Chapter 20

The Anti-Atherogenic Effects of Lycopene

Amany M. M. Basuny

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1. Introduction

Cardiovascular diseases (CVD) are one of the leading causes of death in world. Many epidemiological studies have concluded that a diet rich in fruits and vegetables reduces the incidence of heart disease in humans (Khachik *et al*., 2002). Carotenoids are important photochemical those are considered to be responsible for the health protective effects of fruits and vegetables (Omoni & Aluko, 2005). The carotenoids are a group of over 600 fat soluble pigments that are responsible for the natural yellow, orange, and red colors of fruits and vegetables (Giovannucci, 2002). Lycopene is one of such carotenoids, and is the pigment principally responsible for the distinctive red color of ripe tomato (*Lycopersicon esculentum*) and tomato products (Shi, 2000). Several epidemiological studies have suggested that a high consumption of tomatoes and tomato products containing lycopene may protect against CVD (Wu *et al*., 2003). These epidemiological leads have stimulated a number of animal model studies designed to test this hypothesis and to establish the beneficial effects of lycopene. Evidence from these studies suggests that lycopene has anti-atherogenic effects both in vitro and in vivo. The focus of this chapter is the anti-atherogenic effects of lycopene. This chapter will also highlight the chemical composition of lycopene, its sources and function, as well as potential impact an human health.

2. Sources and function of lycopene

Animals and humans do to not synthesize lycopene, and thus depend on dietary sources. Tomatoes and tomato products are the major dietary sources of lycopene. Other sources include watermelon, pink grapefruit, apricots, pink guava and papaya (Willis & Wians, 2003). Lycopene is the most abundant carotenoid in ripe tomatoes, comprising approximately 80-90% of the pigments present. The amount of lycopene in fresh tomatoes depends on the variety, maturity, and environmental conditions in which the fruit matures (Shi, 2000).

Source	Lycopene content (mg/100g wet basis)
Tomatoes fresh	0.72 – 20
Tomato juice	5.00 – 11.60
Tomato sauce	6.20
Tomato paste	5.40 – 15.00
Tomato soup	7.99
Ketchup	9.90 – 13.44
Pizza sauce	12.71
Watermelon	2.30 – 7.20
Pink guava	5.23 – 5.50
Pink grapefruit	0.35 – 3.36
Papaya	0.11 – 5.30
Carrot	0.65 – 0.78
Pumpkin	0.38 – 0.46
Sweet potato	0.02 – 0.11
Apricot	0.01- 0..05

Table 1. shows the lycopene content of tomatoes, some commonly consumed tomato products and other lycopene containing fruits and vegetables.

Lycopene is also widely distributed in the human body. It is one of the major carotenoids found in the human serum (between 21 and 43% of total carotenoids) with plasma levels ranging from 0.22 to 1.06 nmol/ml (Cohen, 2002). It is also found in various tissues throughout the body such as the liver, kidney, adrenal glands, tests, ovaries and the prostate gland (Basu & Imrhan, 2006). Unlike other carotenoids like α-and β-carotene, lycopene lacks the β.:onone rang structure common to other carotenooids (Agarwal & Rao, 2000). Although it lacks provitamine an activity, lycopene is known to be a potent antioxidant (Livny *et al.*, 2002). Reactive oxygen (ROS) species have been implicated in playing a major role in the causation and progression of several chronic diseases. These ROS are highly reactive oxidant molecules that are generated endogenously through regular metabolic activity. They react with cellular components, causing oxidative damage to such critical cellular biomolecules as lipids, proteins and DNA. Antioxidants are protective agents that inactive ROS and therefore, significantly delay or prevent oxidative damage associated with chronic disease risk. Lycopene is one of the most potent antioxidants among the dietary carotenoids and may help lower the risk of chronic diseases including cancer and heart disease.

3. Chemical composition of lycopene

Lycopene is a lipophelic, 40-carbon atom highly unsaturated, straight chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds. The all-trans isomer of lycopene is the most predominant isomer in fresh tomatoes and is the most thermodynamically stable from (figure 1). The many conjugated double bonds of lycopene make it a potentially powerful antioxidant, a characteristic believed to be responsible for its beneficial effects. The antioxidant

activity of lycopene is high light by its singlet oxygen-quenching property and its ability to trap peroxy1 radicals. This singlet quenching ability of lycopene is twice as high as that of β-carotene and 10 times higher than that of α-tocopherol and butylated hydroxyl toluene.

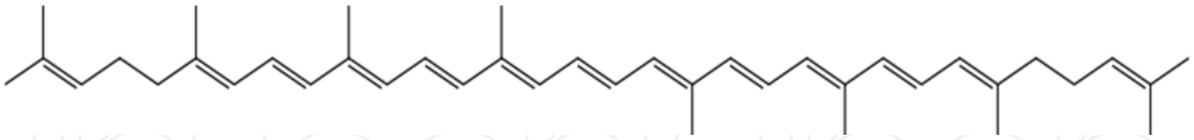

Figure 1. All-*trans* Lycopene.

