Lycopene: Isomerization Effects on Bioavailability and Bioactivity Properties

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Lycopene cis-isomers have shown to be more bioavailable and bioactive than the naturally occurring all-trans-isomer. During food processing, lycopene undergoes geometrical isomerization, increasing the proportion of cis-isomers. However, lycopene tends to retro-isomerize during food storage. Because the stability, bioavailability, and distribution of lycopene isomers are physiochemical characteristics critical for health benefits, it is essential to preserve these properties in food products containing lycopene isomers.

The objective of this article is to review thermal and nonthermal technologies available for lycopene geometrical isomerization with a focus on the stability, bioavailability, and bioactivity of lycopene isomers.

Keywords lycopene, isomerization, thermal and nonthermal treatment, trans-cis-isomers, bioavailability, bioactivity

Introduction

Lycopene is a functional component of dietary importance largely present in tomato and tomato derived products. Its concentration in tomatoes (Lycopersicon esculentum L.) ranges from 0.9 to 4.2 mg/100 g depending on the variety.¹ Other dietary sources include watermelon, apricot, papaya, pink grapefruit, and rosehip but with lower contents.²⁻⁴

The literature reports that lycopene has antioxidant capacities as a potent quencher of singlet oxygen and other electronically excited molecules that are produced by photexcitation or chemiexcitation.⁵ Epidemiological studies have shown dietary intake of tomatoes and tomato products containing lycopene to be associated with decreased risk of chronic disorders such as cancer or cardiovascular disease.¹¹⁻⁹ Evidence from animal and cell culture studies suggested that lycopene has anticarcinogenic and anti-atherogenic potential effects in both vitro and in vivo. Lycopene is also a potential natural food colorant and ingredient in the cosmetic industry.

The general structure of lycopene is an aliphatic hydrocarbon with 13 double bonds (11 conjugated carbon–carbon and 2 nonconjugated). Naturally occurring geometrical isomers of lycopene are mainly above 90% in the all-trans configuration, which is the most thermodynamically stable form. Because it is acyclic, lycopene possesses symmetrical
planarity. The long chromophore in the polyene chain accounts for the red color of lycopene and its powerful antioxidant activity.\(^{(10)}\)

As a result of the 11 conjugated carbon–carbon double bonds in its molecular backbone, lycopene can theoretically assume \(2^{11}\), that is, 2048 geometrical configurations. However, because of steric hindrance, only certain double bond groups of lycopene actually undergo geometrical isomerization.\(^{(11)}\) Among them, 5\textit{cis}-, 9\textit{cis}-, and 13\textit{cis}- or 15\textit{cis}- (Fig. 1) lycopene usually predominate\(^{(12)}\) and are found in plants and animal plasma.\(^{(13)}\) Figure 2 shows the high-performance liquid chromatography (HPLC) chromatogram of isomerized tomato lycopene with peaks corresponding to various lycopene isomers.

Various studies have suggested that isomerization of lycopene from the all-\textit{trans} form naturally present in tomatoes to the \textit{cis} isomeric form may enhance its bioavailability most likely because of the greater solubility of \textit{cis}-isomers in the bile acid micelles/lipids, because of a shorter chain length to fit into micelles/lipids, because it is less prone to crystallization, and due to its lower tendency to aggregate.\(^{(11,14–18)}\) Lycopene undergoes geometrical isomerization during food processing, increasing the proportion of \textit{cis}-isomers\(^{(18–20)}\) and retro-isomerization during storage of processed foods. This phenomenon implies that lycopene-based food products are very dynamic systems where lycopene isomers can be transformed into other isomers.\(^{(11,21)}\)

![Figure 1. Structure of most common lycopene isomers (van Breemen \textit{et al.}\(^{(68)}\).](Image)
Because the stability and the concentration of lycopene isomers are physiochemical characteristics critical for health benefits, it is essential to preserve these properties. Therefore, an ideal source of highly bioavailable and bioactive lycopene should be stable trans-cis-isomers in lycopene-containing products.

