Title: Are the health attributes of lycopene related to its antioxidant function?

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Abstract:
A variety of epidemiological trials have suggested that higher intake of lycopene-containing foods (primarily tomato products) or blood lycopene concentrations are associated with decreased cardiovascular disease and prostate cancer risk. 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. In our review of human and animal trials with lycopene, lycopene-containing extracts, or tomato products, there is limited support for the *in vivo* antioxidant function for lycopene. Moreover, tissue levels of lycopene appear to be too low to play a meaningful antioxidant role. We conclude that there is an overall shortage of supportive evidence for the "antioxidant hypothesis" as lycopene's major *in viv*o mechanism of action. Our laboratory has postulated that metabolic products of lycopene, the lycopenoids, may be responsible for some of lycopene's reported bioactivity.

Keywords: lycopene; lycopenoids; carotenoids; tomato; antioxidant; prostate cancer; cardiovascular disease; oxidative stress; vitamin E; mechanism

Introduction

Maintaining the balance of oxidants and antioxidants within the intracellular and extracellular environment is essential for optimal metabolism and health. We derive energy from oxidative metabolism of dietary macronutrients, but in doing so produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) that can damage lipids, proteins, and DNA. Under normal conditions, we have mechanisms to counteract excess ROS or RNS thereby protecting us from an imbalance of excess oxidants often referred to as "oxidative stress". Sies [1, 2] reminds us that we have an antioxidant enzyme network that constitutes our major defense against oxidative stress. These enzymes intercept ROS and RNS, repair damage to macromolecules, such as DNA, and adapt to changing levels of short and long-term oxidative stress.

Small molecules such as carotenoids, vitamins, and some minerals contribute to antioxidant defense as part of enzymes (e.g. selenium in glutathione peroxidases, manganese in superoxide dismutase), or play a more direct role by intercepting and/or quenching ROS or RNS (e.g. vitamins E and C). Carotenoids can function as chain-breaking antioxidants. The quenching of singlet oxygen or peroxyl radicals by carotenoids directly transfers energy between these molecules [3]. That energy can be dissipated to the aqueous environment as heat or destroy the carotenoid molecule itself. To be effective antioxidants, carotenoids must be present in sufficient concentrations and at the specific location where the ROS or RNS are generated [1].

Researchers have postulated that many chronic diseases; cardiovascular disease, cancer, diabetes, eye diseases and aging itself are the result of long-term oxidative stress. The focus of this review is whether lycopene is in sufficient amounts and right location(s) to be a meaningful antioxidant *in vivo*. Additionally, we review lycopene's proposed mechanisms of action and suggest that lycopene metabolites, termed lycopenoids [4], may be important bioactive molecules that contribute to the decrease in chronic disease risk seen with the consumption of high lycopene-containing foods.

High carotenoid-containing foods and decreased disease risk

There is almost universal agreement that consumption of carotenoid-containing fruits and vegetables is associated with decreased incidence of chronic diseases such as heart disease and cancer. It was assumed that carotenoids in these foods are responsible, or at least contribute to these epidemiological findings, but this assumption requires validation with intervention trials. However, clinical trials with single small molecules like vitamin E, vitamin C, or β-carotene largely have been disappointing [5]. As described earlier, antioxidant defense is multifaceted, thus supplementation with an individual small molecule, unless deficient, likely will have little effect on chronic disease incidence. On the other hand, a portfolio of small molecules, such as those found in fruits and vegetables, may provide significant protection.

Relationship of lycopene-containing foods and cardiovascular disease

A variety of epidemiological studies have suggested that intake of lycopene-containing foods, as well as blood lycopene concentrations, are inversely related to incidence of cardiovascular disease and prostate cancer [6-8]. One notable epidemiological study examined carotenoid and tocopherol adipose concentrations in myocardial infarction patients compared to age-matched controls [9]. Adipose concentrations of these fat-soluble antioxidants are believed

to reflect long-term intake of these compounds. Higher adipose lycopene concentrations were independently associated with decreased risk of myocardial infarction (OR = 0.52, 10^{th} vs. 90^{th} percentile). While not all epidemiological studies agree, most support an inverse association between lycopene intake or tissue concentrations and cardiovascular disease [7].