As a result of the 11 conjugated carbon-carbon double bonds in its backbone, lycopene can theoretically assume 211 or 2048 geometrical configurations (Omani & Aluko, 2005).

However, it is now known that the biosynthesis in plants leads to the all-*trans*-form, and this is independent of its thermodynamic stability. In human plasma, lycopene is an isomeric mixture, containing at least 60% of the total lycopene as cis- isomers (Kim *et al.,* 2012).

All-*trans*, 5-*cis*, 9-*cis*, 13-*cis*, and 15-*cis* are the most commonly identified isomeric forms of lycopene with the stability sequence being 5-*cis*>all-*trans*>9-*cis*>13-*cis*>15- *cis*>7-*cis*>11-*cis*, (Agarwal & Rao, 2000) so that the 5-*cis*-form is thermodynamically more stable than the all-*trans*-isomer. Whereas a large number of geometrical isomers are theoretically possible for all-*trans* lycopene, according to only certain ethylenic groups of a lycopene molecule can participate in *cis-trans* isomerization because of steric hindrance. In fact, only about 72 lycopene *cis* isomers are structurally favorable. Figure 2 illustrates the structural distinctions of the predominant lycopene geometrical isomers.

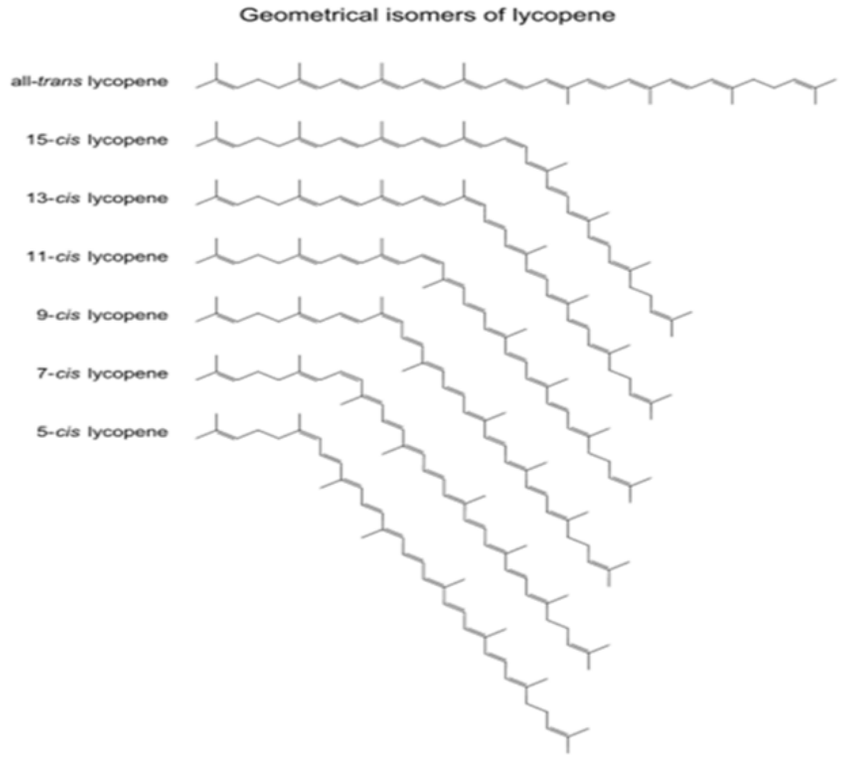

Figure 2. Geometrical isomers of lycopene

4. Mechanisms action of lycopene

A cellular and molecular study have shown lycopene to be one of the most potent antioxidants and has been suggested to prevent atherogenesis by protecting critical bimolecules such as DNA, proteins, lipids and low density lipoproteins (Pool-zobel *et al.*, 1997). Lycopene, because of its high number of conjugated double bonds, exhibits higher singlet oxygen quenching ability compared to β-carotene or α-tocopherol (Di-Mascio *et al.*, 1989). Cis lycopene has been shown to predominate in both benign and malignant prostate tissues, suggesting a possible beneficial effect of high cis-isomer concentrations, and also the involvement of tissue isomerases in vivo isomerization from all trans to cis form (Clinton *et al.*, 1996). Where as Levin *et al.*, (1997) have shown that 9- cis- β-carotene is a better antioxidant than its all-trans counterpart, no such mechanistic data have been reported in case of individual lycopene isomers. Handley *et al.*, (2003) reported a significant increase in 5-cis lycopene concentrations following a 1- week lycopene-restricted diet, and a subsequent reduction in 5-cis, and a concomitant increase in cis-β, cis-D and cis-E lycopene isomers during the 15-day dietary intervention with tomato products in healthy individuals. Although this study reported a decrease in LDL oxidizability due to the intervention with tomato lycopene, the individual antioxidant role of lycopene isomers and their inter conversions remain unclear. At a physiological concentration of 0.3 μmol/1, 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 (Obermuller-Jevic *et al.*, 2003). Lycopene has also been shown to significantly reduce LNCaP human prostate cancer cell survival in a dose-dependent manner, and this anti-neoplastic action may be explained by increased DNA damage at high lycopene concentrations (> 5μm), whereas lower levels of lycopene reduced malondialdehyde formation, with no effects on DNA (Hwang & Bowen, 2005). 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 (Hantz *et al.*, 2005). 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 37% suppression of cellular cholesterol synthesis in J-774A.1 macrophage cell line, and augment the activity of macrophage LDL receptors (Fuhrman *et al.*, 1997). Oxidized LDLs are highly atherogenic as they stimulate cholesterol accumulation and foam cell formation, initiating the fatty streaks of atherosclerosis (Libby, 2006). LDL susceptibility to oxidative modifications is decrease by an acyl analog of platelet-activating (PAF), acyl-PAF, which experts its beneficial role during the initiation and progression of atherosclerosis. Purified lycopene in association with α-tocopherol or tomato lipophillic extracts has been shown to enhance acyl-PAF biosynthesis in endothelial cells during oxidative stress (Balestrieri *et al.*, 2004). Fuhrman *et al.