The objective of this article is to review thermal and nonthermal technologies available for lycopene geometrical isomerization with a focus on the stability, bioavailability, and bioactivity of lycopene isomers.

Geometrical Isomerization of Lycopene

Geometrical isomerization is a chemical conversion in which the relative positions of groups bound to a functional group with restricted rotation are reversed. Carotenoids are rich in conjugated double bonds and hence theoretically can undergo isomerization to produce an array of mono- or poly-cis-isomers, of which 5cis-, 9cis-, and 13cis- or 15cis- are common.\(^\text{(12)}\) Interconversion of trans-cis-isomers is thought to occur with thermal treatment (conventional heating or microwave irradiation) and nonthermal (light irradiation, acid treatment, and radical reaction in presence of light).\(^\text{(11,12,19,20,22)}\)

It was suggested that trans-cis isomerization can be a result of overlapping of the methyl group of the carbon atom adjacent to the double bond and the hydrogen.\(^\text{(23)}\) Yeung et al.\(^\text{(23)}\) studied the mechanism of lycopene isomerization through an ab initio model. From the proposed mechanism the cationic formation converts C4 from its nearly tetrahedral (sp\(^3\) to trigonal planar sp\(^2\)) geometry. Because the positive charge is dispersed throughout the \(\pi\)-network, the C3 has two trigonal planar carbons attached.

Isomerization converts all-trans-isomers into cis-isomers as a result of the additional energy input and results in an unstable state. Isomerization of lycopene requires an appreciable amount of activation energy.\(^\text{(21)}\) Thermal effects on isomerization, bioactivity, bioavailability, and stability of lycopene have been studied in different tomato varieties,\(^\text{(24)}\) tomato extracts,\(^\text{(11)}\) oil-and-water systems,\(^\text{(25)}\) lycopene model systems,\(^\text{(22)}\) cooking conditions on lycopene,\(^\text{(26)}\) and tomato puree.\(^\text{(27)}\)

Lycopene appears to be quite stable within the plant matrix but may quickly degrade and isomerize when solubilized in oil or organic solvents. The geometrical stability of lycopene may be because of the structural specificity of lycopene being present in a
crystalline state and stored within the plant cell.\(^{(24)}\) Lee and Chen\(^{(22)}\) reported that a standard lycopene compound undergoes isomerization at 50°C; however, degradation was the dominant mechanism at 100°C.

**Conventional Heating by Refluxing in Organic Solvents**

Modification of the lycopene isomer profile in a tomato extract requires solubilization of lycopene in organic solvents. After solubilization, lycopene will isomerize so that the isomer’s profile will evolve toward that of the equilibrium state. An isomerized tomato extract with a stable lycopene isomer profile with low levels of 13cis-isomer (the least stable isomer) can be prepared by reaction in organic solvents. Lambelet *et al.*\(^{(11)}\) prepared isomerized tomato extract with 62% cis-isomers from raw tomato extract containing 96.6% all-trans- and 3.4% cis-isomers that was stable for more than one year at room temperature by refluxing tomato extract in ethyl acetate at 76°C for 7 days.

Ethyl acetate is used by food ingredient manufacturers for the preparation of tomato extracts; therefore, extraction and geometrical isomerization can be achieved in a single step. After stereo-isomeric equilibrium has been reached, removal of the solvent down to the level requested for human consumption can easily be achieved by distillation and drying under reduced pressure without causing retro-isomerization. Calvo *et al.*\(^{(28)}\) reported that isomerization rather than degradation of lycopene occurred during heating in ethyl acetate.

Therefore, to prepare an isomerized tomato extract with a potentially bioavailable and stable ingredient, this process is much more convenient at an industrial scale.

