Review Article

LYCOPENE OF TOMATO FAME: ITS ROLE IN HEALTH AND DISEASE

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ABSTRACT

Lycopene; a non-provitamin A carotenoid is responsible for the red to pink colors seen in tomatoes, pink grapefruit, and other foods of fruit and vegetable origin. Processed tomato products are the primary source of dietary lycopene. Lycopene has unique structural and chemical features that may contribute to specific biological properties. Unlike many other natural compounds; lycopene is generally stable to processing when present in the plant tissue matrix. Recently, lycopene has also been studied in relation to its potential health effects. The antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties. Data concerning lycopene bioavailability, tissue distribution, metabolism, excretion, and biological actions in experimental animals and humans are beginning to accumulate although much additional research is necessary. Although promising data from epidemiological, as well as cell culture and animal, studies suggest that lycopene and the consumption of lycopene containing foods may affect cancer or cardiovascular disease risk, more clinical trial data is needed to support this hypothesis. In addition, future studies are required to understand the mechanism(s) whereby lycopene or its metabolites are proven to possess biological activity in humans. This review summarizes the current knowledge with respect to its role in human health.

Keywords: Antioxidant, Free radicals, Chronic diseases, Lycopene, Oxidative stress.

INTRODUCTION

Lycopene; a member of carotenoid family; is a lipid soluble antioxidant synthesized by many plants and microorganisms but not by animals and humans[1] where it serves as an accessory light-gathering pigment and protects them against the toxic effects of oxygen and light. It is a red pigment without provitamin - A activity that imparts colour to many fruits and vegetables. Tomatoes and processed tomato products (juice, sauce, soup, pizza and spaghetti sauce) constitute the major sources and accounts for more than 85% of all the dietary sources of lycopene. The content differs with the varieties of tomatoes and increases as the fruit ripens[2]. It varies from 0.85mg to 13.6 mg/ 100g. The other source includes watermelon, pink grape fruit, guava and papaya. The United States Department of Agriculture (USDA) has quantitated the lycopene content of various foods consumed by Americans. Table 1 estimates the lycopene content of major food items found in the American diet. The lycopene levels are lower for peeled tomatoes as the removed peel is known to have higher content[3]. Shi and Le Maguer[4] reported that the concentration of lycopene is two folds higher in pericarp than in locular cavity and β-carotene is four folds higher in locular cavity.

Although it has been used as a food colourant for many years, it has recently received attention with respect to its antioxidant activity and potential in preventing prostate cancer and cardiovascular diseases in humans. In turn, this has led to the idea of increasing levels of lycopene in crops, particularly in tomatoes by genetic crosses in order to increase the amounts in the diets.[5] Natural mutants of tomatoes such as a high-pigment variety have been used in breeding strategies to alter lycopene levels.[6] Expression of bacterial genes and yeast genes in transgenic tomatoes has also significantly altered lycopene levels.[7, 8] It is a matter of some debate whether raising the levels of lycopene in fruit will have a major influence on bioavailability.[9] Furthermore, it remains unclear whether enhanced lycopene in foods can offer benefits to human health that are substantially different from synthetic lycopene.

Table 1: Lycopene content of various fruits and vegetables

Food	Lycopene content (mg/100 g)
Tomato foods	
Tomatoes, raw	0.9–4.2
Tomatoes, cooked	3.7–4.4
Tomato sauce	7.3–18.0
Tomato paste	5.4–55.5
Tomato soup (condensed)	8.0–10.9
Tomato juice	5.0–11.6
Catsup	9.9–13.4
Other fruits and vegetables	
Apricots, fresh	0.005
Watermelon, fresh	2.3–7.2
Papaya, fresh	2.0–5.3
Grapefruit, pink/red	0.2–3.4
Guava, raw	5.3–5.5
Vegetable juice	7.3–9.7

Lycopene chemistry, isomerization and degradation

It is a highly unsaturated, 40 carbon acyclic molecule containing 11 conjugated and 2 unconjugated double bonds arranged in all trans configuration in tomatoes; the

most thermodynamically stable form. The acyclic structure of lycopene makes it more soluble in organic solvents such as chloroform, hexane, benzene, methylene chloride, acetone and petroleum ether. Structure and physical properties of lycopene are shown in Fig. 1 and Table 2.

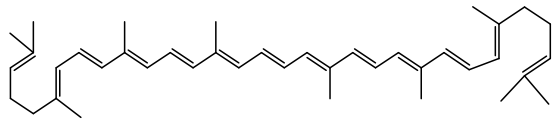

Figure 1: Structure of Lycopene

Table 2: Physical properties of lycopene

Molecular Formula	$C_{40}H_{56}$
Molecular Weight	536.85Da
Melting Point	172-175^{0}C
Crystal Form	Long red needles separate from a mixture of carbon disulfide and ethanol.
Powder Form	Dark reddish brown.
Solubility	Soluble in chloroform, hexane, benzene, carbon disulfide, acetone, petroleum ether and oil; Insoluble in water, ethanol and methanol.
Stability	Sensitive to light, oxygen, high temperature, acids, catalysts and metal ions.

The seven double bonds can isomerize and form mono- or poly-*cis* isomers upon exposure to heat, light, certain chemical reactions or during processing or storage.[4,10] Interestingly, *cis*-isomers account for over 50% of the total lycopene in human serum and over 80% in tissues such as prostate. [11-14] The *cis*-isomers are considered to be more polar and less prone to crystallization, but how they form *in vivo* and their impact on host biology is poorly understood. Amongst the isomers of lycopene (Fig 2), 5-cis lycopene has been found to be the most stable isomer (followed by all trans, 9 cis, 13 cis, 15 cis, 7 cis and 11 cis) and with highest antioxidant properties (followed by 9 cis, 7 cis, 13 cis, 11 cis and all trans isomer).[15]

Lycopene degradation occurs with light, heat, oxygen, metallic ions of copper and iron catalyzing oxidation and acids.[4] The potential of these non-enzymatic reactions to affect lycopene destruction *in vivo* is uncertain, but is critical when considering laboratory investigations of carotenoids in cell culture and in animal models. Carotenoids are not inherently stable *in vitro* and degradation occurs quickly under standard conditions of cell culture.[15-17] Thus, consideration of how degradation products may impact the biology understandably is crucial and investigators can enhance the value of their scientific contributions through inclusion of analytic data in their publications. Rodent studies also require careful consideration regarding lycopene stability. Lycopene, either as a pure agent or as part of tomato components, can be incorporated into semi-purified diets for studies of carcinogenesis or tumorigenesis. Again, careful documentation of concentrations of carotenoids in the ingredients, the formulated diet, and stability under conditions of feeding are essential components of sound scientific technique. Ambient lighting during formulation and the potential of heating and drying processes during pelleting contribute to significant degradation, therefore, is a key consideration.