*, (2000) 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 (5μmol/I) with α-toopherol in the concentration range of 1-10μmol/I 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 phenolics rosmarinic acid and carnosic acid, and garlic acid in inhibiting LDL oxidation in vitro. These observations suggested a superior antiatherogeneic 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. The antiatherogenic effects of lycopene are generally believed to be due to its antioxidant properties. Dietary lycopene increases blood and tissue lycopene levels and acting as an antioxidant, lycopene traps reactive oxygen species and reduce the oxidative damage to lipids (lipoproteins and membrane lipids), proteins including important enzymes, and DNA, therapy lowering oxidative stress. This reduced oxidative stress then leads to a reduced risk for chronic diseases associated with oxidative stress such as cardiovascular disease (Omani & Aluko 2005). Alternatively, some non-oxidative mechanisms may be responsible for the beneficial effects of lycopene. The increased lycopene status in the body may regulate gene functions, improve intercellular communication, modulate hormone and immune response, or regulate metabolism, thus lowering the risk for chronic disease (Agarwl & Rao, 2000). A possible mechanism speculated for the protective role of lycopene in heart disease is via the inhibition of cellular HMGCoA reducate, the rate-limiting enzyme in cholesterol synthesis (Fuhrman *et al.,* 1997).

5. Lycopene stability

Being acyclic, lycopene possesses symmetrical planarity and has no vitamin A activity, and as a highly conjugated polyene, it is particularly susceptible to oxidative degradation. Physical and chemical factors known to degrade other carotenoids, including elevated temperature, exposure to light, oxygen, extremes in pH, and molecules with active surfaces that can destabilize the double bonds, apply to lycopene as well (Rao *et al.,* 2003).

In a study to determine the photoprotective potential of dietary antioxidants including lycopene carried out by Handley *et al*., (2003) carotenoids were prepared in special nanoparticle formulations together with vitamin C and/or vitamin E. The presence of vitamin E in the formulation further increased the stability and cellular uptake of lycopene, which suggests that vitamin E in the nanoparticle, protects lycopene against oxidative transformation. Their findings suggest that lycopene stability may be improved by nanoparticle formulation and incorporation of vitamin E in the lycopene formulation.

Badimon *et al.,* 2010 studied the stability of lycopene during heating and illumination. They carried out various pretreatment steps to the all-trans lycopene standard, which included; dissolving the lycopene standard into hexane and evaporating to dryness under nitrogen in vials, after which a thin film formed at the bottom surface. The resulting lycopene was heated at 50, 100, and 150°C or illuminated at a distance of 30 cm with illumination intensity in the range of 2000–3000 lux (25°C) for varied lengths of time (up to100 hours for heating and 5 days for illumination). After analysis, the degradation of total lycopene (all-*trans* plus *cis* forms) during heating or illumination was found to fit a firstorder model. At 50°C, the

isomerization dominated in the first 9 hours; however, degradation was favored afterwards. At 100 and 150°C, the degradation proceeded faster than the isomerization, whereas, during illumination, isomerization was the main reaction. The degradation rate constant (min−1) of lycopene was found to rise with increasing temperature with an activation energy calculated as 61.0 kJ/mol.

The stability of crystalline lycopene was determined under various temperature conditions (5, 25, and 35°C) while stored in airtight containers, sealed under inert gas, and protected from light. After 30 months of storage, crystalline lycopene remained stable when stored under the recommended conditions (Barros *et al.*, 2011).

Lycopene (synthetically prepared by the Wittig reaction) 5% TG (Tablet Grade) and lycopene 10% WS (Water Soluble) beadlet formulations tested for over 24 months of storage, and Lycopene 10% FS (Fluid Suspension) liquid formulation tested for over 12 months of storage under various temperature conditions (5 and 25°C), were all found to be stable.(25) For the 10% WS lycopene beadlet formulations, an important market application form, stability with respect to oxidation under ambient light conditions and room temperature for 12 months in beverages was found to be 93% of the initial content of the beverage lycopene (Pool-zobel *et al.,* 1997).