**Conventional Heating in Oil**

Because lycopene is liposoluble, isomerized tomato extract free of organic solvents can be prepared by heating lycopene in edible vegetable oil. The process is simple and inexpensive, involving direct solubilization of lycopene in oil followed by heating. Extraction and isomerization is achieved in a single step. The isomerized tomato extract is used in nutraceutical, cosmetic, pharmaceutical, and food products formulations. A study by Bortlik *et al.*\(^{(29)}\) showed that heating a mixture of tomato paste containing 97% trans and 3% cis–lycopene isomers in vegetable oil at 100°C for 15 minutes, 40% of cis lycopene isomers ratio was obtained. Chen *et al.*\(^{(25)}\) reported that hydrophobic fats tend to coat lycopene and interfere with the ability of oxygen to react with lycopene by some sort of blocking action, leading to the reduction in the available oxygen available to interact with lycopene. Therefore, oil may stabilize lycopene and reduce oxidative degradation.

**Microwave Irradiation**

Microwave, although relatively of low energy waves, can cause molecular vibrations in materials, resulting in rapid heating. Subjecting lycopene oleoresin (lycopene, 95% trans and 5% cis–isomers) to a microwave treatment of 150 seconds at 2.45 GHz and temperature of about 105°C, the ratio of cis : trans isomers for lycopene was 65:35.

A study on microwave cooking of tomato slurry resulted in the relatively higher percentage of retained lycopene because the tomato slurry reached its boiling point after only 60 seconds of microwave cooking.\(^{(26)}\) This showed that lycopene isomerization is stronger in the microwave-treated oleoresin and the temperatures needed to generate cis-isomers were lower compared to the conventional heating process.
Photo-Irradiation

Experimental results indicated that light intensity and exposure time greatly affected the stability of lycopene. Chen et al. (25) studied the effects of light-irradiation intensity and exposure time on cis-isomer contents in water and in oil systems. Treatment of tomato extract with irradiation intensity of 700 μmol/m² s for one day, maximum concentration of lycopene cis-isomers of 0.12 mg/100 g was reached. Therefore, high irradiative energy induced isomerization to produce cis-isomers.

Acidic Treatment and Radical Reaction

Re et al. (30) studied the effects of the acidic environment on lycopene. All-trans lycopene supplement capsules were incubated in acidified water for 3 hours at 37°C. Under these conditions, lycopene containing 96% all-trans and 3% cis was isomerized to 40% cis-isomers. On the other hand, photoisomerization of lycopene in dichloromethane and iodine as catalyst for 1 hour at room temperature gave a cis : trans isomer ratio of about 77%. The presence of iodine as catalyst lowered the activation energy required for the reaction, allowing equilibrium to be reached in a short time. (29)

However, such processes can easily be applied on a lab-scale basis; from an industrial point of view is not realistic because iodine is quite difficult to remove from the product afterwards.

Lycopene Bioavailability

Bioavailability is defined as the fraction of an ingested nutrient that is available to the body through absorption for utilization in normal physiological functions and for metabolic processes. (31–33)

Lycopene bioavailability may best be described as a continuum, with raw sources exhibiting the lowest relative bioavailability, mild processed foods slightly better, and thermally processed food sources and purified oily preparations having the highest bioavailability.

Several studies have attempted to compare lycopene bioavailability with respect to absorption in the human body from different tomato preparations. (34–40) The reports indicated that lycopene is more bioavailable from processed food sources than from raw sources and is influenced by dietary factors and food properties. Thermal and mechanical food processing has shown to improve lycopene bioavailability by breaking down cell walls, which weakens the bonding forces between lycopene and tissue matrix, thus making lycopene more accessible and inducing trans-cis isomerization. (2,18) Agarwal et al., (18) Nguyen et al., (24) and Stahl and Sies (41) reported an increase in human serum lycopene levels after consumption of processed tomato juice and not after unprocessed juice. A similar study by Gartner et al. (42) showed that lycopene is 2.5 times more bioavailable from tomato paste than from fresh tomatoes in human serum.

