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Tomato Lycopene: Functional Proprieties and Health Benefits

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***Abstract*—**The growing concerns for physical wellbeing and health have been reflected in the way we choose food in our table. Nowadays, we are all more informed consumers and choose healthier foods. On the other hand, stroke, cancer and atherosclerosis may be somehow minimized by the intake of some bioactive compounds present in food, the so-called nutraceuticals and functional foods. The aim of this work was to make a revision of the published studies about the effects of some bioactive compounds, namely lycopene in human health, in the prevention of diseases, thus playing the role of a functional food. Free radical in human body can induce cell damage and consequently can be responsible for the development of some cancers and chronic diseases. Lycopene is one of the most powerful antioxidants known, being the predominant carotenoid in tomato. The respective chemistry, bioavailability, and its functional role in the prevention of several diseases will be object of this work. On the other hand, the inclusion of lycopene in some foods can also be made by biotechnology and represents a way to recover the wastes in the tomato industry with nutritional positive effects in health.

***Keywords*—**Tomato, lycopene, bioavailability, functional foods, carotenoids, cancer and antioxidants.

I. Introduction

THE recognition that nutrients play an important role in the ability to interact and modulate molecular mechanisms and physiological functions is recognized by many authors.! Epidemiological studies have shown inverse associations of chronic disease not only with dietary fruit, vegetable and carotenoid intake but also with circulating concentrations of carotenoids [1].

Several studies correlated Mediterranean diet pattern with a greater longevity and reduced mortality and morbidity for coronary heart disease (CHD), certain cancers and other nutrition-related diseases [1], [2]. These claims have been studied over epidemiological studies, biochemical investigations and though the examination of the… bioavailability of bioactive compounds from several diets. Nevertheless, defining the term Mediterranean diet is a great challenge given the broad geographical distribution of the Mediterranean countries and the ethnic, cultural, religious, and economic variations among them. Despite these facts, there is a dietary pattern characteristic of this diet. It is a diet rich in fruits, vegetables, bread, cereals, olive oil as the major source of fat, low to moderate amounts of fish and poultry and alcohol. Red meat plays a very small role [3]. An important feature of the Mediterranean diet is the combination of olive oil with tomatoes in food preparation. Tomatoes and tomato products are typical components of the Mediterranean diet. Epidemiological studies have associated tomato consumption with a decreased risk of prostate cancer [4] and cardiovascular health (CVD) [5]. Literature also reports that the tomato protective action is commonly attributed to lycopene. However, tomato products are also sources of other compounds such as vitamins A, B, and E and it is not yet clear which individual compounds present in tomato impart these potential benefits or whether other constituents of tomatoes and tomato products produce beneficial effects [5].

Given the scope of literature published on the potential health benefits of lycopene in the diet, herein we review chemistry, sources, intake, bioavailability and toxicity of lycopene. In addition, we summarize the literature that correlates lycopene with health and discuss the most promising directions for future lycopene research and possible important uses in our diet.

II. Lycopene Chemistry and Sources

More than 600 carotenoids are found in Nature and these are predominantly colorful molecules, built by plants, fungi and bacteria undergoing photosynthesis. They are widespread in vegetables and fruits [6]. Carotenoids consist in two groups: the highly unsaturated hydrocarbons consisting of lycopene, α, β-, and γ-carotene form 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 lack oxygen, whereas xanthophylls, in contrast, consist of at least one oxygenated group on their terminal rings [7]. Modifications of the main structure of the carotenoid like cyclization of terminal groups and insertion of oxygen functions, lead to different types of carotenoids with changes in colors and with different antioxidant qualities [8], [9].

Lycopene, a representative of the hydrocarbon carotenoid with the molecular formula of $C_{40}H_{56}$, has an acyclic open-chain structure consisting of 13 double-bonds. The double bonds are subject to isomerization and various cis isomers (mainly 5, 9, 13, or 15) are found in plants and also in blood plasma [10]. (Fig. 1) The thermodynamically most stable configuration of lycopene is the all-*trans*-isomer. Indeed, heat, light or several chemical reactions can induce isomerization from the *trans*-isomer to various mono- or poly-*cis* forms [11]. Two of them are non-conjugated and eleven are conjugated

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double bonds, thereby building a chromophore responsible for the characteristic ruby color and the antioxidant properties of lycopene [13]. As the human body does not synthesize carotenoids endogenously, diet is the only way of getting these compounds.

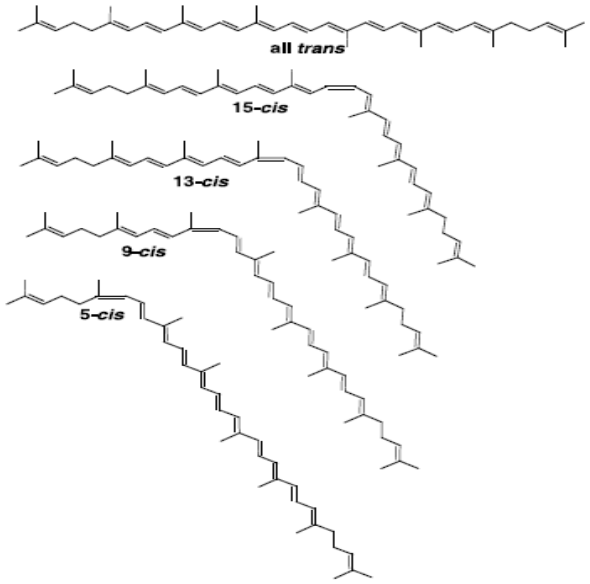

Fig. 1 Structure of the *cis* and *trans* isomers of lycopene [12]

A. Lycopene Sources

Dietary lycopene is derived predominately from tomato and tomato products. Lycopene content varies greatly in different varieties of tomatoes [14] although other dietary sources include apricots, guava, pink guava, watermelon, papaya, pink grapefruit, rosehips and apricots (Table I).