6. Dietary intake of lycopene

The human body is unable to synthesize carotenoids, which qualifies diet as the only source of these components in blood and tissues. At least 85% of our dietary lycopene comes from tomato fruit and tomato-based products, the remainder being obtained from other fruits such as watermelon, pink grapefruit, guava, and papaya, Tomatoes are an integral part of the human diet and are commonly consumed in fresh form or in processed form such as tomato juice, paste, puree, ketchup, soup, and sauce. Kim *et al.,* (2012) used a tomato products consumption frequency questionnaire to estimate the average daily consumption of different tomato products in the Canadian population.

Di-Mascio *et al.,* (1989) estimated that 50% of the dietary lycopene was obtained from fresh tomatoes, while the average daily intake of lycopene was estimated to be 25 mg in the Canadian population. In a British study conducted with elderly females, the daily consumption of lycopene-rich food, such as tomatoes and baked beans in tomato sauce (measured by weight of foods eaten), was equivalent to a daily lycopene intake of 1.03 mg per person (Omani & Aluko, 2005) developed a database from which the carotenoid intake of the German population, stratified by sex and age, was evaluated on the basis of the German National Food Consumption Survey (NVS). The mean total carotenoid intake amounted to 5.33 mg/day. The average intake of lycopene was 1.28 mg/day with tomatoes and tomato products providing most of the lycopene.

A study presenting data on dietary intake of specific carotenoids in The Netherlands, based on a food composition database for carotenoids, was done by Furhman *et al.,* (1997). Regularly eaten vegetables, the main dietary source of carotenoids, were sampled comprehensively and

analyzed with modern analytic methods. The database was complemented with data from literature and information from food manufacturers. Intake of carotenoids was calculated for participants of the Dutch Cohort Study on diet and cancer, aged 55 to 69 in 1986, and the mean intake of lycopene was 1.0 mg/day for men and 1.3 mg/day for women.

6.1. Bioavailability of lycopene

Although 90% of the lycopene in dietary sources is found in the linear, all-trans conformation, human tissues (Particularly liver, adrenal, adipose tissue, testes and prostate) contain mainly cis-isomers. Hollowy *et al.*, (2002) reported that a dietary supplementation of tomato pure for 2 weeks in healthy volunteers led to a completely different isomer pattern of plasma lycopene in these volunteers, versus those present in tomato pure. 5-cis, 13-cis and 9-cis lycopene isomers, not detected in tomato puree, were predominant in the serum (Hollowary *et al.*, 2000).Analysis of plasma lycopene in male participants in the health professionals follow-up study revealed 12 distinct cis-isomers and the total cis-lycopene contributed about 60-80% of total lycopene concentrations (Wu *et al.*, 2003). Studies conducted with lymph cannulated ferrts have shown better absorption of cis-isomers and their subsequent enrichment in tissues (Boileau *et al.*, 1999). Physiochemical studies also suggest that cis-isomer geometry accounts for more efficient incorporation of lycopene into mixed micelles in the lumen of the intestine and into chylomicrons by the enterocyte. Cis-isomers are also preferentially incorporated by the liver into very low-density lipoprotein (VLDL) and get secreted into the blood (Britton, 1995). Research has shown convincing evidence regarding the isomerization of all trans-lycopene to cis-isomers, under acidic conditions of the gastric juice. Incubation of lycopene derived from capsules with simulated gastric juice for 1-min shown a 40% cis-lycopene content, whereas the levels did not exceed 20% even after 3h incubation with water as a control. However, when tomato puree was incubated for 3h with simulated gastric juice, the cis-lycopene content was only 18% versus 10% on incubation with water. Thus, gastric pH and food matrix influence isomerization and subsequent absorption and increased bioavailability of cis-lycopene (Re *et al.*, 2001).

The process of cooking which releases lycopene from the matrix into the lipid phase of the meal increases its bioavailability, and tomato paste and tomato puree are more bioavailable sources of lycopene than raw tomatoes (Gartner *et al.*, 1997 & Porrini *et al.*, 1998). Factors such as certain fibers, fat substituents, plant sterols and cholesterol-lowering drugs can interfere with the incorporation of lycopene into micelles, thus lowering its absorption (Boileau *et al.*, 2002). Several clinical trials have also shown the bioavailability of lycopene from processed tomato products (Table 2). Agarwal and Rao (1998), reported a significant increase in serum lycopene levels following a 1-week daily, consumption of spaghetti sauce (39mg of lycopene), tomato juice (50mg of lycopene) or tomato oleoresin (75 or 150 mg of lycopene), in comparison with the placebo, in healthy human volunteers. There was also indication that the lycopene levels increased in a dose-dependent manner in the case of tomato sauce and tomato oleoresin. Reboul *et al.*, (2005) further demonstrated that enrichment of tomato paste with 6% tomato peel increases lycopene bioavailability in men, thereby suggesting the beneficial effects of peel enrichment, which are usually eliminated