The uptake of lycopene into intestinal mucosal cells is enhanced by the formation of bile acid micelles. Because bile production is stimulated by dietary fat, consuming fat with a lycopene-containing meal could increase the efficiency of absorption. (41) Free lycopene isomers from dietary sources are incorporated into mixed micelles, taken up by the mucosal brush border membrane, and packaged into chylomicrons, which are secreted via the mesenteric lymph system into the blood. Through the action of lipoprotein lipase on chylomicrons, lycopene and other carotenoids have the potential to be taken up passively
by various tissues, including adrenals, kidney, adipose, spleen, lung, and reproductive organs, before clearance of chylomicron remnants by the liver via the chylomicron receptor. Lycopene is a predominant carotenoid in the human liver, adrenals, adipose tissue, testes, and prostate.\(^{(15,43–47)}\)

Release of lycopene from the food matrix is one of important factors modulating lycopene bioavailability, and the literature has suggested that formation of cis-isomers also increases lycopene bioavailability. In contrast to natural sources of lycopene, which is a all-trans-isomer (80–97% all-trans), lycopene has been shown in human and animal tissues to exist mainly as cis-isomers. Study groups have suggested preferential absorption 180 of lycopene isomers\(^{(2,5,14,48)}\) and that cis-isomers of lycopene may be better absorbed than their all-trans parent structure. Stahl and Sies\(^{(41)}\) observed that despite a tomato juice dose having only about 20% cis-isomers, the serum was composed of about 50% cis-isomers after consumption of tomato juice by healthy volunteers.\(^{(36,49,50)}\) demonstrated that cis lycopene isomers are preferentially accumulated in tissues and serum. Animal study on orally dosed ferrets with lycopene and samples collected from the small intestine, lymph, and several tissues to determine cis : trans-isomer ratios showed that despite the dose containing only 9% cis-isomers, the mucosa (58.8%), lymph (77.4%), blood (52%), and tissues contained significantly more cis lycopene isomers than stomach (6%) or intestinal content (17.5%).\(^{(14)}\)

The structure of a carotenoid is a key determinant of the physical properties, chemical reactivity, and biologic functions or actions observed.\(^{(1)}\) The physicochemistry and bioavailability of all-trans- and cis-isomers of lycopene are known to be different. Introduction of one or more cis double bonds into a lycopene molecule reduces its length, allowing the molecules to fit into micelles more easily. Cis lycopene isomers have a lower tendency to aggregate and are more soluble in bile acid micelles and thus are preferentially incorporated into chylomicrons.\(^{(11,14,15)}\) Alternatively, it has been suggested that linear all-trans lycopene isomers may more readily aggregate within the intestine and form crystals, greatly reducing their uptake by micelles.\(^{(15,48)}\) In contrast, some authors proposed that there is no preferential absorption of lycopene isomers and that isomerization to cis-isomers may take place in the digestive tract and/or in plasma.\(^{(51)}\)

The bioavailability and absorption of lycopene have been studied extensively in vitro, in animal models and in humans. The implications of these findings are not yet clear, and further investigations are required to understand the absorption and metabolism pathways and the specific action mechanism of lycopene isomers in humans.