Epidemiological relationship of lycopene/tomato intake and prostate cancer

A 2004 meta-analysis examined the relationship between lycopene/tomato intake and the risk of prostate cancer [10]. The authors found that serum lycopene [RR = 0.71 (0.59-0.92), 7 studies], lycopene intake [RR = 0.89 (0.81-0.98, 10 studies)], and cooked tomato intake [RR = 0.81 (0.71-0.92), 6 studies], but not raw tomato intake [RR = 0.89 (0.80-1.00), 9 studies] were associated with a significant decrease in prostate cancer risk. A number of studies were not included in the analysis [11-15], or were published after the meta-analysis [16-29]. Some of these studies report evidence for decreased prostate cancer risk with increased lycopene/tomato exposure [11, 12, 14-16, 20, 21, 27, 29], while some show little to no effect [13, 17, 18, 22, 23, 25, 26, 28].

Lycopene/tomato and prostate cancer clinical trials

There have been 12 small clinical trials investigating the potential impact of lycopene or tomato consumption on prostate cancer risk/progression. These have mostly been in patients; with prostate cancer scheduled for a prostatectomy, with benign prostatic hyperplasia, or at high-risk of developing prostate cancer. Almost all of these have reported prostate specific antigen (PSA) response (decreased concentration, decreased velocity, increased stabilization) as an outcome related to disease progression or prostate health. Overall, the majority of these trials have found evidence of improved PSA response [30-40] with lycopene or tomato consumption, whereas a few have not [41-43]. It is important that these trials be viewed in the context of their small size and general lack of an appropriate control group.

Lycopene/tomato intake and prostate cancer in animal studies

In our laboratory, a 10% tomato powder diet, but not lycopene alone (250 mg/kg diet), significantly decreased NMU-induced prostate cancer incidence in F344 rats [44]. In the Dunning R3327-H prostate transplantable rat tumor model, we found that 10% tomato powder was more effective in decreasing tumor growth than lycopene alone [45]. In a similar, but faster growing tumor model, lycopene alone (200 mg/kg diet) had no effect on Dunning MatLyLu tumor growth or necrosis levels [46]. One publication [47] evaluated two chemical prostate cancer models with varying results for lycopene in F344 rats. First, 15 mg lycopene per kg of diet decreased prostatic interepithelial neoplasia incidence when administered after the carcinogen, 7,12-dimethylbenz[a]anthracene (DMBA). However, lycopene (5, 15, or 45 mg/kg diet) did not alter 2-amino-1-methylimidazol[4,5-*b*]pyridine (PhIP) induced prostate cancer incidence [47]. In a nude mouse model, 100 and 300 mg/kg body weight, but not 10 mg/kg body weight of gavaged lycopene, significantly inhibited human androgen-independent DU-145 prostate cancer xenograph growth [48]. In another nude mouse model, orally gavaged lycopene (5 or 50mg/kg body weight) failed to decrease androgen-independent human PC-346C prostate cancer xenograph growth, but the combination of low dose lycopene plus vitamin E significantly

decreased tumor growth [49]. Together these studies suggest lycopene moderately alters prostate cancer development and/or tumor growth in experimental animals. Moreover, it appears that lycopene is one of several bioactive compounds in tomatoes that may contribute to decreasing the development and/or progression of prostate cancer.

Is lycopene bioactive in health promotion?

Dietary intake of lycopene, or blood or tissue lycopene, may simply serve as a marker of tomato intake. Lycopene may provide some of the cardiovascular or cancer protection associated with tomato intake, but likely is not the only bioactive compound in tomatoes. Tomatoes contain significant quantities of vitamins C and E, folate, polyphenols, and other carotenoids such as phytoene and phytofluene [6]. Significant concentrations of lycopene are only found in a select number of foods (tomato, watermelon, guava, pink grapefruit), with about 85% of lycopene intake in the U.S. coming from fresh and processed tomato products [50]. Thus, future work should focus not only on lycopene but also upon other tomato components, with consideration given to potential additive or synergistic interactions between bioactives.

***In vitro* and *ex vivo* antioxidant effects of lycopene**

There are a number of *ex vivo* studies that demonstrate delayed chemically-induced LDL oxidation lag time from blood obtained from human subjects fed tomato products or tomato extracts [7]. However, supplementation of lycopene alone rarely significantly decreases serum lipid peroxidation or *ex vivo* LDL oxidation, thus interactions with other tomato compounds may be occurring [7]. For example, the combination of lycopene and the tomato polyphenol, rutin, synergistically decreased copper-induced LDL oxidation lag time [51].