during tomato processing. Richelle *et al.,* (2002) compared the bioavailability of lycopene from tomato paste and from lactolycopene formulation (Lycopene from tomato oleoresin embedded in a whey protein matrix), and reported similar bioavailability of lycopene from the two sources in healthy subjects. Dietary fat has been shown to promote lycopene absorption, principally via stimulating bile production for the formation of bile acid micelles. Consumption of tomato products with olive oil or sunflower oil has been shown to produce an identical bioavailability of lycopene, although plasma antioxidant activity improved with olive oil consumption, suggesting a favorable impact of monounsaturated fatty acids on lycopene absorption and its antioxidant mechanism (Lee *et al.,* 2000). In an interesting study Unlu *et al.,* (2005) reported the role of avocado lipids in enhancing lycopene absorption. In this study, in healthy, nonpregnant, nonsmoking adults, the addition of avocado oil (12 or 24g) to salsa (300g) enhanced lycopene absorption, resulting in 4.4 times the mean area under the concentration-versus-time curve after intake of avocado-free salsa. This study demonstrates the favorable impact of avocado consumption on lycopene absorption and has been attributed to the fatty acid distribution of avocados (66.00% oleic acid), which may facilitate the formation of chylomicrons. In a comparative study by Hoppe et al., (2003), both synthetic and tomato –based lycopene supplementation showed similar significant increases of serum total lycopene above baseline whereas no significant changes were found in the placebo group. In an attempt to study lycopene metabolism, Diwadkar-Navsariwala *et al.,* (2003) developed a physiological pharmcokinetic model to describe the disposition of lycopene, administered as a tomato beverage formulation at five graded does (10, 30, 60, 90, or 120 mg) in healthy men. Blood was collected before dose administration and at scheduled study intervals until 672h. The overall results of this study showed that independent of dose, 80% of the subjects absorbed less than 6mg of lycopene, suggesting a possible saturation of absorptive mechanisms. This may have important implications for planning clinical trials with pharmacological doses of lycopene in the control and prevention of chronic disease, if absorption saturation occurs at normally consumed levels of dietary lycopene.

6.2. The anti-atherogenic effects of lycopene

In a previous study (Basuny *et al.,* 2006 and 2009) was to study the effect of tomato lycopene on hypercholesterolemia. Lycopene of tomato wastes was extracted and determination. The level of tomato lycopene was 145.50ppm. An aliquots of the concentrated tomato lycopene, represent 100, 200, 400 and 800ppm; grade lycopene (200ppm) and butylated hydroxyl toluene (BHT, 200ppm) were investigated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging method. These compounds were administered to rats fed on hypercholestrolemic diet daily from 10 weeks by stomach tube. Serum lipid contents (total lipids, total cholesterol, high density lipoprotein cholesterol and low density lipoprotein cholesterol), oxidative biomarkers (glutathione peroxidase and malonaldhyde), the liver (aspartate aminotransferase, alanine aminotranseferase and alkaline phosphatase activities) and kidney (uric acid, urea and creatinine) function testes were measured to assess the safety limits of the lycopene in tomato wastes. The data of the aforementioned measurements indicated that the administration of tomato lycopene did not cause any

changes in liver and kidney functions. On the contrary, rats fed on hypercholesterolemic diet induced significant increases in the enzymes activities and the serum levels of total lipids, total cholesterol and low and high density lipoproteins cholesterol and decreased levels of the glutathione peroxidase and malonaldhyde. In conclusion, presently available data from epidemiological and a number of animal studies have provided evidence to suggest that lycopene, the naturally present carotenoid in tomatoes and other fruits and vegetables, possesses anti-atherogenic effects. However, there is a need for more human dietary intervention studies in order to better understand the role of lycopene in human health.

Scientific evidence indicates that oxidation of low density lipoprotein (LDL), which carry cholesterol in the blood stream plays an important role in the development of atherosclerosis, the underlying disorder leading to heart attacks and ischemic strokes (Rao, 2002). Several studies indicate that consuming the antioxidant lycopene that is contained in tomatoes and tomato lycopene products can reduce the risk of cardiovascular diseases (CVD). Available evidence from the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study suggests that the thickness of the innermost wall of blood vessels and the risk of myocardial infarction reduced in persons with higher serum and adipose tissue concentrations of lycopene (Rissanen *et al.*, 2003). This finding suggests that the serum lycopene concentration may play a role in the early stages of atherosclerosis. A thick artery wall is a sign of early atherosclerosis, and increased thickness of the intima media has been shown to predict coronary events. Similarly, the relationship between plasma lycopene concentration and intima-media thickness of the common carotid artery wall (CCA-IMT) was investigation in 520 middle-aged men and women 45-69 years as parts of the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study (Rissanen *et al.*, 2000). Low levels of plasma lycopene were associated with a 17.80% increment in CCA-IMT in men, while there was no significant difference among women. These findings also suggest that low plasma lycopene concentrations are associated with early atherosclerosis, evidenced by increased CCA-IMT in middle-aged men.

