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REVIEW

Tomatoes versus lycopene in oxidative stress and carcinogenesis: conclusions from clinical trials

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Objective: To review the effects of tomato product supplementation, containing lycopene, on biomarkers of oxidative stress and carcinogenesis in human clinical trials.
Results: Supplementation of tomato products, containing lycopene, has been shown to lower biomarkers of oxidative stress and carcinogenesis in healthy and type II diabetic patients, and prostate cancer patients, respectively. Processed tomato products like tomato juice, tomato paste, tomato puree, tomato ketchup and tomato oleoresin have been shown to provide bioavailable sources of lycopene, with consequent increases in plasma lycopene levels versus baseline. Dietary fats enhance this process and should be consumed together with food sources of lycopene. The mechanisms of action involve protection of plasma lipoproteins, lymphocyte DNA and serum proteins against oxidative damage, and anticarcinogenic effects, including reduction of prostate-specific antigen, upregulation of connexin expression and overall decrease in prostate tumor aggressiveness. There is limited *in vivo* data on the health benefits of lycopene alone. Most of the clinical trials with tomato products suggest a synergistic action of lycopene with other nutrients, in lowering biomarkers of oxidative stress and carcinogenesis.
Conclusions: Consumption of processed tomato products, containing lycopene, is of significant health benefit and can be attributed to a combination of naturally occurring nutrients in tomatoes. Lycopene, the main tomato carotenoid, contributes to this effect, but its role *per se* remains to be investigated.
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Introduction

An increased oxidative stress has been implicated in the incidence of chronic diseases. Dietary intakes of tomatoes and tomato products containing lycopene have been associated with a decreased risk of diseases such as cancer and cardiovascular diseases (CVDs) in numerous studies (Kohlmeier *et al*., 1997; Giovannucci *et al*., 2002; Sesso *et al*., 2003). Tomatoes account for 85% of lycopene consumption in an average American diet, and is an essential component of the Mediterranean diet, which is well known for its cardioprotective and anticarcinogenic health effects (LaVecchia, 1997; de Lorgeril *et al*., 1999). Tomatoes are a valuable source of several micronutrients and phytochemicals including carotenoids, polyphenols, potassium, folate, ascorbic acid and α-tocopherol. Most of these nutrients in tomatoes can interact with the host to confer a preventive benefit against oxidative stress-associated diseases, through various mechanisms including antioxidant action (Rao and Agarwal, 2000; Rao, 2002; Canene-Adams *et al*., 2005). However, the benefits of tomato intake have been mainly attributed to its lycopene content.

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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. Holloway *et al*. (2000) reported that a dietary supplementation of tomato puree for 2 weeks in healthy volunteers led to a completely different isomer pattern of plasma lycopene in these volunteers, versus those

present in tomato puree. 5-*cis*, 13-*cis* and 9-*cis*-lycopene isomers, not detected in tomato puree, were predominant in the serum (Holloway *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 ferrets 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 showed a 40% *cis*-lycopene content, whereas the levels did not exceed 20% even after 3 h incubation with water as a control. However, when tomato puree was incubated for 3 h 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 substitutes, 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 1). Agarwal and Rao (1998), reported a significant increase in serum lycopene levels following a 1-week daily consumption of spaghetti sauce (39 mg of lycopene), tomato juice (50 mg 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 fruit (75 or 150 g) or avocado oil (12 or 24 g) to salsa (300 g) 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% 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 pharmacokinetic model to describe the disposition of lycopene, administered as a tomato beverage formulation at five graded doses (10, 30, 60, 90 or 120 mg) in healthy men. Blood was collected before dose administration and at scheduled intervals until 672 h. The overall results of this study showed that independent of dose, 80% of the subjects absorbed less than 6 mg 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 diseases, if absorption saturation occurs at normally consumed levels of dietary lycopene.

Mechanisms of action of lycopene

Cellular and molecular studies have shown lycopene to be one of the most potent antioxidants and has been suggested to prevent carcinogenesis and atherogenesis by protecting critical biomolecules such as DNA, proteins, lipids and low-density lipoproteins (LDLs) (Pool-Zobel *et al*., 1997; Agarwal and Rao, 1998; Rao and Agarwal, 1998). 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 *in vivo* isomerization from *all trans* to *cis* form (Clinton *et al*., 1996). Whereas Levin and co-workers (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. Hadley *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*-B, *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 interconversions remain unclear.

