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Review Article

The Chemistry and Biology of Lycopene : Antioxidant for Human Health

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Abstract

More than 600 carotenoids are known to be naturally occurring. These predominantly colourful molecules, found in plants, fungi and bacteria undergoing photosynthesis, are widespread in vegetables and fruits. Carotenoids are divided into two main groups. Of them, the highly unsaturated hydrocarbons consisting of lycopene, α-, β-, and γ-carotene build the first group, whereas xanthophylls, such as β-cryptoxanthin, lutein and zeaxanthin are considered as the second big carotenoid group.

Lycopene, a representative of the hydrocarbon carotenoids with the molecular formula of $C_{40}H_{56}$, has an acyclic open-chain structure consisting of 13 double-bonds. Two of them are non-conjugated, whereas eleven are conjugated double bonds, thereby building a chromatophore. This distinctive conjugated polyene structure accounts for the ruby colour and the antioxidant properties of lycopene. It has a distinct lipophilic character, which makes it nearly insoluble in ethanol, methanol and water. Due to its acyclic structure and the absence of a β-ionone ring, there is no pro-vitamin A activity to be found in lycopene, which is the reason for its differing biochemistry, as compared to α- and β-carotene.

Due to its polyene-structure, providing an electron-rich system, lycopene is an eligible target for electrophilic reagents. Thus, it shows an extreme reactivity towards oxygen and free radicals. Lycopene is known to be the most potent oxygen quenching reagent among carotenoids, and furthermore, it provides the ability to intervene in reactions initiated by free radicals, like $OH^{-\cdot}$ or peroxy radicals. Its excellent anti-oxidant properties are most likely the basis for its preventive role towards cancer and other chronic diseases.

However, the lycopene concentration in fresh fruits and vegetables shows a great variability, depending on seasonal environmental conditions, geographic location, climatic situation, species and maturity which may be taken as indices for the best sowing season, place, species/varieties to be planted and date/time of harvest. The vegetables and fruits thus obtained would be rich in lycopene content, which in turn would have a major beneficial impact on human health.

Keywords: *lycopene, antioxidant, seasonal variation, tomato, carotene, xanthophyll, human health.*

Introduction

More than 600 carotenoids are known to be naturally occurring. These predominantly colourful molecules, found in **plants**, **fungi** and **bacteria undergoing photosynthesis**, are widespread in vegetables and fruits. Carotenoids are divided into **two** main groups. Of them, the highly unsaturated hydrocarbons consisting of **lycopene**, α-, β-, and γ-carotene build the first group, whereas xanthophylls, such as β-cryptoxanthin, lutein and zeaxanthin are considered as the second big carotenoid group. The first class, hydrocarbon carotenoids, contains only carbon and hydrogen-atoms, but lacks oxygen, whereas xanthophylls, in contrast, consist of at least one oxygenated group on their terminal rings.

Lycopene, a representative of the hydrocarbon carotenoids with the molecular formula of $C_{40}H_{56}$, has an acyclic open-chain structure consisting of 13 double-bonds. Two of them are non-conjugated, whereas eleven are conjugated double bonds, thereby building a chromatophore. **This distinctive conjugated polyene structure accounts for the ruby colour and the antioxidant properties of lycopene.** It has a distinct lipophilic character, which makes it nearly insoluble in ethanol, methanol and water. Due to its acyclic structure and the absence of a β-ionone ring, there is no pro-vitamin A activity to be found in lycopene, which is the reason for its differing biochemistry, as compared to α- and β-carotene. The prevalent biologically occurring form of lycopene is the all-*trans*-isomer, which is also the thermodynamically most stable configuration. Indeed, heat, light or several chemical reactions can induce isomerization from the *trans*-isomer to various mono- or poly-*cis* forms.

However, the carotenoid concentration in fresh fruits and vegetables shows a great variability, depending on **seasonal environmental conditions**, geographic location, climatic situation, species and maturity which may be taken as indices for the best sowing season, place, species/varieties to be planted and date/time of harvest. The vegetables and fruits thus obtained would be rich in carotenoid content, which in turn would have a major beneficial impact on human health.