In 2000, the panel on Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids evaluated the potential health impact of β-carotene and other carotenoids [52]. After extensively evaluating the literature, they concluded that there was evidence that β-carotene was an antioxidant *in vitro*, but that there was not convincing evidence that substantially increasing β-carotene intake above current levels had a significant effect on antioxidant status measures. Lycopene was not specifically addressed. However, the authors of this review have found no compelling evidence since the publication of that panel's report to suggest that elevation of β-carotene or lycopene significantly improves antioxidant status measures.

Lycopene as an in vivo antioxidant: the evidence

To identify the evidence to support lycopene as an *in vivo* antioxidant we utilized pubmed and the search terms "lycopene AND antioxidant" and a previous review to identify publications on this topic [53]. Many studies utilized lycopene extracts (mostly from tomatoes), which may contain other compounds, thus these studies were separated from those that reported using a pure lycopene source. In addition, we separated human studies from animal studies resulting in four groups of studies: human lycopene studies (Table 1, n =3), human lycopene extract studies (Table 2, n = 9), animal lycopene studies (Supplemental Table 1, n = 11), and animal lycopene extract studies (Supplemental Table 2, n = 18).

All three human lycopene studies identified were double-blind, placebo-controlled trials (Table 1). Devaraj et al. examined the antioxidant potential of 8 weeks of lycopene

supplementation (6.5, 15, 30 mg/d) following a 2 week washout period in healthy men and women 40 years or older. None of the lycopene doses had an effect on LDL oxidation rate, plasma lipid peroxidation markers (malondialdehyde [MDA] and 4-hydroxynonenal [HNE]), and urinary F2-isoprostanes. However, the 30 mg/d dose did decrease lymphocyte DNA damage and urinary 8-OHdG concentrations compared to baseline [54]. A similarly designed study was undertaken in diabetics supplemented with 10 mg/d of lycopene. Supplementation did not alter total antioxidant capacity or oxidized-LDL antibody levels, but did decrease serum MDA levels compared to baseline [55]. Zhao et al. also used a 2 week washout followed by 56 days of supplementation of 12 mg/d of lycopene to healthy, nonsmoking, postmenopausal women. Lycopene supplementation decreased lymphocyte DNA damage, but did not prevent hydrogen peroxide-induced DNA damage [56].

Of the nine human lycopene extract studies (Table 2), only four provide some evidence to suggest that lycopene is an *in vivo* antioxidant and in each case other measured antioxidant markers were not altered. The animal data (Supplemental Tables 1 & 2) are more difficult to interpret because of model, species, and lycopene administration differences, but overall are more supportive of lycopene having antioxidant action than the human studies. Nevertheless, when considering the data as a whole, there is an overall shortage of supportive evidence, such that we conclude that it is not convincing that lycopene is an *in vivo* antioxidant. More well designed studies, especially in humans, are needed to further clarify this potential mechanism.

Are lycopene concentrations high enough in body tissues?

There is almost universal agreement that lycopene is an excellent *in vitro* antioxidant, especially in quenching singlet oxygen, and may be the best dietary molecule in this regard [57]. It is projected that intact lycopene with its 11 conjugated double bonds will also quench peroxyl radicals in LDL particles or cellular membranes [3]. Carotenoids, while highly concentrated in many foods, are not well absorbed and rarely accumulate in high concentrations in blood and tissues [58]. Lycopene is generally the carotenoid in highest concentration in American's serum, nevertheless, the average adult U.S. serum concentrations are less than 0.013 μm/dL according to NHANES III data [52]. In our experience, it is difficult to exceed 0.14μm/dL lycopene in serum, even when providing a lycopene-enriched diet for a week or more to healthy subjects. These levels fall far short of serum α-tocopherol concentrations [59].

When pooling samples from 10 healthy subjects, Milde et.al. found 11.6 molecules of α-tocopherol per LDL molecule but only 0.9, 0.9 and 0.5 molecules of lycopene, lutein, and β-carotene, respectively [51]. A separate study found 0.7 molecules of lycopene per LDL molecule from pooled serum of seven normolipodemic subjects [60]. It seems unlikely that 1 molecule of lycopene in a LDL particle would have much impact on LDL oxidation. Moreover, when Milde and coworkers enriched human LDL 2-fold with lycopene, it did not increase LDL resistance to copper-induced oxidation.