Findings from the Rotterdam Study (Klipstein-Grobusch *et al.*, 2000) showed modest inverse associations between levels of serum lycopene and atherosclerosis, assessed by the presence of calcified plaques in the abdominal aorta. Study population comprised of 108 cases of aortic atherosclerosis and 109 controls aged 55 years and over. The association between serum lycopene levels and atherosclerosis was most pronounced among subjects who were current and former smokers. No association with risk of aortic calcification for the serum carotenoids α-carotene, β-carotene, lutein and zeaxanthin was observed. These results suggest that lycopene may play a protective role in the development of atherosclerosis. Results from the European Study of Antioxidant, Myocardial Infarction, and Cancer of the breast (the EURAMIC study) also show that men with the highest concentration of lycopene in their adipose tissue biopsy had a 48% reduction in risk of myocardial information compared with men with the lowest adipose lycopene concentrations (Kohlmeir *et al.*, 1997). An increase in LDL oxidation is known to be associated with an increased risk of atherosclerosis and coronary heart disease (Parthasarathy, 1998). Agarwal and Rao (1998) investigated the effect of dietary supplementation of lycopene on LDL oxidation in 19 healthy human subjects. Dietary lycopene was provided using tomato juice, spaghetti sauce and tomato oleoresin for a

period of 1 week each. Blood samples were collected at the end of each treatment, and TBARS and conjugated dienes were measured to estimate LDL oxidation. In addition to significantly increasing serum lycopene levels by a least twofold, lycopene supplementation significantly reduced serum lipid peroxidation and LDL oxidation. The average decrease of LDL –TBARS and LDL-conjugated diene for the tomato products treatment over placebo was 25 and 13%, respectively. These results suggest significance for lycopene in decreasing risk for coronary heart disease. Results from the ongoing Women's Health Study (WHS) showed that women with the highest intake of tomato-based foods rich in lycopene had a reduced risk for CVD compared to women with a low intake of those foods (Sesso *et al.*, 2003). Results showed that women who consumed seven servings or more of tomato based foods like tomato sauce and pizza each week had a nearly 30% risk reduction in total CVD compared to the group with intakes of less than one serving per week. The researchers also found out that women who ate more than 10 servings per week had an even more pronounced reduction in risk (65%) for specific CVD outcomes such as heart attack or stroke. Though not statistically significant, the strongest association of dietary lycopene with CVD protection was seen among women with a median dietary lycopene intake of 20.20 mg/day, who had a 33% reduction in risk of the disease when compared with women with the lowest dietary lycopene intake (3.3 mg/day).

Lycopene has also been shown to have a hypercholesterolemic effect both in vivo and in vitro. In a small dietary supplementation study, six healthy male subjects were fed 60 mg/day lycopene for 3 months. At the end of the treatment period, a significant 14% reduction in plasma LDL cholesterol levels was observed in vivo with no effect on HDL cholesterol concentration (Fuhrman *et al.*, 1997) & Lorenz *et al.*, 2012).

6.3. Safety of lycopene

The safety issue for carotenoids attracted much attention after the publication of the β-carotene supplementation trials, which yielded negative results. It is interesting that in thus studies an increased risk for lung cancer was related to a 12- and 16 fold increase in β-carotene plasma levels due to supplementation. β-carotene plasma levels increased from 0.32μml before supplementation up to 3.90 and 5.90 μm, respectively. Rao *et al.*, (2003), which showed no effect for β-carotene supplementation, only a 5-fold increase in the carotenoid serum level was achieved. Interestingly, the only study with positive results after supplementation with β-carotene was achieved in linxian, a chinese community with very low carotenoid levels (0.11μm) before the intervention (Jonker et al., 2003). Although supplementation caused an 11-fold increase in β-carotene level, the final concentration of β-carotene reached was a relatively low 1.5μm. Interestingly, reviewing many studies which measured serum levels of β-carotene and lycopene after supplementation suggests that β-carotene serum levels are significantly higher than those found for lycopene. Serum levels reached for β-carotene are around 3μm and may exceed 5μm after supplementation; on the other hand lycopene levels above 1.2μm are rarely seen even after long-term application. Moreover, the serum level achieved for lycopene was not directly correlated to the amount of the supplementation carotenoid (Nahum *et el.*, 2001). For example, supplemented as high as 75 mg/day did not increase lycopene serum levels

more than 1μm (Agarwl & Rao 1998). In conclusion, by some unknown mechanism, lycopene plasma levels after supplementation remain relatively low, which may provide a safety value.