LYCOPENE-RICH BY-PRODUCTS FROM FOOD PROCESSING

Food processing by-products from the tomato puree and sauce industry are commonly used in the development of lycopene-rich products (Table 3). Previously, Al-Wandawi *et al*.[18] had reported that tomato skins contained a high amount of lycopene. Food processing waste is commonly used as feed for livestock. Among the agro-industrial by-products (cereal and pulsed, distillery, oil-seeds, sugar industry, textile industry, vegetables and fruits industry, vegetables crop, and miscellancous), tomato wastes are the only by-products that are rich in lycopene.[19]

Table 3: Studies on lycopene from by-products[221]

Country	By-products	References
Algeria	Tomato skin	Benakmoum et al. [38]
Argentina	Tomato skin	Naviglio et al. [24]
Canada	Tomato skin	Kassama et al.[32]
China, Canada	Tomato paste waste	Yang et al. [52]
China	Tomato paste waste	Xi [23]
	Tomato paste waste	Jun [22]
India	Mace (*Myristica fragrans*)	Dhas et al. [40]
	Tomato peels and seeds, tomato industrial waste	Choudhari and Ananthanarayan [26]
	Tomato skin	Kaur et al. [21]
Iraq	Tomato skin	Al-Wandawi et al. [18]
Italy	Tomato peels and seeds	Sandei and Leoni [33]
	Tomato peels	Lavecchia and Zuorro [27]
Hungary	Tomato pomace	Vagi et al. [29]
Japan	Tomato skin	Topal et al. [31]
Portugal, Brazil	Tomato skin and seeds	Nobre et al. [30]
Spain	Tomato peels	Calvo et al. [36]
Taiwan	Tomato pulp waste	Chiu et al. [35]
Turkey, Netherland	Tomato paste waste	Baysal et al.[34]
USA	Tomato pomace	Altan et al. [37]

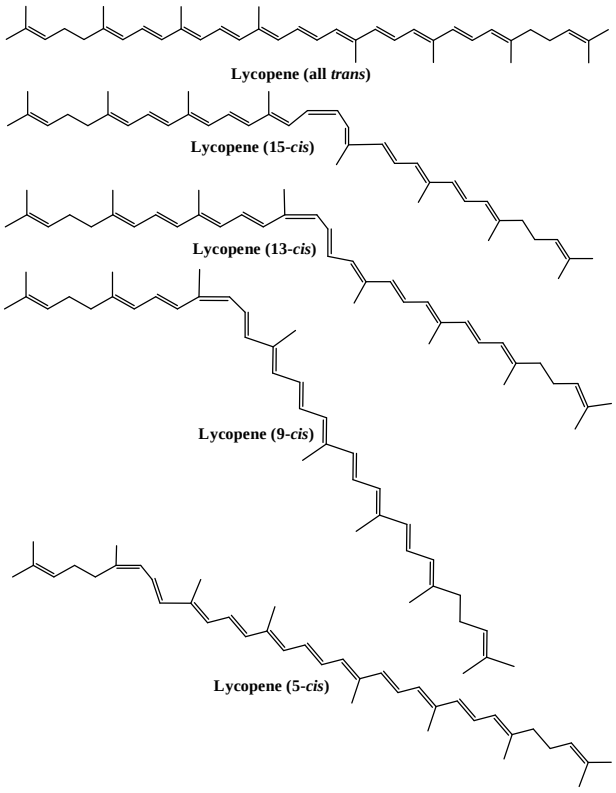

Figure 2: All trans and cis isomeric forms of lycopene

Nowadays, there is an increasing trend towards utilization of food processing by-products as a source of functional components.[20] Many studies have been carried out on the extraction of lycopene from by-products especially tomato waste. Optimization of the solvent extraction procedure was also performed to obtain a maximum lycopene yield from tomato peels using response surface methodology.[21] Application of high hydrostatic pressure processing without heating was reported to provide an increased yield of lycopene from tomato paste waste. [22] High pressure processing of tomato paste waste for 1 min gives a higher lycopene yield than solvent extraction for 30 min.[23] The Extractor Naviglio has been introduced to obtain higher purity lycopene from tomato by-products through pressurized extraction.[24,25] This extraction method requires tap water as extracting solvent with minimum organic solvent and the by-products can be further used as livestock feed. Furthermore, enzymatic treatment using cellulase and pectinase could offer one fold higher in the recovery of lycopene from tomato waste.[26] Lavecchia and Zuorro[27] reported that enzymatic treatment on tomato peels was able to increase the lycopene yield 20-fold. Moreover, supercritical fluid extraction has been applied in extraction of lycopene from several by-products.[28-30] Optimization of different extraction parameters on lycopene-rich by-products using supercritical fluid extraction were also studied.[31-34] Supercritical fluid extract of lycopene-rich tomato pulp waste has been used for encapsulation using an emulsion system in combination with gelatin and poly (γ-glutamic acid) (γ-PGA) as coating materials.[35] On the other hand, there are initiatives by food scientist to recycle the lycopene-rich by-products as food ingredients. Fortification with lycopene in dry fermented sausage was also done by adding dried tomato peel to the meat mixture during the sausage production.[36] The development of extrusion processing using barley-tomato pomace blends and processing into snacks has been demonstrated by Altan et al.[37] Besides, enrichment of low quality edible oils such as refined olive oil, extra virgin olive oil and refined sunflower oil by lycopene from tomato peels or tomato puree was proven to induce thermal stability to these edible oils.[38] The idea of using lycopene-rich by-products from tomato peel and seed for hen feed will further enrich the egg yolk with lycopene. However, only low amounts of lycopene were found to be transferred to the egg yolk (0.1% from tomato peels and 0.7% from tomato seeds)[39]. Another study also determined the quality of lycopene-rich by-products after food processing such as blanching and drying, where blanching in hot water at 75°C for 2 min could help to reduce the drying time and increase the lycopene bio-availability.[40]

LYCOPENE METABOLISM

The enzymatic metabolism of lycopene and other carotenoids is only beginning to be understood. The recent characterization of the enzymes carotenoid mono-oxygenase 1 (central cleavage) and 2 (eccentric cleavage) as mediators of carotenoid cleavage provides a basis for greater understanding of metabolism, particularly when coupled with modern analytic technology.[41] Lycopene, like β-carotene, when metabolized by carotenoid mono-oxygenase 2 will generate apo-lycopenals. Kopec et al.[42] observed that several apo-lycopenals in tomato-derived food products and also in the plasma of individuals who had consumed tomato juice for 8 weeks. Apo-6′-, apo-8′-, apo-10′-, apo-12′-, and apo-14′-lycopenals were detected and quantified in plasma. The sum of apo-lycopenals was 1.9 nmol/L plasma. The presence of apo-lycopenals in plasma may derive from the absorption of apo-lycopenals directly from food and/or human metabolism.[42, 43]

Hormonal status also affects lycopene metabolism and tissue distribution, yet this remains poorly understood. As it has been observed that castration (depriving androgen) results in doubling of hepatic lycopene, despite a 20% lower lycopene consumption in castrated rats.[43] The role of lycopene metabolites is under investigation in regards to lung cancer, but not yet examined in prostate cancer. An apo-10′-lycopenoic acid-fed diet significantly reduced the number of lung tumors in a chemical-induced carcinogenesis animal model.[44] Although the mechanisms are still speculative, lycopenoids, the metabolic products of lycopene, may possess more or less bioactive functions than lycopene itself.[45] The use of new murine models with targeted defects in carotenoid mono-oxygenase 1 and 2 will also provide novel tools for understanding lycopene metabolism and the impact of lycopene metabolites on biological outcomes.[45,46] Study using postmitochondrial fraction of rat mucosa with soy lipoxigenase reviewed that cleavage products and oxidation products will be formed from lycopene

metabolism.[47] These cleavage products (Fig 3) were 3-keto-apo-13-lycopenone and 3,4-dehydro-5,6-dihydro-15,15-apo-lycopenal, while the oxidation products were 2-apo-5,8-lycopenal-furanoxide, lycopene-5,6,5',6'-diepoxide, lycopene-5,8-furanoxide isomer (I), lycopene-5,8-furanoxide isomer (II), and 3-keto-lycopene-5,8-furanoxide. An i*n vitro* study using liposomal suspension showed that 8 carbonyl compounds namely 3, 7, 11-trimethyl-2, 4, 6, 10-dodecatetraen-1-al, 6, 10, 14-trimethyl-3, 5, 7, 9, 13 pentadecapentaen-2-one, acycloretinal,apo-14′-lycopenal, apo-12′-lycopenal, apo-10′-lycopenal, apo-8′-lycopenal, apo-6′-lycopenal and acycloretinoic acid were formed from lycopene oxidation.[48] In rats, 2 cleavage products were detected in the liver, which are apo-8′-lycopenal and apo-12´-lycopenal. However, Hu et al.,[49] reported only apo-10′-lycopenal was found in ferret carotene-9', 10'-monooxygenase catalyzed cleavage of carotenoids. The use of radio-labeled or stable isotope technology will allow investigators to define lycopene metabolism more precisely than in the past.[50,51]