At a physiological concentration of 0.3 μmol/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 (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 antineoplastic action may be explained by increased DNA damage at high lycopene concentrations ($>5\,\mu$M), whereas lower levels of lycopene reduced malondialdehyde formation, with no effects on DNA (Hwang and 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). Animal studies have shown antineoplastic effects of both tomato powder and purified lycopene supplementation. Boileau *et al*. (2003) 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 (Boileau *et al*., 2003). However, in the Dunning rat prostate cancer model, a 4-week supplementation with a higher concentration of lycopene beadlets (4 g lycopene/kg diet), revealed significant downregulation of 5-α-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 (Siler *et al*., 2004). 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*. (2000) 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 (Karas *et al*., 2000). 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 (Liu *et al*., 2006). 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 (Stahl *et al*., 2000, Vine and Bertram, 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 73% 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 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 α-tocopherol or tomato lipophilic 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 (5 μmol/l) with α-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 phenolics 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*.

Interestingly, whereas limited *in vitro* studies show convincing antioxidant and anticarcinogenic effects of lycopene, animal studies and several clinical trials report beneficial effects following consumption of tomato products containing lycopene. There exists limited *in vivo* data on the effects of lycopene *per se*. In this review, we will summarize the effects of lycopene supplementation, as tomato products or purified lycopene, on biomarkers of oxidative stress and carcinogenesis in clinical trials, with supporting epidemiological observations on dietary and plasma lycopene levels and the reduced incidence of certain types of cancer.

Tomato product supplementation and biomarkers of oxidative stress and carcinogenesis: clinical trials in healthy subjects, type II diabetic patients and prostate cancer patients

Table 1 summarizes the clinical trials investigating the effects of supplementation of tomato products or tomato oleoresin, containing lycopene, on biomarkers of oxidative stress and carcinogenesis. Several studies have shown the antioxidant effects of supplementation of tomato products or purified lycopene (providing 6–17 mg lycopene/day), on cellular DNA, in healthy human volunteers (Riso *et al*., 1999, 2004; Porrini and Riso, 2000; Porrini *et al*., 2002; Porrini *et al*., 2005; Zhao *et al*., 2006; Table 1). However, effects on lipid peroxidation have been somewhat conflicting. Riso *et al*. (2004) observed no effects on lymphocyte resistance from lipid oxidation, following a 3-week supplementation of tomato products (8 mg lycopene/day). Briviba *et al*. (2004) also reported null effects on lipid peroxidation in plasma and feces in healthy men following a 2-week supplementation of 330 ml/day of tomato juice. Hininger *et al*. (2001) further supplemented healthy male volunteers with 15 mg of natural tomato lycopene extracts for 12 weeks, and reported no effects on LDL oxidizability. In comparison with these studies showing null effects of tomato lycopene supplementation on lipoprotein oxidation, Bub *et al*. (2000) 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. 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. These baseline plasma lycopene levels were lower than those reported by Riso *et al*. (1999), Briviba *et al*. (2004) and Hininger *et al*. (2001) 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 (2003) 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. Chopra *et al*. (2000) also showed an increase in LDL lag time in healthy adults, following a 1-week supplementation of greater than 40 mg tomato lycopene/day. Hadley *et al*. (2003) reported a significant decrease in lipoprotein oxidizability in healthy elderly subjects, following a 15-day dietary intervention with tomato products. 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*. (2005) 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. 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*. (2000) 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.

This study also confirms the synergy among tomato antioxidants, including lycopene, in reducing lipid peroxidation, as reported by *in vitro* data (Fuhrman *et al*., 2000). 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 (Libby, 2006), 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 (Chen *et al*., 2001; Kucuk *et al*., 2001, 2002; Bowen *et al*., 2002; Table 1). Tomato product or purified lycopene supplementation has previously been shown to decrease oxidative damage in cellular DNA in healthy volunteers (Riso *et al*., 1999, 2004; Porrini and Riso, 2000; Porrini *et al*., 2002, 2005; Zhao *et al*., 2006; Table 1). 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 may then indicate the possible use of lycopene as complementary therapy for prostate cancer and other types of cancer.

Table 1 Summary of clinical trials investigating the effects of supplementation of tomato products, tomato oleoresin or purified lycopene on biomarkers of oxidative stress and carcinogenesis

Study	*Subjects*	*Type and duration of lycopene supplementation*	*Effects on biomarkers of oxidative stress/ carcinogenesis*	*Effects on plasma lycopene levels*
Agarwal and Rao (1998)	19 healthy subjects (mean age 29 years, BMI $24 \pm 2.8\,kg/m^2$)	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 23.1 ± 1.1 years, BMI $20.5 \pm 1.5\,kg/m^2$)	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 34 ± 4 years, BMI $23 \pm 2\,kg/m^2$)	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 37.5 ± 8.5 years, BMI $24 \pm 3.5\,kg/m^2$)	>40 mg lycopene (200 g tomato puree + 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 25.4 ± 2.2years, BMI $20.3 \pm 1.5\,kg/m^2$)	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 63 ± 8years, BMI$30.9 \pm 7\,kg/m^2$)	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 33.5 ± 1 years, BMI- $24.3 \pm 0.5\,kg/m^2$)	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 63.7 ± 6.1 years, BMI $28.0 \pm 4.9\,kg/m^2$)	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 62.15 ± 1.85 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 connexin 43 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 ($P>0.05$)
Porrini *et al.* (2002)	9 healthy subjects (mean age 25.2 ± 2.2 years, BMI $20.2 \pm 1.6\,kg/m^2$)	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 1 *Continued*