6.4. Lycopene relationship with other micronutrients

When reviewing data related to the chemoprevention of various diseases, it become evident that the use of a single carotenoid, or any other micronutrient which has been successful in vitro and animal models, does not prove as favorable in human intervention studies. That is, there is no magic bullet. In fact, accumulating evidence suggests that a concerted, synergistic action of various micronutrients is, more likely to be the basis of the disease-prevention activity of a diet rich in vegetables and fruits. Indeed, the sources of lycopene used in most of the human studies reviewed there were either prepared tomato products or tomato extracts containing lycopene and other tomato micronutrients and carotenoids in various proportions. Pure lycopene has not been tested as a single in human prevention studies. On the other hand, many studies showing the beneficial effect of lycopene in alleviating chronic conditions have been conducted in which the subjects were provided with tomato-based foods, or tomato extracts, but not with the pure compound. For example, the oleoresin preparation used in many of these studies also contained other tomato carotenoids such as phytoene, phytofluene and β-carotene (Amir *et al.,* 1999; Pastori *et al.,* 1998 & Stahl *et al.,* 1998). In a recent study (Bioleau *et al.,* 2003) that compared the potency of freeze-dried whole tomatoes (tomato powder) or pure lycopene in a rat model of prostate cancer. Rats were treated with the carcinogen (N-methyl1-N-nitrosourea) combined with androgens to stimulate prostate carcinogenesis, and the ability of these two preparations containing lycopene to enhance survival was compared. Mortality with prostate cancer was lower by 25 % (p- 0.09) for rats fed the tomato powder diet than for rats fed control feed. Prostate cancer morality of rats fed our lycopene was similar to that of the control group. The authors concluded that consumption of tomato powder but not pure lycopene inhibited prostate carcinogenesis, suggesting that tomato products contain other compounds, besides lycopene, that modify prostate carcinogenesis.

6.5. Epidemiologic studies: lycopene and cardiovascular diseases

Epidemiological observations also report an inverse association between plasma of tissue lycopene levels and the incidence of cardiovascular diseases. In the Kuopio Ischemic Heart Disease Risk Factor Study, lower levels of plasma lycopene were seen in men who had a coronary event compared with men who did not. In addition, a higher concentration of serum lycopene was inversely correlated with a decrease in the mean and maximal intima-mediated thickness of the common carotid artery (CCA-IMT) with lo lycopene, resulting in an 18% increase in CCA-IMT (Rissanen *et al.,* 2003). The European Multiccnter Case-Control Study on antioxidants, Myocardial Infarction and Breast Cancer Study (EURAMIC Study) reported that a higher lycopene concentration was independently protective against cardiovascular diseases (Basu & Imrhan 2006). The Women's Health Study further revealed that a decreased risk for developing cardiovascular diseases was more strongly associated with higher tomato intake than with lycopene intake (Sesso *et al.,* 2003). Processed tomato products definitely provide a bioavailability source of lycopene and have a positive correlation with plasma and tissue

lycopene levels. However, these studies do not suggest a role of lycopene perse, in reducing the risks for cardiovascular diseases, as plasma level of lycopene, in epidemiologic studies, only reflects the consumption of tomato and tomato products.

7. Conclusion

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, particu- larly 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 (Rao and Agarwal, 2000). These foods may have both chemopreventive as well as chemotherapeutic values as outlined in Figure 3. 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. However, until further research establishes sig- nificant health benefits of lycopene supplementation per se, in humans, the conclusion may be drawn that consumption of naturally occurring carotenoid-rich fruits and vegetables, particularly processed tomato products containing lycopene, should be encouraged, with positive implications in health and disease.

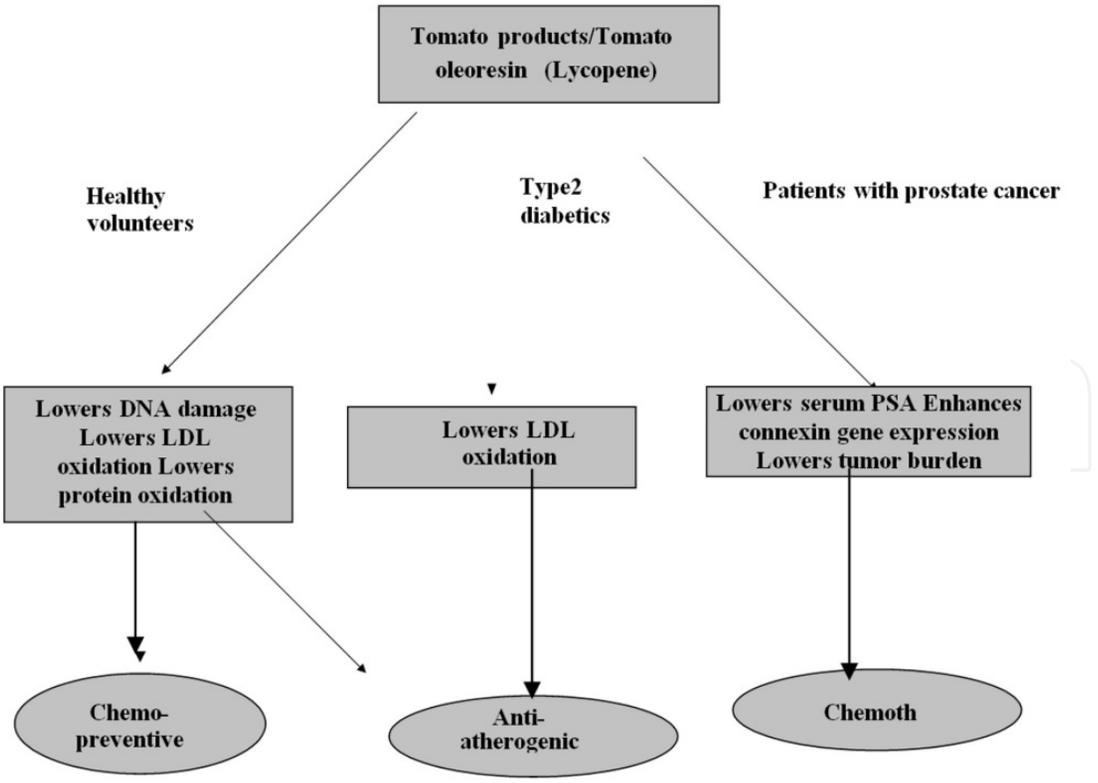

Figure 3. Summary of mechanisms of action of tomato products or tomato oleoresin supplementation, containing lycopene, in health and disease.