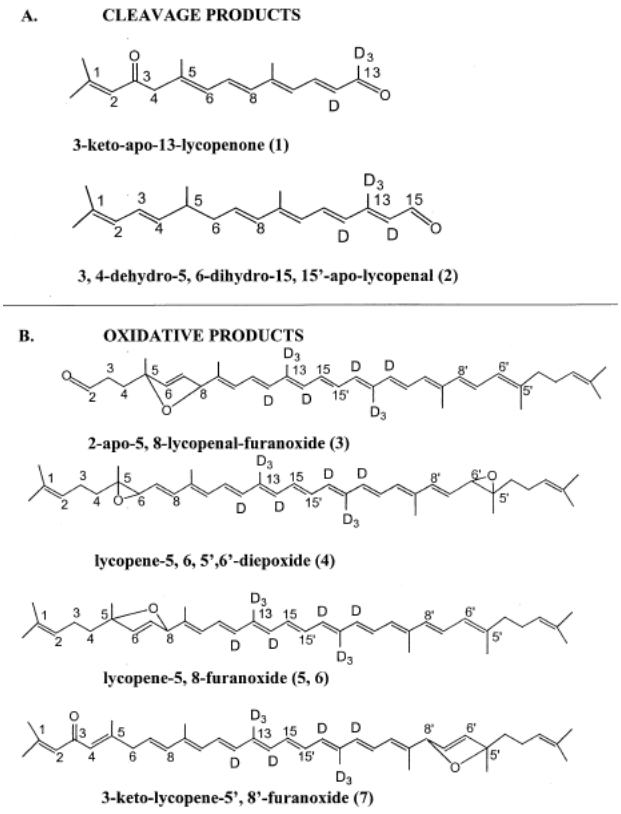

Figure 3: Proposed structures of metabolites detected[47]

LYCOPENE ABSORPTION; BIOAVAILABILITY AND DISTRIBUTION

Absorption of lycopene is similar to other lipid soluble compounds and is absorbed across gastro intestinal tract via a chylomicron mediated mechanism and is released into lymphatic system for transport to the liver. It accumulates in hepatocytes and to a lesser extent in spleen. In general 10-30 % of dietary lycopene is absorbed by humans and is equally absorbed from different sources of lycopene including tomato sauce, juice or tomato oleoresin capsule[53-55]. However, its absorption is influenced by several factors including the breakup of food matrix, cooking temperature, presence of lipids, dosage and other soluble compounds including the other carotenoids. These factors cause the release of lycopene from the food matrix and thus enhance its bioavailability.[53,56-57]

Isomerization of lycopene affects its absorption efficiency, *Cis*-isomers are produced during processing and cooking of tomato products, in addition, some isomerization may occur in the gastrointestinal tract, especially in the environment of the stomach.[58] It has been seen that when animals were fed lycopene containing all trans isomereric form, serum and tissue lycopene showed the presence of cis form. *Cis*-lycopene-rich tomato sauce has higher bioavailability than *trans*-rich tomato sauce in healthy adult subjects.[59] Perhaps, all-*trans*-lycopene, a long linear molecule, may be less soluble in bile acid micelles. In contrast, *cis*-isomers of lycopene may move more efficiently across plasma membranes and preferentially incorporate into chylomicrons. [60] The interaction between the carotenoids in the ingested food influences the absorption of individual carotenoids.[61-63] Studies of humans consuming food with multiple carotenoids may increase or decrease the individual carotenoids in plasma, compared with those consuming purified carotenoids and the mechanisms remain to be defined. The food matrix affects absorption as well, as lycopene from tomato oleoresin or tomato juice (processed tomatoes) was better absorbed compared to lycopene from raw tomatoes.[53,56, 64-66] It is well known that carotenoid–protein complexes are denatured by the cooking of vegetables and may impact bioavailability from the food matrix.[67]

The absorption of a hydrophobic and lipophilic lycopene molecule is affected by dietary lipids. A study reported that salsa with the natural lipid source of avocado greatly enhanced carotenoid absorption from meals.[68] Similarly, the absorption of carotenoids from salad with low-fat salad dressing was impaired compared with the absorption of carotenoids from salad with regular full-fat dressing.[69] It has been seen that ingestion of cooked tomato juice in oil medium increased serum lycopene levels by three folds where as consumption of an equivalent amount of unprocessed juice did not have any effect.[62] Likewise, Fielding *et al*.[70] showed addition of olive oil to diced tomatoes during cooking greatly increases the absorption of lycopene. However, Ahuja *et al*. reported no difference in serum lycopene concentrations when provided with 15% of energy from fat or 38% of energy from fat, suggesting that the relationship is not linear.[71]

Age may be another factor affecting lycopene absorption.[72] The bioavailability of lycopene was less in those 60–75 years of age compared to those 20–35. Interestingly, there was no major difference in the bioavailability of β-carotene, α-carotene, and lutein. Porrini *et al*.[73] suggested the eating behavior of different

individuals makes the lycopene level vary among people. Recently, a study reported that plasma lycopene level could be diverged among married, non-married and divorced subjects.[74]

The absorbed lycopene is distributed throughout the body via circulatory system. It is the most predominant carotenoid in human plasma with half life of about 2-3 days.[75] The distribution of lycopene in human organs and plasma has been reported by Erdman,[60] where higher concentrations of lycopene are found in the liver, adrenal and reproductive tissues (ten times higher than other tissues). The concentrations were within the range of 0.2–21.4 nmol/g tissue. Lycopene is not deposited uniformly (Table 4); these differences suggest that there are specific mechanisms for the preferential deposition of lycopene, particularly in the adrenals and testes. Studies have reported that lycopene concentration was highest in human testes, followed by adrenal gland > liver > prostate > breast > pancreas > skin > colon > ovary > lung > stomach >kidney > fat tissue > cervix.[76,77] A review by Rao and Argawal quoted that lycopene concentrations in human tissues are around 0.15–21.36 nmol/g tissue, but not detectable in brainstem tissue.[78] Studies with lymph-cannulated ferrets demonstrated that a lycopene dose that contained <10% *cis*-lycopene, lead to higher concentrations of *cis*-isomers in the small intestinal mucosal cells (58%), mesenteric lymph (77%), serum (52%), and tissues (47–58%), primarily the 5-*cis*-isomer.[16] Zaripheh *et al*.[79] showed that lycopene was highly distributed in the liver. Besides, high lycopene content was found in adipose tissue, the spleen and adrenal tissue. The excretion of lycopene through feces and urine was also reported. In human, total serum carotenoids is about 1–2 µM, with lycopene being one of the major carotenoids present in human serum.[80] The level of plasma lycopene can vary among the people from different countries (Table 5).