TABLE I
LYCOPENE CONTENT OF FOODS [14]

Food	Content (mg/100g)
Fresh tomatoes	0.88-4.20
Cooked tomatoes	3.70
Tomato sauce	6.20
Tomato paste	5.40-150.00
Ketchup	9.90-13.44
Dried apricot	0.86
Pink grapefruit	3.36
Guava	5.40
Watermelon	2.30-7.20
Papaya	2.00-5.30

Lycopene intake differs considerably among countries and among populations within the same country. According to dietary surveys, regular intakes of lycopene from natural dietary sources in different populations in Europe are estimated to be on average between 0.5 and 5 mg/day, with high intakes up to about 8 mg/day. High consumption of fruits and vegetables, especially tomato products, may result in occasional intakes of 20 mg lycopene/day or more. It was shown that about 50–65% of the total exposure to lycopene (excluding lycopene added as a novel food ingredient) was originating from natural sources. Based on data from France, tomatoes, soups (other than tomato soups) and pasta dishes, and from UK, pasta dishes, tomato sauces and tomato ketchup were the most important natural sources [15]. However, differences in the lycopene intake between countries were observed. It was shown that adults in Spain consume less lycopene (1.64 mg/day) compared to adults from France, UK, Republic of Ireland or the Netherlands where the intake was from 4.43 to 5.01 mg/day. When we considered the total daily intake of tomato products in Italy represents up to 175 g, in Spain up to 65 g and England about 30 g [16], [17].

III. LYCOPENE BIOAVAILIBILITY

The beneficial health effects of dietary carotenoids have made the study of their bioavailability, absorption and metabolism an area of considerable interest, since humans cannot synthesize these molecules *de novo* and must obtain them from the diet.

Lycopene bioavailability can be affected by a number of factors: 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 [18].

The effects of processing and storage on lycopene structure and stability are of interest for a number of reasons. Improper processing and storage (i.e., exposure to light and oxygen) may alter the ratio of lycopene isomers or degrade lycopene entirely, making these food products less desirable to the consumer [19]. Isomerization of lycopene affects its absorption efficiency. 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 [20].

Traditional commercial processing methods do not have a significant effect on lycopene levels or on cis/trans isomerization. In fact, thermal processing generally improves lycopene bioavailability by disrupting cellular membranes, which allows lycopene to be released from the tissue matrix. Multiple studies have shown that lycopene from thermally processed tomato products is more bioavailable than lycopene from fresh tomatoes [21], [22]. However and according to [23], the absolute amount of lycopene absorbed seems to be more dependent on inter-individual differences rather than on its dose.

The interaction between the carotenoids in the ingested food influences the absorption of individual carotenoids [24].

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. Lycopene bioavailability is greatly affected by dietary composition. Given that lycopene is a lipid-soluble compound, consuming it with fat increases its bioavailability. For example, consuming salads with full-fat dressing results in higher blood carotenoid levels than eating salads with reduced

fat dressing. When salads were consumed without fat [25] in the same study, no measurable lycopene uptake occurred. A study by [26] showed a similar result, whereby the consumption of tomato salsa with avocado (as lipid source) led to a 4.4-fold increase in lycopene absorption as compared with salsa without avocado. Also carotenoid–protein complexes are denatured by the cooking of vegetables and may impact bioavailability from the food matrix. The studies performed by Fabian and Elmadfa in a group of 17 women who consumed probiotics for a total of 4 weeks also demonstrate that lycopene absorption may be affected by probiotics [27]. Further [28] reported that human blood carotenoid levels are influenced by SNPs in apolipoproteins A-IV and B, which are associated with lipid transport.

Age may be another factor affecting lycopene absorption. The bioavailability of lycopene was less in those 60–75 years of age compared to those 20–35 [29]. Interestingly, there was no major difference in the bioavailability of β-carotene, α-carotene, and lutein. Porrini et al. suggested the eating behavior of different individuals makes the lycopene level vary among people [30]. Recently, a study reported that plasma lycopene level could be diverged among married, non-married and divorced subjects [31].

A schematic of lycopene digestion and absorption is shown in Fig. 2. Once ingested, lycopene must first be released from the food matrix before it is incorporated into mixed micelles. Micelles contain bile salts, cholesterol, and fatty acids from the meal, and the amphiphilic nature of the micelle structure helps to keep the lipophilic nutrients soluble in the aqueous digesta. The micelles approach the unstirred water layer of the apical side of the intestinal cells (enterocytes), and lycopene passively diffuses across the apical membrane [32]. Historically, researchers believed that lycopene was absorbed by the same route as dietary lipids, i.e., passive diffusion and this is still believed to be at least partially true. However, in the past five years, investigators have discovered that lycopene absorption can be facilitated by a cholesterol membrane transporter known as scavenger receptor class B type I (SR-BI). Research has also suggested that lycopene absorption may be facilitated by other transporters, but this has not yet been confirmed [33]. Once inside the enterocyte, lycopene is packaged with other dietary lipids into chylomicrons (Chylomicrons are then transported across the basolateral membrane and make their way into the lymphatic system, which eventually releases chylomicrons into the blood [34].