Anti-Oxidant Properties

Carotenoids constitute a ubiquitous group of isoprenoid pigments. They are very efficient physical quenchers of singlet oxygen and **scavengers** of other **reactive oxygen species (ROS)**. Carotenoids can also act as chemical quenchers undergoing irreversible oxygenation. The **antioxidant potential of carotenoids is of particular significance to human health**, due to the fact that losing antioxidant-reactive oxygen species balance results in “**oxidative stress**”, a critical factor of the pathogenic processes of various chronic disorders. Data coming from epidemiological studies and clinical trials strongly support the observation that adequate carotenoid supplementation may significantly reduce the risk of several disorders mediated by reactive oxygen species.

Due to its polyene-structure, providing an electron-rich system, lycopene is an eligible target for electrophilic reagents. Thus, it shows an extreme reactivity towards oxygen and free radicals. **Lycopene is known to be the most potent oxygen quenching reagent among carotenoids**, and furthermore, it provides the ability to intervene in reactions initiated by free radicals, like $OH^{-\cdot}$ or peroxy radicals. **Its excellent anti-oxidant properties are most likely the basis for its preventive role towards cancer and other chronic diseases**.

Lycopene has also been shown to upregulate the so-called **antioxidant response element** (ARE). Cellular enzymes, like glutathione S-transferase, superoxide dismutase or quinone reductase are activated by lycopene, resulting in another way of protecting cells against the highly reactive oxygen species.

Lycopene-Content in Different Sources

Natural sources of lycopene include watermelon, rosehips, pink grapefruit, guava, apricots and, above all, **tomatoes**. As all tomato products contain high concentrations of lycopene, they are, at the same time, the **most important source of this carotenoid** for humans, accounting for over 85% of all dietary sources. However, the lycopene concentration in fresh fruits shows a great variability, depending on environmental conditions, geographic location, climatic situation (Sen and Mukherji 1998a,b, 2000, 2009), species and maturity, but with an average of about 5 to 10 mg lycopene per 100 g tomato. Up to 15 mg lycopene in 100 g fruit has been found for deep-red tomato varieties, whereas yellow species are less rich in lycopene, with a content of only about 0.5 mg per 100 g. Processed and, therefore, less hydrated tomato-products have been found to be richer in lycopene than whole, raw tomatoes.

Many lifestyle factors, like smoking, consumption of alcohol, blood lipid levels, and also biological factors, such as age or hormonal status, have an influence on the absorption of lycopene (Rao and Agarwal 1999). Studies have also shown that absorption from processed tomato products is better than from raw tomatoes.

Seasonal Variation in Lycopene Content

10 day old fruit samples collected for experimental work in different seasons for Lycopene content (Fig.1) showed an identical trend as carotene and xanthophyll *i.e.* winter > summer >rainy (Sen and Mukherji, 2000)

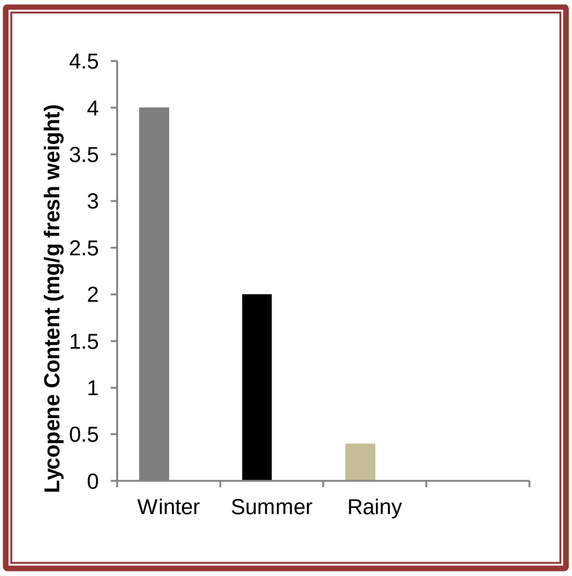

Fig. 1 Lycopene Content in 10 day old Tomato fruit S.E. = 0.74; C.D. of Season=1.17 (5%)

Lycopene content was estimated by Ranganna (1977). The data obtained from three replications were statistically analyzed. Standard Error (S.E.) and Critical Difference (C.D.) values of both season and stage at 5 % level were calculated from the respective analysis of variance (ANOVA) tables.