Table 4: Lycopene levels in human tissues[81-83]

Tissue	Lycopene (nmol/g wet weight)	Tissue	Lycopene (nmol/g wet weight)
Adipose	0.2 – 1.3	Testis	4.3 – 21.4
Adrenal	1.9 - 21.6	Lung	0.2 - 0.6
Brainstem	Not detectable	Ovary	0.3
Breast	0.8	Prostate	0.8
Colon	0.3	Skin	0.4
Liver	1.3 - 5.7	Stomach	0.2

Table 5: Plasma lycopene levels in people from different countries[221]

References	Country	Plasma Lycopene levels(µmol/L)	
		Male	Female
Scott et al. [84]	UK	-	0.32 ± 0.12
Michaud et al. [85]	USA	0.82 ± 0.38	0.76 ± 0.32
Olmedilla et al. [86]	France	0.66 (0.18-1.47)	0.66 (0.31-2.06)
	Republic of Ireland	0.73 (0.09-2.12)	0.57 (0.09-0.65)
	The Netherland	0.54 (0.08-1.72)	0.53 (0.04-1.98)
	Spain	0.53 (0.21-1.16)	0.51 (0.07-1.72)
	Ireland	0.30 ± 0.13	0.25 ± 0.11
Al-Delaimyl et al.[87]	Italy(Varese/Turin)	1.03 ± 0.43	0.90 ± 0.37
	Italy (Florence)	1.01 ± 0.37	0.90 ± 0.36
	Italy (Ragusa/Naples)	1.29 ± 0.46	1.32 ± 0.46
	Greece (Athens)	0.90 ± 0.38	0.87 ± 0.47
	Spain (Granada)	0.69 ± 0.40	0.69 ± 0.33
	Spain (Murcea)	0.66 ± 0.30	0.74 ± 0.35
	Northern Spain	0.53 ± 0.31	0.43 ± 0.29
	UK (vegetarians)	0.98 ± 0.45	0.89 ± 0.44
	UK (Cambridge)	0.72 ± 0.30	0.77 ± 0.38
	Germany (Potsdam)	0.60 ± 0.30	0.69 ± 0.33
	Germany (Heidelberg)	0.62 ± 0.31	0.54 ± 0.25
	The Netherland	0.54 ± 0.33	0.47 ± 0.26
	Denmark	0.58 ± 0.34	0.53 ± 0.29
	Sweeden (Malmo)	0.46 ± 0.24	0.52 ± 0.27
	Sweeden (Umea)	0.56 ±0.37	0.44 ± 0.25
Ozasa et al. [88]	Japan	0.11 (0.04-0.33)	0.20 (0.08-0.52)
Boonsiri et al.[89]	Thailand	0.46 ± 0.33	0.74 ± 0.38

BIOCHEMICAL ROLE

Lycopene as Antioxidant and Its Mechanism of Action

The reactivity of carotenoids, especially lycopene, in biological systems depends on their molecular and physical structure, location or site of action within the cells, ability to interact with other antioxidants, concentration and the partial pressure of oxygen.[90,91] Biologically, lycopene tends to act as singlet oxygen ($^1O_2$) and peroxyl radical scavenger ($LOO^{\bullet}$).[92] Lycopene degradation may result in color loss when exposed to free radicals or oxidizing agents. This is due to the reaction with free radicals and causes interruption of the polyene chain, in which the conjugated double bond system may either be affected by cleavage or addition to one of the double bonds.[93] The highly conjugated double bonds of lycopene play the most important role in energy transfer reactions.[91,94] Lycopene has quenching ability towards singlet oxygen ($^1O_2$), based on the excited energy state, and is greatly related to the length of the conjugated double bond system.[91] Among the carotenoids, lycopene is the most efficient singlet oxygen quencher.[95,96] The physical quenching rate of lycopene was two times higher than β-carotene and 10 times higher than α-tocopherol.[96] Lycopene has been demonstrated to be the most potent antioxidant with the ranking: Lycopene > α- Tocopherol > α- carotene > β –Cryptoxanthin > Zeaxanthin = β-carotene > lutein.[97] Basically, chain lipid autoxidation reactions can be interrupted by antioxidants such as phenols, vitamin E and flavonoids, which eliminate the lipid peroxyl radicals by donating the hydrogen atom to form lipid peroxide and a resonance-stabilized antioxidant radical.[98] However, as a carotenoid compound, lycopene may scavenge the radicals by other ways. The mechanism of action for lycopene towards the reactive species can be predicted through three possible mechanisms: (1) adduct formation, (2) electron transfer to the radical and (3) allylic hydrogen abstraction[93-100] and is also shown in Fig. 4.

1. Adduct formation: Lycopene + $R^{\bullet}$ ⟶ R-Lycopene$^{\bullet}$

2. Electron transfer: Lycopene + $R^{\bullet}$ ⟶ Lycopene$^{\bullet+}$ + R^-

3. Allylic H abstraction: Lycopene + $R^{\bullet}$ ⟶ Lycopene$^{\bullet}$ + RH

Figure 4: Three Possible Reactions of Carotenoids with Radical Species ($R^{\bullet}$).[93]

Adduct formation is the formation of resonance-stabilized carbon centered-peroxyl radicals where the free radical will attach to the polyene chain, the highly conjugated double bonds of lycopene, to form a lycopene-peroxyl radical adduct (ROO-lycopene$^{\bullet}$).[98,101] This reaction is described in (1) where the lipid peroxyl radical ($ROO^{\bullet}$) reacts with lycopene.

(1) Lycopene + $ROO^{\bullet}$ ⟶ ROO-lycopene$^{\bullet}$

Under high oxygen concentrations, the ROO-lycopene$^{\bullet}$ may possibly react with O_2 to form a new radical (reaction 2). This reaction was reported as reversible and related to the pro-oxidant effect which may occur in carotenoid compounds.[100]

(2) ROO-lycopene$^{\bullet}$ + O_2 ⟷ ROO-lycopene-OO$^{\bullet}$

The pro-oxidant effect of the peroxyl radical-lycopene adduct (ROO-lycopene$^{\bullet}$) can be explained if this compound is further reacted with oxygen forming a new lycopene-peroxyl radical (ROOlycopene-OO$^{\bullet}$).[101] This intermediate species (ROO-lycopene-OO$^{\bullet}$) will subsequently act as a prooxidant or initiator for lipid peroxidation by reacting with lipid (RH) (reaction 3) and forming another peroxyl radical ($ROO^{\bullet}$) with oxygen (O_2) (reaction 4).

(3) ROO-lycopene-OO$^{\bullet}$ + RH ⟶ ROO-lycopene-OOH + $R^{\bullet}$

(4) $R^{\bullet}$ + O_2 ⟶ $ROO^{\bullet}$

However, the peroxyl radical-lycopene adduct may also be terminated in the occurence of another peroxyl radical by forming the inactive end products (reaction 5).[101]

(5) ROO-lycopene$^{\bullet}$ + $ROO^{\bullet}$ ⟶ inactive products

Lycopene is one of the carotenoids prone to oxidation.[99] It is the best antioxidant based on electron transfer reactions.[102] Electron transfer, is the reaction with formation of carotenoid radicals such as lycopene cation radical (lycopene$^{+\bullet}$), anion radical (lycopene$^{-\bullet}$) or alkyl radical (lycopene$^{\bullet}$). Nitrogen dioxide radical ($NO_2^{\bullet}$) from smoking, an environmental pollutant and the powerful oxidant trichloromethylperoxyl ($CCl_3O_2^{\bullet}$) may convert lycopene into radical cations (reaction 6 and 7).[99]

(6) $NO_2^{\bullet}$ + Lycopene ⟶ NO_2^- + Lycopene$^{+\bullet}$

(7) $CCl_3O_2^{\bullet}$+Lycopene ⟶ [CCl_3O_2- Lycopene]$^{\bullet}$ ⟶ $CCl_3O_2^-$+ Lycopene$^{+\bullet}$