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. The distribution of lycopene in human organs and plasma has been reported by [20] 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; 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. A review by [35] quoted that lycopene concentrations in human tissues are around 0.15–21.36 nmol/g tissue, but not detectable in brainstem tissue. 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. Zaripheh et al. [36] 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 [37].

Ross et al. also indicate that lycopene or its metabolites are transported to skin and may remain there for several days before being turned over [38].

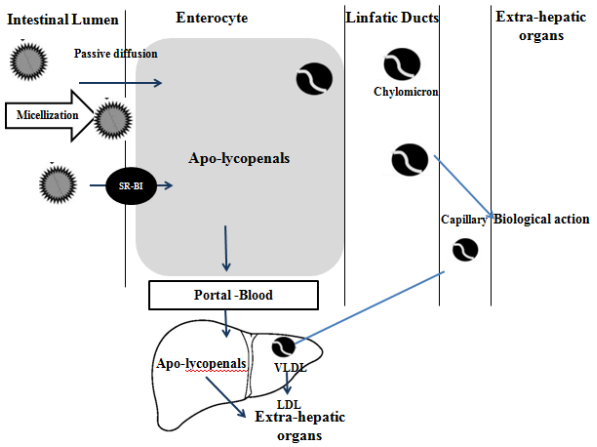

Fig. 2 Schematic illustration of digestion and absorption of lycopene in the small intestine

IV. Lycopene Toxicity

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 [39].

The toxicity of the carotenoids found in observational studies or in intervention studies seems to be dependent of the several parameters. When the dose of *β*-carotene was higher than those in fruits and vegetables: the activity of carotenoids can be shifted from antioxidant to prooxidant according to their concentration, partial pressures of oxygen, or interactions with other co-antioxidants (i.e., vitamins E and C) [39]. Furthermore, as the dietary *β*-carotene is formed by several isomers like 9-cis and all-trans, it maybe that the 9-cis *β*-carotene provides more 9-cis retinoic acid than all-trans *β*-carotene with a subsequent more powerful result on the lipid profile [40]. In Fig. 3 we show the prooxidant effects of carotenoids, explaining the conditions that can make their

effects harmful. Also, cigarette smoke has been invoked as a pro-oxidant, and it has been suggested that in the presence of high concentrations of β-carotene, cigarette smoke might led to oxidative destruction of β-carotene, resulting in the formation of oxidized metabolites that might facilitate carcinogenesis [41]. It is unclear whether there is an interaction between smoke and lycopene metabolism, as exists for beta -carotene, and whether the function of lycopene is organ specific. That is, lycopene may protect against prostate cancer, but might also interact with tobacco smoke to produce undesirable degradative products of lycopene that could have unexpected adverse effects in other tissues (e.g., lung). The detrimental effects of lycopene may be related to the lycopene dose administered *in vivo*, the accumulation of lycopene in a specific organ, the interaction of lycopene with tobacco and alcohol, the lycopene metabolites, and their effects on cell signaling pathways and molecular targets [42].

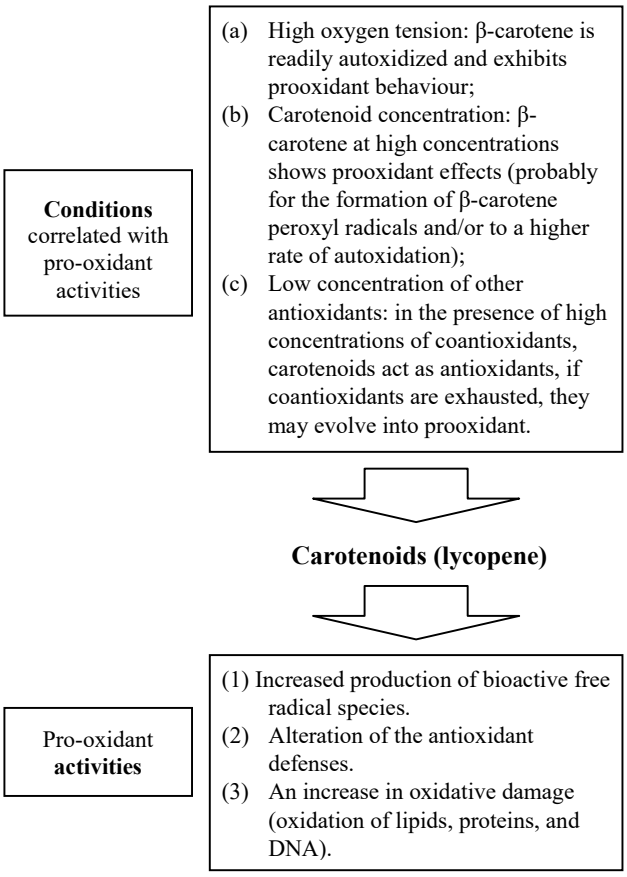

Fig. 3 Prooxidant activity of carotenoids (lycopen) [104]

The possible beneficial or adverse effects of carotenoids as pro-oxidant molecules in health should not be considered only by their mechanism of action. Numerous gaps still exist in our understanding of the role of carotenoids as pro-oxidants. Many of the results on the pro-oxidant activity of carotenoids have been demonstrated only *in vitro*. Our knowledge of the influence of carotenoids as pro-oxidants *in vivo* remains fragmented and incomplete. Moreover, the products of carotenoids directly responsible for their pro-oxidant activity have not been identified yet. Improved knowledge of the pro-oxidant role of carotenoids *in vivo* will help in understanding their potential role in health and disease.