We and others have measured carotenoid concentrations in human tissues, and lycopene is generally the highest carotenoid in individual tissues [61, 62]. We also evaluated human prostate and determined that lycopene was the predominant carotenoid, but is generally lower in concentration than other tissues [63]. Freeman and co-workers [64] found that α-tocopherol concentrations were 162-fold higher than lycopene in the human prostate. In LDL, the molar α-tocopherol concentration is 17-fold higher than lycopene [60]. In nonsmokers, Peng et al. found

plasma and skin α-tocopherol concentrations to be 53-fold and 269-fold higher, respectively, than lycopene concentrations [59].

Lycopene was shown to be 2 and 10-fold more efficient at quenching singlet oxygen than β-carotene and α-tocopherol, respectively, *in vitro* [57]. But given the substantially higher α-tocopherol content in serum, LDL, and human tissues, even if α-tocopherol has a 10-fold lower antioxidant potential [57], it seems unlikely that lycopene plays a meaningful a role as a fellow fat-soluble antioxidant. That is not to say that lycopene, or its metabolites, may not have biological effects, as will be discussed below.

Potential *in vivo* mechanisms of action of lycopene

While there has been great interest in the antioxidant properties of lycopene, other mechanisms of action that may or may not be related to antioxidant function, have also received research attention and have been reviewed previously [65-67]. The following is an abbreviated overview focused on the *in vivo* evidence to support lycopene's mode of action beyond its potential antioxidant function (see Table 3).

Apoptosis is controlled through many tightly-regulated steps which may be modified by dietary intervention. One human [31, 68] and six animal [45, 48, 69-72] studies suggest that lycopene induces apoptosis of cancer cells, whereas one human study [32] found no effect. In contrast, in a mouse emphysema model lycopene decreased the apoptosis rate [73]. The little *in vivo* evidence available suggests that lycopene induces apoptosis in cancer cells.

Decreases in cell growth can also be achieved through cell cycle inhibition. We found 2 animal studies that suggest lycopene inhibits cell cycle progression in an oral cancer model and a subcutaneous prostate cancer mouse model [48, 74]. Overall, more *in vivo* studies are necessary to determine whether lycopene alters cell cycle progression.

Several studies have suggested an inverse correlation between the insulin-like growth factor-1 (IGF-1) axis and prostate cancer incidence [75, 76]. We identified 12 human or animal studies investigating the relationship between IGF-1, its receptor protein (IGF-1R), its binding proteins (IGFBP-1 or IGFBP-3), and lycopene or tomato product supplementation. Only two human studies (colon cancer patients or healthy subjects) report a positive impact of lycopene in decreasing IGF-1, IGF-1R, or increasing IGFBP-1 or IGFBP-3 [77, 78]. Three animal studies suggest that lycopene decreases IGF-1 or increases IGFBP-1 or IGFBP-3 [46, 71, 79]. In contrast, five studies found no relationship between lycopene intake and IGF-1 level [32, 39, 40, 80, 81]. Lastly, one trial investigated the effects of lycopene on the IGF-1 axis in two female populations [82]. Only when the two populations were separated were significant effects identified. There was a decrease in IGF-1 in women at high familial breast cancer risk, but no effect on IGF-1 and IGFBP-3 levels with lycopene consumption in premenopausal breast cancer survivors [82]. Thus, the existing *in vivo* data is mixed in regards to the impact of lycopene on the IGF-1 axis.

Gap junction communication allows small molecular signaling between cells through channels that are formed by gap junction proteins such as connexin 43. Only one *in vivo* study found a positive association between gap junction communication or connexin 43 expression with lycopene consumption [83]. Krutovskikh, et al. investigated the effect of gavaged lycopene on gap junction communication in rat liver. Interestingly, the lower dose (5mg/kg/d) enhanced communication while the higher dose (50mg/kg/d) inhibited communication. A randomized clinical trial of lycopene supplementation reported a near significant increase in connexin 43

protein levels [32]. Overall, there is relatively little *in vivo* evidence to support an increase in gap junction communication with lycopene consumption.