In addition, the reaction between lycopene and superoxide radical ($O_2^{-\bullet}$) through electron transfer can form the lycopene anion radical (reaction 8).[103]

(8) Lycopene + $O_2^{-\bullet}$ ⟷ Lycopene $^{-\bullet}$ + O_2

However, hydrogen abstraction is the reaction of carotenoids as hydrogen donor to reduce the radical. The reaction is presented in reaction 9.[100]

(9) Lycopene + $ROO^{\bullet}$ ⟶ Lycopene$^{\bullet}$ + ROOH

Again, the modes of action for antioxidants were depended on their position in the cell.[91] Carotenes such as lycopene lie parallelly with the membrane surface.[104,105] Thus, lycopene is expected to be a poor antioxidant due to its limited interaction with aqueous phase radicals in the lipid bilayer as compared to more polar carotenoids such as zeaxanthin.[91] Besides, high concentration of lycopene in the membranes may cause aggregation that may affect the properties of membrane by leading to increase in membrane fluidity and permeability, and finally will result in pro-oxidant type effects.[106] However, lycopene is still important in inhibiting lipid radicals at membranes as the first defense system of cells. Moreover, a combination of lycopene and other antioxidants is also important in scavenging of reactive species.

INTERACTION OF LYCOPENE WITH OTHER ANTIOXIDANTS

In lipid bilayer of cellular membrane, lycopene is expected to be a poor antioxidant due to its lesser interaction with aqueous phase radicals. However, the role of lycopene as a lipid phase antioxidant should not be neglected. The combinations of lycopene and other antioxidants such as vitamin C, vitamin E and β-carotene has exhibited higher scavenging activity on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical than their individual antioxidant activity.[107] Besides, lycopene combined with other antioxidants also gave a better inhibiting effect towards diene hydroperoxides produced from linoleic methyl ester with 2,2'-azobis (2,4-dimethylvaleronitrile) (AMVN) induced oxidation.[108] Lycopene was also reported to help in repairing the vitamin E radical (reaction 10) and the products from this reaction radical cation will be repaired by vitamin C (reactions 11 and 12).[109]

(10) Lycopene + $TOH^{+\cdot}$ ⟶ TOH + $Lycopene^{+\cdot}$

(11) $Lycopene^{+\cdot}$ + $ASCH_2$ ⟶ Lycopene + $ASCH^{\cdot}$ + H^+

(12) $Lycopene^{+\cdot}$ + $ASCH^-$ ⟶ Lycopene + $ASCH^{\cdot -}$ + H^+

Previously, lycopene was reported to react effectively with vitamin E radical in the lipophilic compartment.[91] Inversely, their reaction with the hydrophilic vitamin C was expected to be less effective.[110] In one study, the author had suggested a model for the synergistic interactions among the antioxidants located in the hydrophilic and lipophilic compartments of plasma. Besides, there might be lycopene-carotenoid interaction in biological system (reaction 13). A study done using multilamellar liposomes showed that lycopene and lutein was the best combination toward AMVN-induced oxidation.[97] Lycopene is the strongest reducing agent and able to reduce the radical cations of lutein and zeaxanthin, but not β-carotene.[111-112]

(13) $Carotenoid^{+\cdot}$ + Lycopene ⟶ Carotenoid + $Lycopene^{+\cdot}$

Different interpretations of reactions between lycopene with vitamin E and vitamin C is also reported.[100,113-114] Lycopene is suggested to protect tocopherol through the electron transfer to form α-tocopheroxyl radical (α-$TO^{\cdot}$) (reaction 14).[115]

(14) α-$TO^{\cdot}$ + Lycopene ⟶ α-TOH + $Lycopene^{+\cdot}$

On the other hand, some researchers suggested that α-tocopherol (α-TOH) could reduce $lycopene^{+\cdot}$ to regenerate the intact lycopene (reaction 15).[93]

(15) α -TOH + $Lycopene^{+\cdot}$ ⟶ α-$TO^{\cdot}$ + Lycopene

However, a different reaction of lycopene radical cation ($lycopene^{+\cdot}$) and α-tocopherol (α-TOH) or δ-tocopheroxyl radical (δ-$TO^{\cdot}$) was also reported[116] as the following reactions (reactions 16 and 17).

(16) α-TOH + $Lycopene^{+\cdot}$ ⟶ α-$TO^{\cdot}$ + Lycopene

(17) δ-$TO^{\cdot}$ + Lycopene ⟶ δ-TOH + $Lycopene^{+\cdot}$

In non-polar solvents, carotenoids will probably react with α-tocopherol radical cation (α-$TOH^{+\cdot}$) rather than with α-tocopherol anion (α-TOH^-) as given in the reaction 18.[93]

(18) α -$TOH^{+\cdot}$ + Lycopene ⟶ α-TOH^- + $Lycopene^{+\cdot}$

However, the reaction between lycopene and ascorbic acid increase the decay rate of $Lycopene^{+\cdot}$ due to the following reaction (reaction 19).[93,100, 117]

(19) $Lycopene^{+\cdot}$ + $AscH^-$ ⟶ Lycopene + $Asc^{\cdot -}$ + H^+

Lycopene in combination with other antioxidants such as vitamins E and C, polyphenols and other carotenoids have wide potential for human health.[118] Recent formulations of antioxidant mixtures in the development of nutritional products have been in favour for their health benefits.[119]

ANTIOXIDATIVE EFFECTS

Of the carotenoids tested, lycopene has been demonstrated to be the most potent *in vitro* antioxidant leading many researchers to conclude that the antioxidant properties of lycopene are responsible for disease prevention.[120]

A study conducted by Anese et al. [121] reported that there is an overall increase of antioxidant potential by heating tomato juice due to the formation of melanoidins during the advanced steps of the maillard reaction. The authors further emphasized that with prolonged thermal treatment, stability and shelf life of tomato derivatives or food products containing tomatoes are improved. However, short time heat treatment results in the depletion of overall antioxidant potential through the formation of compounds with pro oxidant properties. Lavelli et al.[122] studied the radical scavenging activity of fresh and air dried tomatoes by three model reactions and concluded that fresh and air dried tomato extracts could act as radical scavengers both in ROS mediated reaction and in lipid peroxidation. They further stated that drying decreased the ascorbic acid content as well as antioxidant effectiveness as measured in xanthine/xanthine oxidase system, however, retained in the other two systems. Kaur et al.[21] reviewed the antioxidant status of fresh and processed tomato and concluded that tomatoes can be used as a source of food additives for fortification and stabilization; further emphasized its high stability against degradation and isomerization during commercial processing makes it a molecule worth exploitation.

Analysis of the antioxidant status of blood in rats revealed that some antioxidant enzymes such as superoxide dismutase (SOD), glutathione reductase and glutathione peroxidase (GSHPx) can be induced by lycopene and GSH and phase II GST enzymes can be increased.[123-125] Dietary supplementation of lycopene resulted in significant increase in serum levels and decreased TBARS.[126] Furthermore, the serum levels are influenced as a result of oxidative stress in the form of diet induced metabolism and smoking.[127] Tomato powder appeared to be more

protective than lycopene beadlet against the H_2O_2 - induced rise in serum MDA and seemed to lower liver triglycerides more because of its additional ability.[128] Studies suggests that small amounts of tomato juice, tomato puree or other processed tomato products such as juices, soups or pasta sauces added to the diet over a short period can increase carotenoid concentration and the resistance of lymphocytes to oxidative stress[73]; reduces lymphocyte strand breaks ex- vivo induced by H_2O_2 exposure[129]; endogenous strand breaks[130-131] or lymphocyte 8-oxodeoxyguanosine[126] pointing towards the possibility that lycopene provides protection from generalized DNA damage.