V. Functionality of Lycopene

The consumer interest in the role of specific foods or physiologically active food components, the called functional foods that improve health, has increased significantly. It should be noted that the category of "functional food" is still not legally recognized in Europe. These are classified as "new foods" by UE Regulation nº258/97 of the European Parliament and Council and defined as “foods that contain substances that provide specific functional beneficial effect on health and consumer wellbeing (affecting one or more functions body) that may reduce the risk of contracting a particular disease”. During the last decade, however, the functional term applied to food has adopted a different connotation which is to provide additional physiological benefit, other than the one to satisfy the basic nutritional requirements [9], [10].

A. Oxidative Stress vs Chemical Structure

Oxidative stress is recognized as one of the major contributors to the increased risk of cardiovascular disease and cancer. Among the common carotenoids, lycopene is known as the most potent antioxidant, demonstrated by *in vitro* experimental systems [11]. Carotenoids seem to have the ability to disable singlet oxygen and Mascio, Kaiser and Sies showed that among the carotenoids, lycopene acts by the deactivation of the singlet oxygen [11]. This capacity of deactivation of the singlet oxygen $1O_2$ occurs by physical and chemical pathways being the physical way the predominant (99.05%) [43], [44].

Physical deactivation involves the transfer of energy from the $1O_2$ for the carotenoid, generating O_2 (to the fundamental state) and the carotenoid stays in an excited triplet state. The energy absorbed by carotenoid is dissipated by vibrations and rotations and remains intact at the end of the process, being fit for new deactivation.11 of the 13 conjugated double bonds (Fig. 2) develop a key role for the lycopene antioxidant activity [43]. This ability of the carotenoid depends on the number of double conjugated bonds and of the carotenoid terminal groups.

Several authors have demonstrated that lycopene can have positive effects in health. Researchers have postulated that many chronic diseases, cardiovascular diseases, cancer, diabetes, eye diseases, and aging itself are the result of long-term oxidative stress [6], [46]. The lycopene antioxidant function can also explain the observations made in a recent European multicenter study in which the carotenoid levels in adipose tissue were inversely associated with the risk of myocardial infarction [44].

B. Lycopene as Antioxidant and Its Mechanism of Action

Oxidative stress is recognized as one of the major contributors to the increased risk of cardiovascular disease and cancer. Among the common carotenoids, lycopene is known as the most potent antioxidant, demonstrated by *in vitro*

experimental systems [11]. The reactivity of carotenoids, especially lycopene, in biological systems depends not only of their molecular and physical structure but is affected by their location or site of action within the cells, ability to interact with other antioxidants, concentration and the partial pressure of oxygen [18], [47]-[49].

Due to its polyene structure, providing an electron-rich system, lycopene is an eligible target for electrophilic reagents. Thus, it performs an uttermost reactivity towards oxygen and free radicals [45]. 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 [50].

Carotenoids or lycopene, respectively, act as antioxidants through several mechanisms. Highly reactive oxygen species, also named singlet oxygen ($^1O2$), which are able to oxidize nucleic acids, unsaturated fatty acids or amino acids, can be quenched by carotenoids/lycopene exerting the reaction stated below [39]:

$$^1O2 + LYC \rightarrow {}^3O2 + {}^3LYC$$
$$^3LYC \rightarrow LYC + heat$$

The exceeding amount of energy, the lycopene molecule gained in this reaction reaching the triplet state, is dispensed through vibrational, as well as rotatory interactions with the solvent, resulting in the release of thermal energy. Once more, the extensive conjugated polyene structure of lycopene is responsible for this reaction. As the molecule re-establishes its ground state immediately, another $^1O2$ quenching cycle can be activated, thereby providing the possibility of each single carotenoid-molecule to quench about 1000 molecules of $^1O2$ [45]. 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 as it can be seen in Fig.4: (1) adduct formation, (2) electron transfer to the radical and (3) allylic hydrogen abstraction and is also shown:

1. Adduct formation: Lycopen + $R^{\bullet}$ → R-Lycopene $^{\bullet}$
2. Electron transfer : Lycopen + $R^{\bullet}$ → R-Lycopene $^{\bullet\bullet}$ + R^{-}
3. Allylic H abstraction: Lycopen + $R^{\bullet}$ → R-Lycopene $^{\bullet}$ + RH

Fig. 4 Mechanism of action for lycopene

Lycopene and other carotenoids are known for their antioxidant activities towards inhibiting free radical reactions. Peroxyl radicals are built in the organism during the process of lipid peroxidation, which can lead to destruction of lipophilic sections. Inactivation of these reactive species results in the development of radical adducts that build a resonance-stabilized carbon centered radical. The carotenoid oxidation products include formation of epoxides located at the β-ionone ring, as well as located at the central double bond of the conjugated polyene chain. More products of this reaction are the formation of ketones and aldehydes at the β-ionone ring. Inhibition of these radical reactions by lycopene may shelter membranes from lipid peroxidation [50].