High antioxidant (carotene, xanthophylls and lycopene, in this study) content in winter indicates optimum scavenging of ROS species while in rainy it is *vice versa.* High antioxidant (carotenoid) content in winter is indicative of better yield quality and a low amount in rainy indicates the reverse. Carotenoids decreased in post flowering in all three seasons, an indication of approaching senescence. In earlier works on crop plants, carotenoid content was reported to decline significantly from the pre-flowering to the post-flowering stage under natural environmental conditions and the decreased carotenoid content can be a significant reason for ushering senescence (Sen and Mukherji, 1999, 2000, 2006, 2009, 2014).

High antioxidant content in winter > summer > rainy is indicative of an optimum physiological status of the concerned plant and *vice versa* and hence winter season can be taken as the most favourable season for growth, yield and yield quality (Sen and Mukherji 1998a, b), followed by summer and finally rainy. There have been earlier reports showing the decrease in carotenoid content during periods of environmental stress – in this case, the rainy season (Young, 1991; Prochazkova *et al*. 2001). The parameter(s) measured/assayed serve as useful **bioassay indices/markers** of the changing seasonal environmental conditions. High antioxidant (in this case, lycopene) content in winter > summer > rainy has significant implications for human health.

Thus, lycopene concentration in Tomato shows a great variability, depending on **seasonal environmental conditions** maturity which may be taken as an index for the **best sowing season**, and **date of sowing and time of harvest**. The fruits thus obtained would be **rich in lycopene (carotenoid) content**, which in turn would have a major **beneficial impact on human health**.

Lycopene and Prostate Cancer

Androgen has been reported Goo *et al*. (2007) to induce an increase of ROS in prostate cancer cells. Researchers investigated changes in protein-expression of androgen-depleted and androgen-sufficient LNCaP cells by conducting quantitative proteomic analysis. After treatment with 0.2 μM lycopene, they found increased numbers of detoxification proteins, such as epoxide hydrolase-1, which is involved in the hydrolysis of epoxides to transfer these proteins to less reactive species. **Furthermore, the protein, superoxide dismutase-1, which degrades radicals in cells, and catalase, which protects cells from hydrogen peroxide, have been found to be increased.** This has also been detected for metal binding protein, transferrin, which binds to iron and prevents it from producing oxidative stress. Lycopene has been found to induce a moderate increase of these detoxification proteins in androgen-sufficient and a significant increase in androgen-depleted LNCaP cells. Though the amount of detected proteins has been low, **it can be hypothesized that lycopene provides a protective mechanism in preventing DNA damage, due to an increased expression of these proteins**.

Another study (Qiu *et al*. 2013) analysed protein expression by using iTRAQ proteomics after exposure of prostate epithelial cells to 2 μmol/L lycopene for 48 hours. Lycopene increased the amount of phase II protective enzymes, such as glutathione-*S*-transferase-omega-1, peroxiredoxin-1 and sulphide-quinone oxidoreductase. Proteins, such as ERO1-like protein-α or CLIC-1, usually involved in ROS generation, have been shown to be downregulated after treatment with lycopene. **This indicates the potential of lycopene to lower the risk for the generation of ROS and to reduce oxidative stress**.

Effects on Tumour Cell Proliferation and Growth

Researchers (Kotake-Nara *et al.* 2001) examined 15 different carotenoids with regard to the potential of growth inhibition to the prostate cancer cell lines, PC3, DU145 and LNCaP. The authors found a significantly reduced cell viability after treatment with acyclic carotenoids at concentrations of 20 μmol/L. Treatment at a concentration of 5 μmol/L resulted in an enhanced reduction of cell viability in particular for lycopene.