Lycopene contains shielding methyl (-CH_3) groups and is optimally positioned in LDL particles by its phytyl side chains; in addition, it protects LDL against peroxidative modification and maintains its ability to act as ligand for LDL receptors.[132] Another study reported that pretreatment of lycopene to γ-irradiated hepatocytes resulted in decreased lipid peroxidation and improved antioxidant status thus prevented the cellular damage by inhibiting peroxidation of membrane lipids and free radicals induced DNA strand break formation.[133] Hadley et al.[134] showed that the consumption of tomato products significantly enhanced the protection of lipoproteins to ex- vivo oxidative stress. In the same vein another study demonstrated that incubation of plasma with lycopene protects LDL from copper induced oxidation reactions.[135]

Age related macular degeneration (AMD), is the leading cause of blindness in the elderly population of the developed world. The retina, especially the macula is exposed to high levels of focused radiant energy in a highly oxygenated environment. The simultaneous presence of light and oxygen together gives the potential for oxygen free radicals and singlet oxygen to be generated. Lycopene protects against experimental cataract development by virtue of its antioxidant properties, and it may be useful for prophylaxis or therapy against cataracts. Lycopene supplementation in enucleated rat lenses culture has significantly ($p < 0.001$) restored glutathione and malondialdehyde levels, superoxide dismutase ($p < 0.05$), catalase and glutathione *S*-transferase ($p < 0.01$). Likewise, another study concluded that dietary tomatoes have a protective effect on oxidative stress and nitrostative stress in retinal pigment epithelium. [136-137]

PREVENTIVE EFFECT OF LYCOPENE TOWARD DISEASES

Several studies have been reported that a diet rich in tomatoes and tomato products containing lycopene, protect against various chronic diseases by mitigating oxidative damage. Dietary lycopene protected lipids, proteins and DNA from oxidation. Such oxidized products have been thought to play an important role in cancer and chronic diseases and have been found to increase significantly in the chronic disease condition. In addition, dietary intake of lycopene decreases the risk of chronic diseases and the serum and tissue levels are inversely related to the risk of these diseases. Several epidemiological studies have been published which show an inverse correlation with tomatoes and lycopene-rich diets and the incidence of several cancers and CHD (Table 6). The beneficial effects are attributed to its antioxidant properties but other mechanisms like modulation of intercellular gap junction, communication, hormonal and immune system, metabolic pathways may also be involved (Fig. 5).[78,127,138-139]

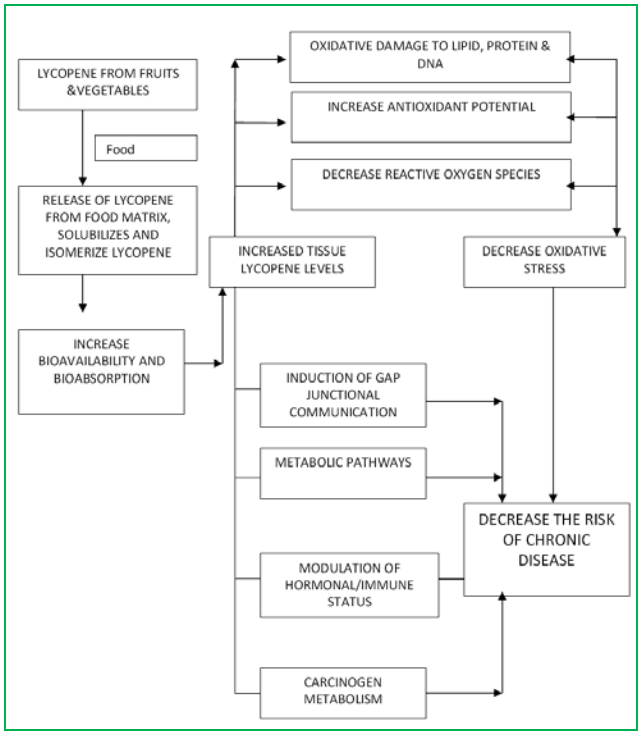

Figure 5: Proposed role of lycopene in human health

Cancer

The evidence in support of lycopene in prevention of chronic diseases comes from epidemiological studies[140-143] as well as tissue culture studies using human cancer lines[144-146], animal studies[76,147] and also human clinical trials.[148]

Of all the cancers, the role of lycopene in the prevention of prostate cancer has been studied the most. Prostate cancer is the most common malignancy and cause of death in men. Although genetic factors and age are important determinants of the risk, environmental exposures, including diet are increasingly being associated with the disease. A follow up met analysis of 72 different studies showed that lycopene intake as well as serum lycopene levels were inversely related to several cancers including prostate, breast, cervical, ovarian, liver and other organ sites.[142] Several other studies since then demonstrated that with increased intake of lycopene and serum levels of lycopene the risk of cancers were reduced significantly.[149-151] Rao et al.[152] studied the status of oxidative stress and antioxidants in prostate cancer patients and the results showed significant differences in levels of serum carotenoids, biomarkers of oxidation and prostate specific antigen (PSA) levels. Although there were no differences in the levels of β-carotene, lutein,

cryptoxanthin, vitamin E and A between cancer patients and their controls, levels of lycopene were significantly lower in cancer patients. The PSA levels were significantly elevated in cancer patients who also had higher levels of lipid and protein oxidation indicating higher levels of oxidative stress in cancer patients. Furthermore, lycopene is utilized to minimize lipid oxidation suggesting that low levels of lycopene in cancer cases were caused by the disease rather than the cause of the disease.[152] Lycopene was shown to decrease the levels of PSA as well as the growth of prostate cancer in newly diagnosed cancer patients receiving 15 mg of lycopene daily for 3 weeks prior to radical prostactomy.[149,153] Studies indicate that regular consumption of lycopene rich food has been reported to be associated with 30 to 40% lower risk of prostate cancer.[143] Another study reported that feeding tomato sauce, providing 30 mg lycopene/day for 3 weeks preceding prostatectomy in men diagnosed with prostate cancer significantly elevated serum and prostate lycopene levels.[154] Oxidative damage to DNA was reduced and serum PSA declined significantly by 20% with lycopene treatment.

In pilot studies with cancer patients, daily ingestion of lycopene from tomato sauce or tomato extract inhibited tumor growth and invasiveness and decreased the growth of prostate cancer perhaps by up regulating connexin 43 (Cx43) (tumor suppressor protein).[155] Similarly, Heber and Lu [156] reported that studies of human and animal cells have identified a gene, connexin 43, whose expression is up regulated by lycopene and that allow direct intercellular gap junctional communication (GJC). GJC is deficient in many human tumors and its restoration or upregulation is associated with decreased proliferation.

In the same manner several animal studies have confirmed the inverse association between dietary lycopene and growth of both spontaneous and transplanted tumors.[157-158] It has been found to inhibit proliferation of several types of cancer cells including those of breast, lung and endometrium and suppress insulin like growth factor I stimulated growth.[159] Moreover, it inhibits growth and development of KB-I human oral tumor cells[160] and C-6 glioma cells transplanted into rats.[161] Nkondjock *et al.,*[162] suggested that a diet rich in tomatoes and tomato based products with high lycopene content may help to reduce the risk of pancreatic cancer. Investigations have indicated that dietary lycopene (10 ppm) significantly reduced the lipid and protein oxidation and demonstrated an apparent protective effect against azoxymethane induced colonic preneoplastic lesions in rats.[78]

Overall epidemiological studies, in vitro tissue culture studies, animal studies and some human intervention studies are showing that increased intake of lycopene will result in increased intake of lycopene will result in increased circulatory and tissue levels of lycopene. *In vivo*, lycopene can act as a potent antioxidant and protect cells against oxidative damage and thereby prevent or reduce the risk of several cancers. Further studies are needed to get further proof and to gain better understanding of the mechanisms involved.