C. 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 [51]. 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 [52]. Lycopene was also reported to help in repairing the vitamin E radical and the products from this reaction radical cation will be repaired by vitamin C. Previously, lycopene was reported to react effectively with vitamin E radical in the lipophilic compartment [39].

A study done using multilamellar liposomes showed that lycopene and lutein was the best combination toward AMVN-induced oxidation [52]. Lycopene is the strongest reducing agent and is able to reduce the radical cations of lutein and zeaxanthin, but not β-carotene [53].

Lycopene in combination with other antioxidants such as vitamins E and C, polyphenols and other carotenoids have wide potential for human health [54]. Recent formulations of antioxidant mixtures in the development of nutritional products have been in favor for their health benefits [55].

D. 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.

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 [56].

At a physiological concentration of 0.3μmol/l, lycopene has been shown to inhibit growth of non-neoplastic human prostate epithelial cells *in vitro*, through cell cycle arrest which may be of significant implications in preventing benign prostate hyperplasia, a risk factor for prostate cancer. [57]. Lycopene has also been shown to significantly reduce LNCaP human prostate cancer cell survival in a dose-dependent manner, and this antineoplastic action may be explained by increased DNA damage at high lycopene concentrations (>5 μM), whereas lower levels of lycopene reduced malondialdehyde formation, with no effects on DNA [58]. Physiologically attainable concentrations of lycopene have been shown to induce mitochondrial apoptosis in LNCaP human prostate cancer cells, although no effects were observed on cellular proliferation or necrosis [59]. Animal

studies have shown antineoplastic effects of both tomato powder and purified lycopene supplementation. Boileau et al. [60] reported a significant inhibition of *N*-methyl-*N*-nitrosourea –testosterone- induced carcinogenesis in male Wistar-Unilever rats following consumption of tomato powder (13 mg lycopene/kg diet), whereas no effects were observed with lycopene supplementation *per se* (161 mg lycopene/kg diet). This study suggests the synergistic effects of lycopene with other antioxidants in tomatoes, in exerting an antineoplastic effect [60]. However, in the Dunning rat prostate cancer model, a 4-week supplementation with a higher concentration of lycopene beadles (4 g lycopene/kg diet), revealed significant downregulation of 5-μ-reductase, reduced steroid target genes expression and prostatic insulin-like growth factor-1 (IGF-1) and interleukin-6, thereby causing a subsequent reduction in the growth of tumor tissue [61]. Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. FASEB J). As evident from *in vitro* and animal studies, purified lycopene may inhibit prostate cancer growth only at higher concentrations, in comparison with tomato antioxidant supplementation. Karas et al. have further reported inhibitory effects of lycopene on MCF7 human mammary cancer cell growth, owing to interference in IGF-1 receptor signaling and cell cycle progression [62]. Thus, interference in androgen metabolism, and inhibition of growth factors and cytokine activity, appear to be the major pathways through which lycopene inhibits prostate and breast cancer growth. Tomato lycopene supplementation (1.1 mg/kg/day corresponding to 15 mg lycopene intake in a 70 kg person) has also been shown to prevent the change in p53, p53 phosphorylation and p53 target genes, induced by cigarette smoke exposure in the gastric mucosa of ferrets. This further suggests a protective effect of lycopene against the development of gastric cancer [63]. Studies using human and animal cells have identified a gene, connexin 43, correlated with reduced indexes of neoplasia, and whose expression is upregulated by lycopene and which allows direct intercellular gap junctional communication, thereby reducing the rate of proliferation [64]. Lycopene has also been shown to interfere in lipid metabolism, lipid oxidation and corresponding development of atherosclerosis. Lycopene treatment has been shown to cause a 73% suppression of cellular cholesterol synthesis in J-774A.1 macrophage cell line, and augment the activity of macrophage LDL receptors. Oxidized LDLs are highly atherogenic as they stimulate cholesterol accumulation and foam cell formation, initiating the fatty streaks of atherosclerosis [65]. LDL susceptibility to oxidative modifications is decreased by an acyl analog of platelet-activating factor (PAF), acyl-PAF, which exerts its beneficial role during the initiation and progression of atherosclerosis. Purified lycopene in association with μ-tocopherol or tomato lipophilic extracts has been shown to enhance acyl-PAF biosynthesis in endothelial cells during oxidative stress [66]. Fuhrman et al. [67] further reported comparative data in which tomato oleoresin exhibited superior capacity to inhibit *in vitro* LDL oxidation in comparison with pure lycopene, by up to fivefold. A combination of purified lycopene (5 μmol/l) with μ-tocopherol in the concentration range of 1–10 μmol/l resulted in a significant greater inhibition of *in vitro* LDL oxidation, than the expected additive individual inhibitions. In this study, purified lycopene was also shown to act synergistically with other natural antioxidants like the flavonoid glabridin, the phenolic rosmarinic acid and carnosic acid, and garlic in inhibiting LDL oxidation *in vitro*. These observations suggest a superior antiatherogenic characteristic of tomato oleoresin over pure lycopene. The combination of lycopene with other natural antioxidants, as in tomatoes, may be more potent in inhibiting lipid peroxidation, than lycopene *per se*.