**Lycopene Bioactivity**

As the most potent quencher of singlet oxygen and free radicals among the carotenoids, antioxidant activity is at least one probable mechanism of action for lycopene, and this bioactivity has been observed experimentally both in vitro and in vivo. An antioxidant may be broadly defined as any substance that when present at low concentrations compared to those of an oxidizable substrate significantly delays or prevents oxidation. The 11 conjugated and two nonconjugated double bonds in lycopene make it highly reactive toward oxygen and free radicals, and this antioxidant activity probably contributes to its efficacy as a chemoprevention agent.\(^{(48,52,53)}\) In addition to antioxidant activity, in vitro experiments indicate other mechanisms of chemoprevention by lycopene, including induction of apoptosis and antiproliferation in cancer cells,\(^{(54–56)}\) anti-metastatic activity,\(^{(57,58)}\) and the upregulation of the antioxidant response element leading to the synthesis of cytoprotective enzymes.\(^{(59,60)}\)
Evidence from epidemiological studies indicating an inverse relationship between lycopene intake and prostate cancer risk have been supported by in vitro and in vivo experiments showing that oral lycopene is bioavailable, accumulates in prostate tissue, and is localized to the nucleus of prostate epithelial cells.\textsuperscript{61–63} It has been observed that more than 50\% of the lycopene present in human serum and tissues is in cis forms,\textsuperscript{50,64} and cis-isomers can contribute up to 90\% of the total lycopene contents in prostate tissue.\textsuperscript{65} These results led to the possibility that specific lycopene isomers perform unique biological functions in human serum and tissue.

Shi and Le Maguer\textsuperscript{66} pointed out that the bioactive potency of cis lycopene isomers is different from that of the all-trans form because of structural differences. Bohm \textit{et al.}\textsuperscript{67} studied the in vitro antioxidant activity of lycopene isomers using Trolox-equivalent antioxidant capacity (TEAC) assay, and cis lycopene isomers demonstrated stronger antioxidant activity than the all-trans lycopene isomer. The in vitro study and accumulation of cis lycopene isomers in tissue and serum observed reflects the possibility that cis lycopene participates in biological reactions and has higher potential health benefits than the all-trans lycopene.

Little has been reported on the specific biological importance of these lycopene isomers or synergism in human health. More work remains to be done to determine whether there are biological differences between all-trans- and various cis-isomers of lycopene regarding their antioxidant properties or other biological functions.

**Future Prospective**

Lycopene isomerization from all-trans- to cis-isomers would lead to a change in lycopene stability, bioactivity, and bioavailability during cooking, industrial food processing, and storage; hence its health benefits. Extensive study on emerging technologies such as high-pressure–low-temperature, pulse electric fields, and several new approaches in food packaging, for example, modified atmospheres and active packages, in modifying lycopene isomers contents is required. Also, more information is required to firmly establish the effect of tomato processing and storage conditions on bioactivity, bioavailability, and stability of lycopene isomers. There are contradicting views on absorption and biological activities of lycopene isomers; therefore, more investigation is needed to fully characterize the preference and mechanism of lycopene isomers in absorption and biological actions and the possibility to interact with other food components, providing additive or synergistic effects and biological importance in human health.

Another possible important aspect of lycopene research could be the assessment of the nutritional quality and healthy benefits of processed tomato-based food, which might depend not only on the total lycopene content but also on the distribution and stability of lycopene isomers. The relative biological significance in terms of absorption and effectiveness of various geometrical isomers and their metabolism to derivatives that might also exhibit biological activities contributing to the health potential properties of lycopene are not clear at present.

**Conclusion**

Research findings show that lycopene trans-cis-isomers are in dynamic systems. In contrast, an ideal source of highly bioavailable and bioactive lycopene should be a tomato extract containing stable proportions and distribution of all-trans and cis forms. Different
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methods are available for all-trans-cis lycopene isomers’ isomerization, but conventional thermal treatment provides better results because the lycopene isomers proved to be more stable and viable for industrial scaling. Lycopene is one of the important contents of human dietary foods. The majority of lycopene found in tomatoes and tomato products is present as all-trans lycopene. This is in contrast to the lycopene isomer profile reported for biological tissues. Clinical studies indicated that human and animal tissues, including serum, contain significantly more cis lycopene than the foods in which the lycopene originated. The results have led to the hypothesis that cis-isomers of lycopene are more bioavailable and thus higher biological activity is implicated with lycopene consumption. The few in vitro and in vivo experiments done so far have supported the hypothesis. More information is needed to fully acknowledge the biological benefits of lycopene isomers.

References


