modulation of the metabolism of these could plausibly be of considerable relevance to humans. There are no human data suggesting that P450 upregulation is effective.

2.1.4. Inhibition on iNOS and COX-2 Expression

Lycopene counters iNOS (inducible nitric oxide synthase) effects, for example through inhibiting the production of nitric oxide (NO). The effects of lycopene as well as quercetin and tyrosol (natural antioxidants), gene expression of iNOS, and cyclooxygenase-2 (COX-2), have been studied in vitro. In particular, the gliadin and interferon-gamma (INF-γ)-stimulated macrophage cell line (RAW 264.7) was used, wherein this combined therapeutic strategy was able to reduce iNOS and COX-2 expression. Lycopene can therefore decrease the gene expression of iNOS and COX-2 as a non-toxic agent via controlling pro-inflammatory genes [32]. This mechanism is also supported by another study, which was performed by Rafi et al. They found that 10 μmol/L of lycopene was capable of reducing the lipopolysaccharide (LPS)-induced NO production by approximately 40% when compared to a control in the RAW 264.7 mouse macrophage cell line. They also claimed that the lycopene caused a decline in the LPS-induced protein and mRNA expression of iNOS, after performing Western blotting and RT-PCR expression analysis as previously described [33].

2.1.5. Downregulation of NF-kB Modulation

Evidently, NF-kB is the first among the transcription factors that is also activated by oxidative stress in eukaryotes. This is accredited to the following mechanisms: the first involves the improvement of the ROS-mediated degradation of IkB, while the second leads to the oxidative improvement of the upstream signal cascade [34][35][36].

It is well-documented that lycopene inhibits NF-kB binding activity and target gene expression, especially of NF-kB and MMP-9-associated gene targets, which prohibits the cell invasion of hepatoma in humans. This inhibition occurs when IkB phosphorylation and expression of NF-kB are downregulated, also due to p56 subunit nuclear translocation [37].

The LPS (lipopolysaccharide) stimulation activates the MAPK signal path along with NF-kB. Lycopene treatment significantly inhibits NF-kB, p-ERK, p-JNK, and p-p38 upregulation induced by LPS [38].

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