When considering the effects of a dietary component on health, it is difficult to separate the effect of a single compound from that of multiple compounds found in whole foods and whole diets. If lycopene in tomatoes does affect health, is it the major active component, or does it act synergistically with other bioactive compounds in tomatoes (provitamin A, flavonoids, vitamin C, fiber, etc.). In fact, tomato flavonoids, including rutin, quercetin, naringenin, have been reported to have potential health effects. Quercetin and rutin have been shown to reduce IGF-1-induced prostate cell proliferation *in vitro*. Quercetin has been shown to reduce neutrophil-induced LDL oxidation [68]. Naringenin chalcone from tomato skin has also been shown to produce anti-inflammatory effects in mice [69]. These studies provide evidence that flavonoids may play a role in the health effects of tomatoes and tomato products. Other studies have demonstrated that glycoalkaloids present in tomato also produce multiple biological effects. In addition, recent research has suggested that water soluble components of tomatoes may reduce platelet aggregation, a risk factor for cardiovascular disease [70] although the components present in this fraction have not been clearly identified. Likewise, some authors have suggested that blood levels of lycopene and other carotenoids are simply indicative of a diet that includes fruits and vegetables. A growing body of evidence indicates that whole foods may be more effective than individual compounds for lowering disease risk [71]. Several studies have shown that the antioxidant effects of supplementation of tomato products or purified lycopene (providing 6–17 mg lycopene/day), on cellular DNA, in healthy human volunteers [72]. However, effects on lipid peroxidation have been somewhat conflicting. Riso et al. observed no effects on lymphocyte resistance from lipid oxidation, following a 3-week supplementation of tomato products (8 mg lycopene/day) [73]. Lycopene and vitamin C concentrations increased in plasma and lymphocytes after tomato intake. Null effects on lipid peroxidation in plasma and feces in healthy men following a 2-week supplementation of 330 ml/day of tomato juice were also reported by [74]. Supplementation of a diet low in carotenoids with tomato or carrot juice does not affect lipid peroxidation further supplemented healthy male volunteers with 15 mg of natural tomato lycopene extracts for 12 weeks, and reported no effects on LDL oxidizability [75]. In comparison with these studies showing null effects of tomato lycopene supplementation on lipoprotein oxidation,

[76] reported a 18% increase in LDL lag time in 23 healthy men, following a 2-week tomato juice consumption providing a higher dose of lycopene (40 mg/day). It should also be noted that following a 2-week carotenoid depletion period, the plasma lycopene levels in these healthy volunteers were reduced to a concentration of 0.16 μmol/l of all-*trans* lycopene and 0.15 μmol/l of *cis*-lycopene [76]. Rao and Shen (2002) also reported a significant decrease in serum lipid peroxidation and protein oxidation in healthy volunteers, following a 2-week consumption of tomato ketchup or oleoresin capsules, with baseline serum lycopene levels less than 0.2 μmol/l [77]. These baseline plasma lycopene levels were lower than those reported by [74] and [75] in their studies (0.34, 0.2 and 0.63 μmol/l, respectively. Thus, there may be a possibility that a depleted baseline lycopene level shows a better response to tomato antioxidant supplementation, than subjects with higher values. Kiokias and Gordon [78] reported a significant decrease in biomarkers of oxidative stress in young healthy volunteers, following a 3-week supplementation of lycopene, in combination with other natural carotenoids. Hadley et al. reported a significant decrease in lipoprotein oxidizability in healthy elderly subjects, following a 15-day dietary intervention with tomato products [79]. As oxidized lipoproteins have been related to the pathogenesis of CVD, consumption of tomato products may exert a protective effect against oxidative stress in healthy elderly adults.

LDL oxidation has been shown to be reduced by paraoxonase (PON) an enzyme bound to high-density lipoprotein (HDL) and may therefore attenuate the development of atherosclerosis. A recently reported study by Bub et al. involving a 2-week supplementation of tomato juice (37 mg of lycopene/day) showed a reduced lipid peroxidation in healthy men carrying the R-allele of the PON1-192 genotype, compared to QQ subjects [80]. These volunteers with the QR/RR genotype also showed an increased lipid peroxidation at baseline as compared to QQ subjects. These studies reveal that the dose and duration of tomato lycopene supplementation, the synergistic action of lycopene with natural carotenoids, the baseline plasma levels of lycopene, the choice of biomarkers of oxidative stress and gene polymorphisms affecting the rate of oxidative stress are critical factors in modulating the response to antioxidant supplementation, containing lycopene, in healthy volunteers.

Few studies have been reported on the effects of tomato or lycopene supplementation on oxidative stress-associated diseases. Upritchard et al. showed a protective effect of 500 ml/day of tomato juice consumption on lipoprotein oxidation (42% increase in LDL lag time) in well-controlled type II diabetic patients [81].