Effects on the Cell-Cycle

The loss of the ability to regulate the cell-cycle is characteristic for cancer cells and results in uncontrollable proliferation. Processing cells through the first gap (G_1) phase of the cell cycle is a step which is frequently disordered in cancer. Lycopene has been investigated in different studies for its ability to mediate cell cycle arrest.

Potential to Induce Apoptosis

Through the elimination of damaged abnormal cells, the maintenance of a healthy, physiological organism is guaranteed. Cancer cells are, amongst others, characterized by the loss of the ability to undergo apoptosis.

Lycopene has been investigated for its capability to induce apoptosis. Scientists (Hwang and Bowen 2005) detected apoptosis in the hormone sensitive prostate cancer cell line, LNCaP, after treatment with tomato paste extract for 24 and 48 h using an annexin V-FITC detection kit. Apoptosis has been detected predominantly in late stages, and most of the treated cells responded after 24 h of exposure to the tomato paste extract. Importantly, a significant increase in apoptosis has been reported after treatment with the physiologically relevant concentration of 1 μM (Hwang and Bowen 2005).

Other Effects of Lycopene on Prostate Cancer Cells

Several *in vitro* studies have been undertaken trying to explain the mechanistic effects of lycopene on prostate cancer. A dose-dependent influence on androgen receptor element expression has been detected in LNCaP cells using a luciferase-reporter assay Zhang *et al.* (2010). It has been shown that lycopene inhibits the androgen receptor element, resulting in decreased PSA velocity, and may, therefore, provide an anti-hormonal potential. Lycopene might also have an impact on invasion and migration of prostate cancer cells by reducing the expression of integrins, which are known to be involved in signalling processes regarding adhesion and invasion.

Additionally, lycopene has been shown to inhibit signalling of insulin-like growth factor-I (IGF-I) and, therefore, disrupts one pathway in the development of prostate cancer. Signalling of IGF-I and IGF-II via their receptor, IGF-IR, facilitates survival and proliferation of cancer cells using PI3K/Akt and MAPK pathways. Mobilization of Akt, which plays a key role in inducing IGF-I signals, may have a significant role in the development of an androgen-independent type of prostate-cancer (Wertz 2009). After exposure of LNCaP cells to lycopene, a reduction of IGF-IR expression, as well as an Akt activation and an increase in the expression of insulin-like growth factor binding protein 2 (IGFBP2) has been shown. IGFBP2 is a binding protein for IGF-I, which has been shown to be highly expressed in LNCaP cells.

In addition to its antioxidant characteristics, research shows that lycopene has at least four other important health-promoting mechanisms

- Lycopene facilitates cell-to-cell communication at sites called "gap junctions" — essential for cells to know when to stop growing, which is key for preventing cancer from developing.
- It stimulates the immune system to help destroy invading microorganisms and early cancer cells.
- It regulates endocrine (glandular) communication pathways.
- It regulates the cell reproductive cycle, preventing cancer development.

Lycopene and cardiovascular disease

People with low blood lycopene levels are shown to suffer from increased risk for atherosclerosis, including greater thickness and stiffness of their arteries. Research shows that people with atherosclerosis visible on ultrasound in their carotid arteries (those leading to the brain) have lower blood levels of lycopene than do those with normal carotids (Mordente *et al*. 2011). Conversely, those with the highest lycopene blood levels have a 45% lower risk of atherosclerosis, more flexible arteries than those in the lower lycopene group, and a reduced risk of heart attack.

Lycopene protects heart and blood vessel tissue by several mechanisms, including antioxidant function:

- Lycopene scavenges the powerful oxidant hypochlorous acid, which is associated with atherosclerosis.
- It also decreases fat and LDL cholesterol oxidation, steps that occur early in the chain of events that leads to atherosclerosis.