Cardiovascular Diseases

Cardiovascular disease (CVD) affects the normal function of the cardiovascular system involving heart and blood vessels. It is the major cause of deaths in western world and an important contributor of morbidity and mortality in developing countries. The World Health Organization (WHO)[163] reported that CVD is the world's largest killer, claiming 17.1 million lives a year. Tobacco use, unhealthy diet, physical inactivity and high intake of alcohol increase the risk of CVD. Plasma low density lipoprotein (LDL) is the major risk factor of CVD. Increase in LDL oxidation is hypothesized to be causally associated with increasing risk of atherosclerosis and coronary heart disease. Cumulative evidences in literature support the role of lycopene in the prevention of cardiovascular diseases (CVD).[132,164-166] Arab and Steck[132] stated that it has a protective effect against intimal wall thickness and myocardial infarction. The authors proposed that some other mechanism beside its antioxidant effect may be responsible for the protective effect. Similarly, Rissanen et al.[167] concluded that low plasma lycopene concentration is associated with early atherosclerosis and increased intima media thickness of common carotid artery wall (CCA-IMT).

Serum cholesterol levels have traditionally been used as a biomarker for the risk of CHD. Oxidation of the circulating low density lipoprotein (LDL), which carries cholesterol into the blood stream, to oxidized LDL (LDLox) is also thought to play a key role in the pathogenesis of arteriosclerosis which is the underlying disorder leading to heart attack and ischemic strokes.[168-170] Owing to its lipophilic nature, lycopene concentrates in LDL and VLDL fractions and not in HDL fractions.[75] It has been shown to significantly reduce the levels of oxidized LDL and lipid peroxidation in subjects consuming tomato sauce, tomato juice and lycopene oleoresin capsules[113] and also protects native LDL from oxidation *in vitro*.[135] Studies *in vitro* and *in vivo* have shown that lycopene can suppress cholesterol synthesis by inhibiting 3-hydroxy-3-methyl glutaryl coenzymeA (HMG Co A).[132,171] Ahuja *et al.*,[172] reported that the diet high in olive oil and rich in lycopene decreased the risk of CHD by improving the serum lipid profile as compared to high carbohydrate and low fat diet.

Although epidemiological studies have provided convincing evidence in support of the protective role of lycopene in CVD. These observations need to be validated by conducting well controlled human intervention studies in future.

Other Diseases

Since the recognition of lycopene as a potent antioxidant and its preventive role in oxidative stress mediated chronic diseases, researchers are beginning to investigate its role in other human diseases. Male infertility, a

common reproductive disorder is now being associated with oxidative damage of the sperm leading to the loss of its quality and functionality. Significant levels of ROS are detectable in the semen of up to 25% of infertile men where as fertile men do not produce detectable levels of ROS in their semen.[180,181] Researchers are beginning to investigate the role of lycopene in protecting sperm from oxidative damage leading to infertility. Studies show that men with antibody mediated infertility were found to have lower serum lycopene levels than their fertile controls.[182] In another study, a significant increase in serum lycopene concentration and improvement in sperm motility, sperm motility index, sperm morphology and functional sperm concentration was observed in infertile men when supplemented with 8 mg lycopene for 12 months. Furthermore, it was found lycopene treatment resulted in 36% successful pregnancies.

Oxidative stress may contribute to the pathogenesis of skeletal system including osteoporosis, the most prevalent '*metabolic bone disease'*. Lycopene has a stimulatory effect on cell proliferation and the differentiation marker alkaline phosphatase of osteoblasts as well as inhibitory effects on osteoclasts formation and resorption. There have been results of a possible decrease in bone turnover and oxidative stress markers and an increase in antioxidant status in postmenopausal women taking tomato juice or lycopene capsules. Thus lycopene plays a role in bone health and provides dietary alternative to drug therapy for women who are at risk of osteoporosis.[183-187]

Hypertension, a *'silent killer,'* is a disorder in which symptoms are not observed until a more advanced and a fatal stage is reached. The antioxidant property of lycopene has attracted scientific research into its protective role in hypertension. A recent study showed lycopene supplementation of 15 mg/ day for 8 weeks significantly decreased systolic blood pressures from baseline values to 144mm Hg to 134 mm Hg in mildly hypertensive subjects. In another study a significant reduction in plasma lycopene was observed in the hypertensive patients compared to normal subjects. Recognizing the importance of antioxidants in the management of hypertension a 'dietary approach to control hypertension (DASH)' diet is recommended that contains substantially higher levels of lycopene along with other carotenoids, polyphenols, flavanols, flavanones and flavan-3-ols. [188-191]

Brain is a vulnerable organ for oxidative damage due to high levels of oxygen uptake and utilization, high lipid content and low antioxidant capacity. Rao and Balachandran [192] suggested the role of lycopene in neurodegenerative diseases including Alzeheimers disease**.** Lycopene was shown to cross the blood brain barrier and be present in central nervous system (CNS) in low concentration. Significant reduction in the levels of lycopene was reported in patients suffering from Parkinson's disease and vascular dementia.[193] Likewise, Suganuma et al. [194] reported that tomato ingestion might serve as a preventive therapy against neurodegenerative diseases such as Parkinson's disease caused by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and other environmental toxins. Moreover, it was also suggested to provide protection against amyotrophic lateral sclerosis (ALS) disorder in humans.[195]

Intake of tomatoes was also inversely and significantly associated with respiratory infections.[196]A study showed protective role of lycopene in the prevention of emphysema in a mouse model. At a conference held to deliberate on the role of processed tomatoes in human health, data was provided for the protective role of lycopene in the prevention of emphysema in Japanese population.[197]

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It is reported that persons with a high intake of carotene reduce the incidence of risk of cataract[200] and the relationship between nuclear cataract and intakes of α-carotene, β-carotene, lutein, lycopene and cryptoxanthin stratifying by gender and by regular multivitamin use.[201] It has been reported that lycopene prevents cataractogenesis *in vivo* and *in vitro* by virtue of its antioxidant properties.[136] In previous studies, it was found that lycopene prevented sugar-induced diabetic cataract.[202]

In a prospective study, Fawazi *et al.,*[196] found that an intake of tomatoes for 2-3 days compared with zero days was associated with significant reduction in mortality (48%) and with a reduced risk of death associated with diarrhoea.

Several findings indicate that lycopene is an important part of the human organism's natural defense mechanism that protects us from harmful oxidizing agents. Lower serum lycopene levels were also reported in human immuno deficiency virus (HIV) positive women and children.[203-204]

Undoubtedly, future research will also explore the role of lycopene in other human diseases including diabetes, rheumatoid arthritis, periodontal diseases and inflammatory disorders.[151] Antioxidant potential of lycopene are opening up new applications in

pharmaceutical; neutraceutical and cosmoceutical products and can prevent the progression of many human diseases at an early stage and improve the quality of life.[205] Treatment of lycopene (1, 2 and 4 mg/kg; p.o.) in streptozotocin-induced diabetic rats has significantly attenuated cognitive deficit, increased acetylcholinesterase activity, oxidative-nitrosative stress and inflammation.[206] The treatment of lycopene using 3-nitropropionic acid-induced rats has significantly improved the memory and restored glutathione system functioning.[207] Akbaraly et al.[208] also suggested that low plasma lycopene levels could contribute to cognitive impairment. The list of lycopene effect on improvement of other disease impairments is shown in Table 7.