Study	*Subjects*	*Type and duration of lycopene supplementation*	*Effects on biomarkers of oxidative stress/ carcinogenesis*	*Effects on plasma lycopene levels*
Rao and Shen (2002)	12 healthy subjects (mean age 31 ± 2.7 years, BMI $22.6 \pm 1.2\,kg/m^2$)	5, 10, 20 mg of lycopene from tomato ketchup or Lyc-O-Mato capsule per day for 2 weeks	10% decrease in serum MDA 23.6% increase in reduced thiols ($P<0.05$)	Increase at 2 weeks versus baseline ($P<0.05$)
Kiokias and Gordon (2003)	32 healthy volunteers (mean age 31.7 ± 11.3 years, BMI $22.4 \pm 3.0\,kg/m^2$)	4.5 mg lycopene (as Lyc-O-Mato, in combination with β-carotene, α-carotene, bixin, lutein and paprika carotenoids) + 4 g fish oil, or 4 g fish oil only per day for 3 weeks	Decreased LDL oxidizability ($P<0.05$) but nonsignificant decrease in DNA damage (8-hydroxy-2′-deoxyguanosine in urine) in carotenoid group + fish oil versus fish oil only	Increase at 3 weeks versus baseline ($P<0.05$)
Hadley *et al*. (2003)	60 healthy subjects (mean age 52.6 ± 1.8 years, BMI not reported)	35 mg lycopene (condensed tomato soup), 23 mg lycopene (ready to serve tomato soup), or 25 mg lycopene (V8 vegetable juice), per day for 15 days	Increase in LDL lag time in all groups ($P<0.05$) No effects on urinary 8-hydroxy-2′-deoxyguanosine or urinary F_2-isoprostanes	Increase at 15 days versus baseline ($P<0.05$)
Visioli *et al*. (2003)	12 healthy subjects (mean age 30 years, BMI $21\,kg/m^2$)	8 mg lycopene (tomato products: raw tomatoes, tomato sauce, tomato paste), with 5 g olive oil per day for 3 weeks (21 days)	Decrease in LDL oxidizability; Decrease in excretion of urinary F_2-isoprostanes ($P<0.05$)	Increase at 3 weeks versus baseline ($P<0.05$)
Briviba *et al*. (2004)	22 healthy men (mean age and BMI not reported)	37 mg lycopene (330 ml of tomato juice) for 2 weeks	No effects on lipid peroxidation in plasma and feces ($P>0.05$)	Increase at 2 weeks versus baseline ($P<0.001$)
Riso *et al*. (2004)	12 healthy subjects (mean age 25.2 ± 4.3 years, BMI $20.6 \pm 1.8\,kg/m^2$)	8 mg lycopene (100 g raw tomatoes, 60 g tomato sauce, 15 g tomato paste) per day for 3 weeks	Decreased DNA oxidative damage ($P<0.05$); No effects on lymphocyte MDA levels ($P>0.05$)	Increase at 3 weeks versus baseline ($P<0.001$)
Rao (2004)	17 healthy subjects	30 mg lycopene (tomato juice, tomato sauce, tomato paste, ketchup, spaghetti sauce, and ready-to-serve tomato soup) per day for 4 weeks	Decreased lipid and protein oxidation ($P<0.05$)	Increase at 4 weeks versus baseline ($P<0.05$)
Porrini *et al*. (2005)	26 healthy subjects (mean age 25.8 ± 2.8 years, BMI $21.3 \pm 1.7\,kg/m^2$)	5.7 mg lycopene (Lyc-O-Mato, 250 ml), or placebo drink, per day for 26 days	42% decrease in DNA damage in lymphocytes ($P<0.05$)	Increase at 26 days versus baseline ($P<0.0001$)
Bub *et al*. (2005)	22 healthy volunteers with different PON1-192 genotypes (mean age 29 ± 6 years, BMI $23 \pm 2\,kg/m^2$)	37 mg lycopene (330 ml of tomato juice) per day for 2 weeks	Decreased lipid peroxidation in volunteers carrying the R-allele of the PON1-192 genotype; decreased plasma malondialdehyde in QR/RR subjects ($P<0.05$)	Increase at 2 weeks versus baseline ($P<0.001$)
Zhao *et al*. (2006)	37 healthy nonsmoking postmenopausal women (mean age 60 ± 2 years, BMI $25.48 \pm 1.08\,kg/m^2$)	12 mg of synthetic lycopene, or 4 mg of synthetic lycopene as part of mixed carotenoids, or placebo, per day for 56 days	Decreased endogenous DNA damage in both carotenoid supplemented groups versus baseline and placebo ($P<0.01$)	Increase at 56 days versus baseline in lycopene only supplemented group ($P<0.01$)

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; TBARS, thiobarbituric acid reactive substances; CD, conjugated diene; MDA, malondialdehyde.