The risk of prostate cancer is strongly associated with androgen status [84, 85] and lycopene may modulate androgen metabolism. Serum testosterone concentrations were significantly decreased in rats fed lycopene for 4 days [86], while feeding lycopene for 22 weeks did not alter these levels [45]. In addition, expression of the androgen metabolizing enzyme, 5α-reductase, was downregulated in the prostate and MatLyLu Dunning prostate tumor when rats were fed lycopene for four or eight weeks, respectively [46, 79]. In a rat model of testicular toxicity lycopene supplementation had no effect on androgen status [87]. Overall the available evidence suggests that short-term lycopene feeding may decrease androgen concentrations or signaling. A few studies have also investigated the effects of lycopene consumption on serum estrogen concentrations. All three *in vivo* human studies identified suggest that lycopene decreases estrogenic activity [88-90]. The evidence is mildly suggestive that lycopene may lower estrogen concentrations and/or activity.

Another possible mechanism of action is that lycopene may induce detoxification enzymes. Our search yielded three publications that suggest lycopene induces rat hepatic phase II enzymes [91-93]. However, Breinholt, et al [92] failed to find that higher doses of lycopene induced phase II enzymes. Further, one human study and one rat study reported no effect of lycopene on detoxifying enzymes [94, 95]. The mixed results of these trials most likely relate to the doses/dietary levels of lycopene making it difficult to discern the effect of lycopene on phase II enzyme levels.

A number of epidemiological studies suggest that lycopene decreases the inflammation marker, C-reactive protein (CRP). In healthy subjects, one human study reported that lycopene decreases CRP [96], while two studies reported no effect [97, 98]. There is little *in vivo* data on this topic, therefore we conclude that there is insufficient evidence to support that lycopene decreases CRP.

It has also been suggested that lycopene may prevent atherosclerosis by decreasing the cell surface adhesion molecules expression and intima-media thickness. Three human studies [99-101] suggest that lycopene decreases cell surface adhesion and intima-media thickness, while three human [97, 98, 102] and one rat [103] study reported no relationship. Taken together, there is a lack of evidence to suggest that lycopene limits atherosclerosis by decreasing cell surface adhesion molecule expression or intima-media thickness.

Lastly, it has been suggested that lycopene may act as a hypocholesterolemic agent. There are two extensive reviews on carotenoids and cardiovascular disease risk factors [104, 105]. Only one human trial reported decreased total serum cholesterol with lycopene [96] while one study reported no effect on serum total, LDL, or HDL cholesterol [106]. In conclusion, there is little *in vivo* evidence to suggest that lycopene decreases cardiovascular disease risk by improving serum cholesterol profiles.

Overall, the mechanisms with the greatest *in vivo* support include decreasing androgen and/or estrogen status or activity, and induction of apoptosis. However, only a limited number of studies have addressed the biochemical effects of lycopene. Many mechanistic studies lack *in vivo* experiments to support their findings, therefore more work is needed to clarify the mechanisms of action of lycopene.

Conclusions

The focus of this paper was to review whether the health attributes of lycopene can be ascribed to its *in vivo* antioxidant function. A pubmed search was carried out with the search terms "lycopene AND antioxidant" and human intervention and animal studies were reviewed and evaluated. Evidence for lycopene's *in vivo* mechanisms of action was also presented We conclude that there is limited experimental support for the "antioxidant hypothesis" as a major mechanism of lycopene's *in vivo* action. As an alternative hypothesis, we suggest that the metabolic products of lycopene, the lycopenoids [4], may be more bioactive than the parent molecule and that lycopenoids may be more central to the health outcomes seen *in vivo* than the antioxidant properties of lycopene. Lycopenoids would not be expected to have direct antioxidant activity because of an insufficient number of conjugated double bonds. Instead, their impact on health would be more likely to through altering gene expression.

Table 1. Double-blind, placebo-controlled trials human studies examining the antioxidant potential of lycopene.

Subjects [Ref]	Source	Amount (mg/day)	Groups	Admin	Duration	Outcome(s)
Healthy Men & Women, ≥40 yrs [54]	DSM Redivivo	6.5, 15, 30	Pl (n = 18) 6.5 (n = 21) 15 (n = 17) 30 (n = 21)	Capsule taken with low-fat milk	2 wk Wo 8 wk Sup	30 mg ↓ lymphocyte DNA Damage (Comet), urinary 8-OHdG conc. vs. BL. NE - LDL oxidation rate, lipid peroxidation (MDA & HNE), and F2-isprostane.
Diabetics, 35-70 yrs [55]	Unknown	10	Pl (n = 19) Lyc (n = 16)	Unknown	2 wk Wo 8 wk Sup	Lyc ↓ MDA vs. baseline & placebo. NE - TAC, oxidized LDL antibodies.
Healthy Nonsmoking, postmenopausal women, 50-70 yrs [56]	BASF	12	Pl (n= 6) Lyc (n = 8)	Take with 1st meal that contained > 10g fat	2 wk Wo 56 d Sup	Lyc ↓ lymphocyte DNA damage (Comet). NE - hydrogen peroxide-induced DNA damage.