Table 6: Epidemiological studies involving lycopene and lycopene-containing foods in chronic diseases

Disease	Major Conclusion	Reference
Prostate Cancer	Intake of tomato products inversely associated with prostate cancer	Giovannucci et al. [140] Clinton et al. [83]
Digestive Tract Cancer	Reduced risk with high tomato intake	Franceschi et al.[173]
Bladder Cancer	Serum lycopene associated with decreased risk	Helzlsour et al.[174]
Skin Cancer	Decrease in skin lycopene on exposure to light	Ribago-Mercado et al. [175]
Breast Cancer	Serum lycopene associated with decreased risk	Dorgan et al. [176]
Cervical Cancer	Lycopene level showed inverse risk	Sengupta and Das [177]
Cardiovascular Disease	Adipose tissue lycopene associated with lower risk, low serum lycopene with increased mortality.	Kohlmeier et al.[178] Kristenson et al. [179]

Table 7: Action of lycopene in improving the impairment of other diseases[221]

Lycopene doses	Method	Impairment	Improvement
0.2 mg/kg b.w. daily	*In vivo*–rats	Cataract	Significant delay in onset and progression of galactose cataract and reduced the incidence of selenite cataract.[136]
2.5, 5 and 10 mg/kg b.w. daily	*In vivo*–rats	Cognitive function	Significant improvement in memory.[207]
60 mg/kg b.w. daily	*In vivo*–hyperlipemia rabbits	Lipid peroxidation injury	Significant reduction in the levels of serum TG and MDA, increased serum SOD activity, increase serum NO[209]
0.1, 0.5, 1, 2 g/kg b.w. daily	*In vivo*– mouse ear oedema model	Swelling	Decreased swelling of the croton oil-induced ear.[210]
0, 5 and 10 µg/mL Carried by liposomes	*In vitro*–Calu-3 cells	Inflammation of cells infected by rhinovirus or exposed to lipopolysaccharide	Reduced the release of interleukin-6 and interferon-gamma induced protein-10.[211]
8 or 16 mg/kg/day by i.p. injection	*In vivo*–murine model of asthma	Ovalbumin-induced inflammation	Significant inhibition of the infiltration of inflammatory immunocytes into the bronchoalveolar lavage.[212]
2 mg twice daily	In vivo–primigravida women	Pre-eclampsia and Intrauterine growth retardation	Significant reduction in pre-eclamsia incidence and intrauterine growth retardation in the lycopene group compared to placebo group.[213]
9 mg/kg b.w. twice a day for 2 weeks	*In vivo*–rats	Chronic bacterial prostatitis	Significant decrease in bacterial growth and improvement of prostatic inflammation.[214]
0.025–2 mg per 20 mg b.w.	*In vivo*–white heterozygote mouse	X-ray radiation lesions	Moderate curative effect on the radiation lesions and increased survival rate.[215]

The scientific interest to explore innovative strategies for the prevention of human diseases underlines the common etiological and mechanistic nature of these diseases. The fact that oxidation of cellular components as an initial event eventually leading to the incidence of several diseases brings the focus to the use of antioxidants. Lycopene by acting as an antioxidant can prevent the progression of many human diseases at an early stage and improve the quality of life

DAILY INTAKE LEVEL ESTIMATION AND SUGGESTED LEVELS OF INTAKE

Reports about the daily intake levels of lycopene have varied significantly due to the methods of estimation used. In general they range from 3.7 to 16.2mg in United States of America, 25.2 mg in Canada, 1.3mg in Germany, 1.1mg in United Kingdom and 0.7mg in Finland.[216] However, it is important to note that close to half of the population in North America is estimated to consume less than 2mg of lycopene per day. It is evident that the average intake levels of lycopene are lower than required to provide its beneficial effects. Although the beneficial effects of lycopene in the prevention of human diseases have been well documented it is not yet recognized as an essential nutrient. As a result there is no official recommended nutrient intake (RNI) level set by health professionals and government regulatory agencies. However based on reported studies a daily intake level of 5-7mg in normal healthy human beings may be sufficient to maintain circulating levels of lycopene at levels

sufficient to combat oxidative stress and prevent chronic diseases.[55] Under the condition of disease such as cancer and cardiovascular diseases, higher levels of lycopene ranging from 35 to 75mg per day may be required.[148]

SAFETY EVALUATION

The safety aspect of bioactive compounds in products has been received much attention from food scientists to avoid any side effects. Either synthetic lycopene or from natural sources have been reported to be safe (Generally Recognized as Safe, GRAS) when used in as food additive.[217] Several studies have been conducted to evaluate acute toxicity, sub chronic and chronic safety as well as reproductive effects and genotoxicity.Long back a single dose of 3g/kg crystalline (unformulated) lycopene by various routes was administered. There were no adverse effects with orally or intraperitoneally administered lycopene. However, a transient decrease in body tone was observed when lycopene was given subcutaneously. Furthermore, up to 3g/kg/day of formulated lycopene exhibited no effects on body weight, hematology, blood chemistry, ophthalmologic variables or histology in rats.[218-219] Similarly when a dog was given 100mg/kg/day of crystalline lycopene for 6 months, no abnormal histological, hematological or variables were observed. [217]

Consumption of 1g/kg/day of formulated lycopene during gestation resulted in no signs of maternal toxicity or teratogenic effects in rats. Furthermore, there was no mutagenic activity for formulated lycopene. However, the degradation products of crystalline lycopene formed by the exposure to light and air were shown to exhibit some mutagenic activity.[219] A study reported that high intake of lycopene containing food, (~2L of tomato juice daily for several years) resulted in orange discolouration of skin lycopenemia. Although there were deposits of lycopene and fatty deposits in the liver but there was no hepatic dysfunction. Moreover, the discoloration faded after 3 weeks by consuming a diet free of tomato juice. Thus, there are no adverse effects and it is safe to consume dietary or formulated lycopene.

Thus, with its broad spectrum of potential applications to human health, lycopene is being considered as a functional ingredient having neutraceutical properties. The emerging area of complementary healthcare offers many opportunities for food products containing compounds such as lycopene would be of great interest to the food related industries as well as to public health organizations. However, the aspect calls for purposeful investigations.[220]

FUTURE DIRECTIONS

Consumers' demand for healthy food products provides an opportunity to develop lycopene-rich products as new functional foods, as well as food-grade and pharmaceutical-grade lycopene as new nutraceutical products. An industrial-scale, environment friendly lycopene extraction and purification procedure with minimal loss of bioactivity is highly desirable for the food, feed, cosmetic, and pharmaceutical industries. High-quality lycopene products that meet food safety regulations will offer potential benefits to the food industry. The current dietary recommendation to increase the consumption of fruits and vegetables rich in antioxidants has generated interest in the role of lycopene in disease prevention. However, the evidence thus far is mainly suggestive, and the underlying mechanisms are not clearly understood. Further research is critical to elucidate the role of lycopene and to formulate guidelines for healthy eating and disease prevention. More information on lycopene bioavailability, however, is needed. The pharmacokinetic properties of lycopene remain particularly poorly understood. Areas for further study include epidemiological investigations based on serum lycopene levels, bioavailability and effects of dietary factors, long-term dietary intervention studies, metabolism and isomerization of lycopene and their biological significance, interaction with other carotenoids and antioxidants, and mechanism of disease prevention.

As research on lycopene is becoming intensive and reaching logical conclusions in various aspects, there is a concomitant need to undertake application based research endeavours to make this gold nugget of neutraceutical nature reach out to the masses for enhancing health and ameliorate disease.

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