This study also confirms the synergy among tomato antioxidants, including lycopene, in reducing lipid peroxidation, as reported by *in vitro* data [82]. As patients with type II diabetes are at an increased risk of developing coronary heart disease, and oxidized LDLs have been shown to contribute to this risk of arterial disease [83] tomato product supplementation maybe of potential benefit in these patients. Tomato lycopene consumption in patients before prostatectomy has been reported in few studies to lower prostate DNA oxidative damage, serum prostate-specific antigen, and cause an overall reduction in disease aggressiveness [84]. Tomato product or purified lycopene supplementation has previously been shown to decrease oxidative damage in cellular DNA in healthy volunteers [85]. Although purified lycopene has not been tested in prostate cancer patients, the substantial amount of lycopene accumulating in the prostate tissue in these patients, as reported by the clinical studies, may partially explain the role of lycopene *per se* in the reduction of prostate DNA damage and biomarkers of prostate carcinogenesis. However, further clinical trials with lycopene alone will determine its prostate-specific anticarcinogenic effects, versus those with tomato products, and might then indicate the possible use of lycopene as complementary therapy for prostate cancer and other types of cancer.

VI. Potential Health Benefits of Lycopene

The study of the effects of lycopene in a wide range of diseases (namely various cancers and CVD) has been subject of several studies over the past decades.

Not all carotenoids show anticancer effects; next we make a brief summary of these data relating recent human studies examining lycopene's biological effects on some disease processes

A. Cancer

The consumption of tomato and tomato products has been associated with a reduced incidence of a number of different types of cancers, most notably prostate, lung, and stomach [86].

Regarding prostate cancer and the benign prostatic hyperplasia (BPH) some of the strongest epidemiological evidences support an association between tomato product consumption and a reduced incidence of prostate cancer namely made by the Health Professionals Follow-Up Study (HFPS). A prospective observational study made by [86] collected food frequency questionnaire (FFQ) data from the HPFS group of 47,365 men in 1986, 1990, and 1994. The intake of ≥2 servings of tomato sauce per week was associated with a reduced risk of prostate cancer [relative risk (RR) = 0.77 relative to <1 serving of tomato sauce per month, Ptrend < 0.001.

Ford et al. made a study in 2011 that lycopene significantly reduced the proliferation of DU145 cells (human prostate cancer cells) at a supraphysiological concentrations (15and 25 μM) but not at physiological concentrations (>2 μM). The effects of lycopene on the proliferation of DU145 cells were also investigated in 3 previous studies. Two of those studies demonstrate that supraphysiological doses reduced proliferation, while one found no changes in proliferation with physiological concentrations (16,19,21). The proliferation results of this study were in alignment with previous *in vitro* findings [87].

Collectively, these studies suggest that the consumption of lycopene or lycopene-containing foods reduces the risk for

developing prostate cancer. In contrast, other observational studies (Barber and Barber; Campbell) have found weak inconclusive evidence supporting a link between prostate cancer or BPH and lycopene intake [88], [89].

Since 1999, at least 12 clinical trials have examined the relationship between tomato products or lycopene containing supplements and prostate cancer. Most of these studies measured prostate specific antigen (PSA). Consumption of tomatoes and tomato products daily (target intake level 25 mg/day lycopene) for eight weeks reduced serum PSA levels in 34% of the subjects [90].

In contrast to the clinical trials showing a reduction in PSA levels as a surrogate marker for prostate cancer status, some studies observed [91] a weak effect of tomato consumption or lycopene supplementation on prostate cancer risk.

Epidemiological evidence has suggested that consumption of lycopene containing foods may decrease risk for breast cancer [92].

A study made by Cui et al. stated that lycopene consumption [93] was inversely associated with estrogen and progesterone receptor positive breast cancer risk in postmenopausal women (n = 84,805) followed for an average of 7.6 years (RR = 0.85 for highest quartile of intake as compared with lowest quartile of intake, Ptrend = 0.064). Two case-control studies comparing the dietary habits of women with and without breast cancer also observed a significant decrease in the odds ratio of those who consumed the highest amount versus the lowest amount of dietary lycopene.

A randomized, placebo-controlled, double-blind, crossover trial conducted by Voskuil et al. determined that tomato-extract supplementation (Lyc-o-Mato®, 30 mg/day lycopene) for two months in premenopausal women with a high breast cancer risk (n = 36) reduced free insulin-like growth factor-I (IGF-I) by 7.0% ($p < 0.05$) [94].

Despite these promising reports, it is difficult to directly relate available experimental data to human pathophysiology.

A limitation of cell culture studies is the extremely hydrophobicity of lycopene, which is an obstacle for conducting cell culture studies. Since lycopene is insoluble in water, steps must be taken to enhance its solubility in cell culture media or buffers before *in vitro* studies may be carried out [95].

The meta-analysis by Gallicchio et al. summarizes the relation between lycopene and lung cancer [96].

Few studies have investigated the effect of lycopene on pancreatic cancer. Early evidence has suggested that increased levels of serum lycopene were associated with a reduced risk of pancreatic cancer

After adjustment for age, province, BMI, smoking, educational attainment, dietary folate, and total energy intake, lycopene provided mainly by tomatoes, was associated with a 31% reduction in pancreatic cancer risk among men [odds ratio (OR) = 0.69; 95% CI: 0.46-0.96; P = 0.026 for trend] when comparing the highest and lowest quartiles of intake. Both beta-carotene (OR = 0.57; 95% CI: 0.32-0.99; P = 0.016 for trend) and total carotenoids (OR = 0.58; 95% CI: 0.34-1.00; P = 0.02 for trend) were associated with a significantly reduced risk among those who never smoked. The results of this study suggest that a diet rich in tomatoes and tomato-based products with high lycopene content may help reduce pancreatic cancer risk [97].