		Type and duration of lycopene supplementation	Effects on biomarkers of oxidative stress/ carcinogenesis	
Agarwal and Rao (1998)	19 healthy subjects (mean age 29 years, BMI 2472.8 kg/m²)	0 mg lycopene (placebo), 39 mg lycopene (spaghetti sauce), 50 mg lycopene (tomato juice), or 75 mg lycopene (tomato oleoresin) per day for 1 week	25% decrease in LDL-TBARS 13% decrease in LDL-CD for all groups versus placebo (P<0.05)	Increase at 7 days in all groups versus placebo (P<0.05)
Riso et al. (1999)	10 healthy subjects (mean age 23.171.1 years, BMI 20.571.5 kg/m²)	16.5 mg lycopene (60 g tomato puree), per day for 21 days	38% decrease in DNA damage in lymphocytes (P<0.05)	Increase at 21 days versus baseline (P<0.001)
Bub et al. (2000)	23 healthy volunteers (mean age 3474 years, BMI 2372 kg/m²)	40 mg lycopene (330 ml tomato juice) for 2 weeks	12% decrease in plasma TBARS 18% increase in LDL lag time (P<0.05) no effects on water-soluble antioxidants, FRAP, glutathione peroxidase and reductase activities (P<0.05)	Increase at 2 weeks versus baseline (P<0.05)
Chopra et al. (2000)	34 healthy females (mean age 37.578.5 years, BMI 2473.5 kg/m²)	440 mg lycopene (200 g tomato puree þ 100 g watermelon) per day for 7 days	Significant decrease in LDL oxidizability in nonsmokers (P<0.05); no effects in smokers (P<0.05)	Increase at 7 days versus baseline (P<0.05)
Porrini and Riso (2000)	9 healthy subjects (mean age 25.472.2years, BMI 20.371.5 kg/m²)	7 mg lycopene (25 g tomato puree), per day for 14 days	50% decrease in DNA damage in lymphocytes (P<0.05)	Increase at 14 days versus baseline (P<0.001)
Upritchard et al. (2000)	15 well-controlled type II diabetics (mean age 6378years, BMI30.977 kg/m²)	Tomato juice (500 ml) per day or placebo for 4 weeks	Decreased LDL oxidizability versus baseline (P<0.001)	Increase at 4 weeks versus baseline (P<0.001)
Hininger et al. (2001)	175 healthy volunteers (mean age 33.571 years, BMI-24.370.5 kg/m²)	15 mg lycopene (natural tomato extract) or placebo per day for 12 weeks	No effects on LDL oxidation, reduced glutathione, protein SH groups and antioxidant metalloenzyme activities (P<0.05)	Increase at 12 weeks versus baseline (P<0.05)
Chen et al. (2001)	32 patients with localized prostate adenocarcinoma (mean age 63.776.1 years, BMI 28.074.9 kg/m²)	30 mg lycopene (200 g spaghetti sauce) per day for 3 weeks before surgery or a reference group with no supplementation	Decreased leukocyte and prostate tissue oxidative DNA damage; decreased serum PSA levels (P<0.05)	Increase at 3 weeks versus baseline (P<0.001)
Kucuk et al. (2001)	26 patients with newly diagnosed, clinically localized prostate cancer (mean age 62.1571.85 years, BMI not reported)	15 mg lycopene (Lyc-O-Mato capsules) twice daily or no supplementation for 3 weeks before surgery	Decreased tumor growth in the intervention group versus control(P<0.05); decreased plasma PSA levels and increased expression of connexin43 in prostate tissue in the intervention group versus control (P<0.05);decreased plasma IGF-1 levels in intervention and control groups(P<0.05)	No effects at 3 weeks versus baseline (P<0.05)

		Type and duration of lycopene supplementation	Effects on biomarkers of oxidative stress/ carcinogenesis	
Porrini et al. (2002)	9 healthy subjects (mean age 25.272.2 years, BMI 20.271.6 kg/m^2)	7 mg lycopene (25 g tomato puree) with 150 g of spinach and 10 g of olive oil per day for 3 weeks	Decreased DNA oxidative damage ($P<0.05$)	Not reported

Table 2. Summary of clinical trials investigating the effects of supplementation of tomato products, tomato oleoresin or purified lycopene on biomarkers of oxidative stress and Carcinogenesis

Author details

Amany M. M. Basuny
Department of Fats & Oils, Food Technology Research Institute, Agriculture Research Centre, Giza, Egypt

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