Abbreviations: Admin, administration; BL, baseline; d, day; conc, concentration; HNE, 4-hydroxynonenal; LDL, low-density lipoprotein; Lyc, lycopene; MDA, malondialdehyde; NE, no effect; OHdG, 8-hydroxy-2'-deoxyguanosine; Pl, placebo; Ref, reference; Sup, supplementation; TAC, total antioxidant capacity; vs., versus; wk, week; Wo, washout; yrs, years.

Table 2. Human Studies examining the antioxidant potential of lycopene extracts[1].

Subjects	Source	Amount (mg/day)	Groups	Admin	Duration	Outcome(s)
Healthy men (n = 18) and women (n = 9), 21-24 yrs. [98]	Lyc-O-Mato®	80 mg Lyc extract supplement, ~75 mg/d Lyc	Intervention Only	4 capsules in morning & evening	1 wk Wo 1 wk Sup	NE - serum MDA levels vs. baseline.
Grade 1 Hypertensives (n = 31), 30-70 yrs. [107]	Lyc-O-Mato®	15 mg/d	Intervention Only	Take with main meal of day	4 wk Pl 8 wk Sup 4 wk Pl	↓ plasma TBARS vs. baseline. NE - plasma GSH thiols or GPx activity.
Postmenopausal women (n = 20), < 60 yrs. [108]	LycoRed	2 capsules (4 mg Lyc total	Intervention Only	Oral	6 mo	↑ serum GSH conc vs. baseline. NE -serum MDA.
Double-blind placebo crossover, male nonsmokers (n = 28), 18-60 yrs. [109]	LycoRed	15 mg/d Lyc	Lyc-Pl Pl-Lyc	Oral	4 wks	NE - lymphocyte DNA damage (Comet).
Double-blind, placebo-controlled, healthy nonsmokers & smokers, ave. age 34.3 yrs. [110]	Lyc-O-Mato®	3 capsules (~15 mg/d Lyc	Pl nonsmokers (n = 15), smokers (n = 13) Sup nonsmokers (n = 15), smokers (n = 12)	Given after dinner	2 wk Wo 2 wk Sup	↑ lymphocytes with class 1 or 2, or no DNA damage vs. Pl in nonsmokers. NE - lymphocyte DNA damage (Comet) overall.
Randomized, cross-over, ave. age 31.3 yrs. [111]	Lyc-O-Mato®	5, 10, 20 mg/d	Males (n = 6) Females (n = 6)	Oral	2 wk Wo 2 wk Sup	↓ serum MDA, ↑ serum thiols.
Randomized, 2-armed, men with PCa prior to prostatectomy, <75 yrs. [33]	Lyc-O-Mato®	2 capsules (15 mg Lyc)/d	Cases (n =15) Controls (n = 11)	Oral	3 wk	NE - lymphocyte 5-OhmdU.

Single-blind, placebo-controlled, male nonsmokers, 25-45 yrs. [112]	Tomato Extract (Makhetsim Chem Works)	1 capsule (15 mg Lyc)/d	Pl (n= 46) Sup (n = 52)	Oral	12 wk	NE - LDL susceptibility to oxidation, FA ratio, GPx, SOD, GSH, GSSG, SH.
Double-blind, placebo-controlled, healthy, 63-83 yrs. [113]	Lyc-O-Pen™	1 capsule (13.3 mg Lyc)/d	Pl (n = 16) Sup (n = 16)	Oral	12 wk	NE - LDL oxidation.

Abbreviations: 5-OhmdU, 5-hydroxymethyl-deoxyuridine; Admin, administration; Ave., average; d, day; FA, fatty acid; GPx, glutathione peroxidase; GSH, glutathione; GSSG, glutathione disulfide; LDL, low-density lipoprotein; Lyc, lycopene; MDA, malondialdehyde; NE, no effect; PCa, prostate cancer; Pl, placebo; SH, thiol; Sup, supplementation; TBARS, thiobarbituric acid reactive substances; vs., versus; wk, week; Wo, washout; yrs, years.