Studies show that lycopene supplementation can decrease total cholesterol by 5.9% and LDL cholesterol by 12.9% (and by 50% in animal studies). Some of this effect may be due to lycopene's ability to inhibit cholesterol synthesis. Laboratory and human studies demonstrate that lycopene decreases production of multiple pro-inflammatory mediators and markers of inflammation involved in the development of atherosclerosis.

One dramatic human study by Korean scientists at Yonsei University in Seoul, showed that 15mg a day of lycopene orally improved endothelial function by 23%. At the same time the inflammatory marker C-reactive protein (hs-CRP) fell dramatically, along with systolic blood pressure and important vascular adhesion molecules that trap platelets and immune cells to form inflammatory plaques. Some of that reduced inflammatory response is attributed to lycopene's ability to block fat oxidation in arterial lining cells.

Lycopene and diabetes

Diabetes, like other chronic age-related conditions, is powerfully driven by oxidation and inflammation. Not surprisingly, then, blood lycopene levels in diabetics are typically much lower than they are in healthy control patients, presumably the result of consumption of lycopene by reactive oxygen species, say scientists. Diabetics may be able to protect themselves by increasing their lycopene intake; studies show that high consumption of tomato products can improve resistance to oxidation in people with type 2 diabetes, say researchers in Diabetes Care, in June 2000.

Diabetics with the highest blood lycopene levels are also shown to have greater glucose tolerance than do those with lower lycopene levels Valero *et al*. (2011). Eating a lycopene-rich Mediterranean diet increases lycopene levels and can reduce levels of haemoglobin A1c, the blood marker of sustained blood sugar elevations, from 7.1% to 6.8%, say Australian researchers from the faculty of health, University of Canberra. (Tomatoes have other beneficial compounds such aschlorogenic acid that may have accounted for these marked reductions in haemoglobin A1c.)

Other complications of diabetes are also less severe in those with higher lycopene levels. For example, diabetics with healthy eyes have higher levels of lycopene than do those with the blindness-inducing condition called diabetic retinopathy. Similarly, diabetic neuropathy, a painful and debilitating nerve condition that is among the hardest of pain syndromes to treat, is substantially ameliorated in animal studies of lycopene supplementation. Finally, cognitive decline associated with diabetes can be decreased with long-term lycopene supplementation.

Lycopene and the Brain

Oxidative stress plays a major role in the neuro-degenerative diseases of ageing. Most of the carotenoid antioxidant nutrients, including lycopene, are reduced in one or more of those diseases such as Alzheimer's disease, vascular dementia and Parkinson's disease with dementia, say scientists. They were also shown to be depleted in mild cognitive impairment. These facts make lycopene an important dietary component for maintaining brain health, say experts.

Alzheimer's disease is practically the perfect example of brain destruction by oxidant stress (Qu *et al*. 2011). Lycopene may prevent Alzheimer's by inhibiting formation of oxidant-producing Abeta proteins. As a result, studies show decreased death rates of neurons, especially in the memory-processing hippocampus area of the brain.

There is also growing evidence that lycopene can prevent the inflammatory response to an acute stroke, and can reduce the total size of the damaged brain area, say Indian researchers from Rayalaseema University's department of Biotechnology, in Kurnool, Andhra Pradesh (Obulesu *et al.* 2011). Finally, lycopene has also recently been shown to be protective against environmental neurotoxins and excessive levels of certain elements such as manganese, again through its antioxidant effects (Mohamed *et al.* 2012).

Conclusion

Further research on the chemistry and biology of lycopene will perhaps reveal its true potential in combating chronic diseases to promote human health and well-being. Studies reveal that lycopene concentration shows a great variability, depending on **seasonal environmental conditions** and developmental stage, which may be taken as an index for the **best sowing season**, and **date of sowing and time of harvest**. The fruits thus obtained would be **rich in lycopene (carotenoid) content**, which in turn would have a major **beneficial impact on human health**.

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