There is a limited number of epidemiological studies that have been done regarding lycopene and ovarian cancer. A recent meta-analysis suggested the potential role of dietary lycopene against the risk of ovarian cancer among postmenopausal women, which provided an opportunity for developments in the prevention of ovarian cancer. This study demonstrated an insignificant reverse association between dietary lycopene and ovarian cancer risk (OR, 0.963; 95% CI, 0.859–1.080), and subgroup analysis stratified by study design, location, histological type of ovarian cancer, and length of dietary recall showed no statistically significant results. No heterogeneity was observed ($p = 0.336$, $I2 = 11.6\%$) [98].

B. Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) is the leading cause of death in the majority of the developed countries.

Increased plasma lycopene levels have been associated with reductions in CVD risk and have also been reported to improve biomarkers associated with CVD. Bohm developed a project named Lycocard that provided information on the connection between the consumption of lycopene and/or tomato products and the risk of heart illnesses. He found that there was a missing link in the chain of developing healthy new foods and nutritional guidelines that could bring evidences of this positive interaction [99].

Some clinical trials have also supported a relationship between cardiovascular disease and lycopene intake.

Gajendragadkar et al. [100] studied the mechanisms by which a 'Mediterranean diet' reduces cardiovascular disease (CVD) and tried to investigate the effects of lycopene on the vasculature in CVD patients and separately, in healthy volunteers (HV). They demonstrated, in a double blind, randomised, controlled mechanistic trial, that lycopene improves endothelial function in CVD patients but not in age-matched, healthy volunteers. They also reinforced the need for a healthy diet to augment endothelial function in at-risk populations despite optimal medical therapies.

Although studies on the ability of lycopene to modify cancer and CVD risk are most prevalent, there have been numerous other diseases that have also been investigated in relation to lycopene consumption. These conditions include ultra violet (UV)-induced sunburn, gingivitis, osteoporosis, mental disorders, and asthma. Thus, it can be concluded that moderate amounts of whole food-based supplementation (2–4 servings) of tomato soup, tomato puree, tomato paste, tomato juice or other tomato beverages, consumed with dietary fats, such as olive oil or avocados, leads to increases in plasma carotenoids, particularly lycopene. The recommended daily intake of lycopene has been set at 35 mg that can be obtained by consuming two glasses of tomato juice or through a combination of tomato products. These foods may have both chemopreventive as well as chemotherapeutic values as

outlined in Fig. 5. In the light of recent clinical trials, a combination of naturally occurring carotenoids, including lycopene, in food sources and supplements, is a better approach to disease prevention and therapy, versus a single nutrient. Lycopene has shown distinct antioxidant and anticarcinogenic effects at cellular levels, and definitely contributes to the health benefits of consumption of tomato products.

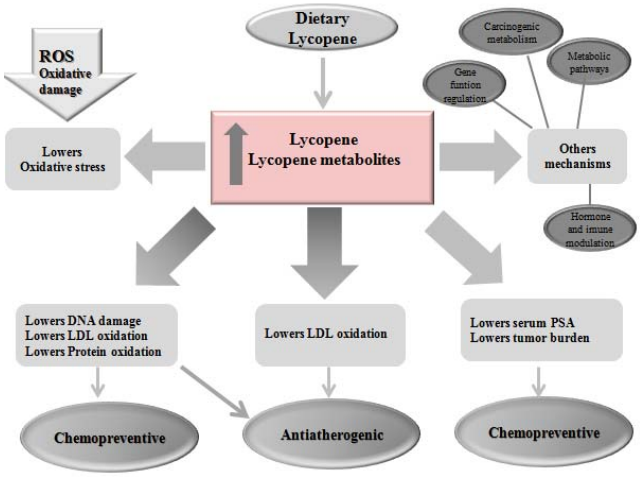

Fig. 5 Summary of potential mechanisms by which lycopene and its metabolites prevent chronic diseases and cancer

The use of biotechnology has introduced a new vision to agriculture and health bringing innovation and offering efficient and cost-effective means to produce various products and tools.

Metabolic engineering and/or breeding has recently been used specially in tomato fruits to increase nutritional quality of some products [101]. The tomato processing industry originates large amounts of waste, especially in the form of seeds and peels. These products remain unused and can aggravate environmental pollution. As the tomato peel is rich in lycopene, the direct addition of the shell to food can be a way to use this by-product and get a new product enriched with lycopene [102].

The fact is that the American Heart Association Diet and Lyfestyle recommendations [103] suggest the inclusion in dairy diet of approximately 2-4 daily doses of fruit and vegetables. Despite of this, the consumed values are incredibly lower. To overcome this problem, metabolic engineering can improve by fortification the doses and the role of dietary phytonutrients in diet, turning into the recommended healthy values.

VIII. Conclusion

This work was helpful to recognize importance of lycopene in our meals. A higher intake of fruit and vegetables can help to prevent numerous cancers, heart diseases, stoke, among others. However, more information is needed to clarify the relation between the intake of single nutrients, such as carotenoids, and the risk of some diseases because it is difficult to undertake a meta-analysis or conduct a detailed systematic review about the real health effects of carotenoids in human body since the results are frequently ambiguous. Nevertheless, the addition of tomato products to diet seems to bring health benefits, namely cooked tomato products containing oil, or supplements of tomato extract suspended in oil.

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