Epidemiologic studies: lycopene, CVD and cancer

A systematic review of 72 epidemiological studies reported a consistent inverse relationship between intakes of tomatoes and plasma lycopene levels and prostate, lung and stomach cancer (Giovannucci, 1999). In the meta-analysis, 10 out of 14 studies reported a significant inverse association between tomato or lycopene consumption and lung cancer risk. These were case–control studies, adjusted for smoking history, an important confounding factor for lung cancer (Giovannucci, 1999). In the Health Professionals Follow-Up Study, an intake of $\geqslant 2$ servings a week of tomato products resulted in a lower risk of prostate cancer (Giovannucci *et al*., 2002). Using plasma samples from men enrolled in the Physicians' Health Study, lycopene was found to be the only antioxidant at significantly lower levels in prostate cancer cases than in the matched controls. This inverse association was particularly evident for aggressive types of prostate cancer and for men not taking a β-carotene supplement (Gann *et al*., 1999). Several epidemiologic studies have also reported an inverse association between tomato intake and the risk of gastric cancer (La Vecchia *et al*., 1987; Buiatti *et al*., 1989; Hansson *et al*., 1993).

Epidemiological observations also report an inverse association between plasma or tissue lycopene levels and the incidence of CVD. 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 low lycopene, resulting in an 18% increase in CCA-IMT (Rissanen *et al*., 2003). The European Multicenter Case–Control Study on Antioxidants, Myocardial Infarction and Breast Cancer Study (EURAMIC Study) reported that a higher lycopene concentration was independently protective against CVD (Kohlmeier *et al*., 1997). The Women's Health Study, further revealed that a decreased risk for developing CVD was more strongly associated with higher tomato intake than with lycopene intake (Sesso *et al*., 2003).

Processed tomato products definitely provide a bioavailable source of lycopene and have a positive correlation with plasma and tissue lycopene levels. However, these studies do not suggest a role of lycopene *per se*, in reducing the risks for cancer and CVD, as plasma level of lycopene, in epidemiologic studies, only reflects the consumption of tomatoes and tomato products.

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, 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 (Rao and Agarwal, 2000). These foods may have both chemopreventive as well as chemotherapeutic values as outlined in Figure 1. In the light of recent clinical

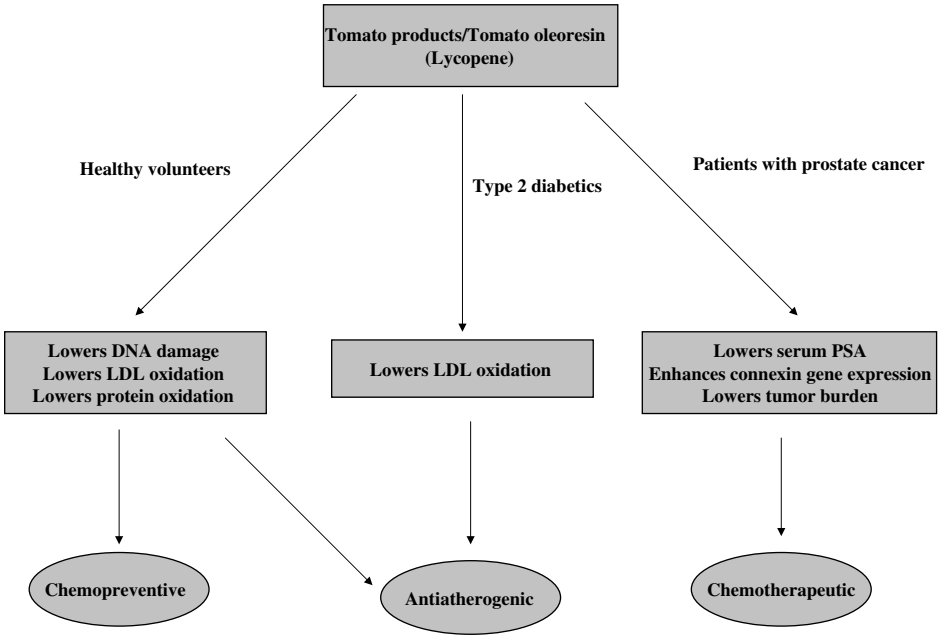

Figure 1 Summary of mechanisms of action of tomato products or tomato oleoresin supplementation, containing lycopene, in health and disease.

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 significant 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.

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