[1] Lyc-O-Mato® & Lyc-O-Pen™ are produced by LycoRed Ltd. (Beer Sheva, Israel).

Table 3. Modulation of chronic diseases biomarkers by lycopene or lycopene containing products[1].

Potential Mechanisms of Action	References
Decrease growth & inflammation	
↑ Apoptosis	[31, 32, 45, 48, 68, 69, 72, 73]
↓ Cell cycle progression	[48, 74]
↓ IGF-1 & ↑ IGFBP-3	[32, 40, 46, 71, 77-80, 82]
Increase gap junction communication	[32, 83]
Inhibit androgen / estrogen signaling	[45, 46, 79, 86-90]
Induce detoxification enzymes	[91-95]
Decrease cell surface adhesion & intima-media thickness	[97-103]
Decrease serum cholesterol	[96, 106]
Decrease C-reactive protein	[96-98]

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Supplemental Table 1. Animal Studies examining the antioxidant potential of lycopene.

Model	Source	Amount (mg/kg)	Admin	Groups	Duration	Outcomes
New Zealand White Rabbits [13]	Huavei Pharmaceuticals Limited Co (90 % Pure)	4, 12	Diet	High-Fat diet + Low Lyc (4) or High Lyc (12)	8 wk	Both Lyc diets ↑ serum TAC, ↓ serum MDA, & LDL oxidation vs. high-fat diet alone.
Female Sprague Dawley Rats [14]	Unknown	50	Diet	Lyc after DMBA	120 d	↓ Serum & breast MDA vs. DMBA alone. ↑ Breast SOD, CAT, & GPx vs. DMBA alone.
Male Sprague Dawley Rats [15]	DSM Redivivo	10 BW	Gavage	Lyc alone Lyc + Cyc A	21 d	↓ renal TBARs, ↑ GPx vs. Cyc A alone. NE - renal GSH, CAT vs. Cyc A alone. NE - Lyc alone vs. control.
Male Sprague Dawley Rats [16]	BASF	50	Diet	Lyc alone	6 wk	NE - cardiac TBARs, hepatic GSH, erythrocyte SOD.
Male Wistar-Albino Rats [17]	Unknown	10 BW	Gavage	Lyc alone Lyc + cadmium	20 d	↓ serum & renal MDA vs. cadmium alone. NE - renal SOD, CAT, GPx vs cadmium alone. NE - Lyc alone vs. control.
Male Sprague Dawley Rats [18]	DSM Redivivo	10 BW	Gavage	Lyc + Saline Lyc + Cyc A	21 d	↓ testis MDA, GPx, CAT vs. Cyc A alone. NE - Lyc alone vs. control.
Male Sprague Dawley Rats [19]	DSM Redivivo	4 BW	Gavage	10 days before or 5 d after cisplatin treatment		NE of Lyc treatment on testes MDA, GPx vs. cisplatin alone.
Male Sprague Dawley Rats [20]	DSM Redivivo	4 BW	Gavage	10 days before (Pre) or 2 d before & 3 d		Post ↓ cardiac MDA, GSH, & CAT vs. adriamycin alone. Pre & Post ↓ renal MDA levels.

				after (Post) adriamycin		NE - of Pre or Post on renal GSH or CAT.
Male Sprague Dawley Rats [21]	DSM Redivivo	4 BW	Gavage	10 d before or 5 d after cisplatin treatment		↓ renal MDA, GPx ,↑ renal GSH & CAT vs. cisplatin alone.
Japanese Quail [22]	DSM	100 or 200	Diet	100 mg/kg (Low) 200 mg/kg (High)	285 d	↓ serum & hepatic MDA vs. control. High ↓ serum & hepatic MDA vs. Low.
F344 Male Rats [23]	BASF	1000	Diet	Lyc + PhiP Lyc + IQ	15 d	↑ DNA & Protein adducts in liver (PhiP) & protein adducts in albumin (IQ) vs. control. NE - DNA adducts in colon, prostate, & liver (IQ) or protein adducts in albumin (PhiP) & liver (IQ), hepatic GST vs. control.

Abbreviations: Admin, administration; BW, body weight; CAT, catalase; Cyc A, cyclosporine A; d, days; DMBA, 7,12-dimetnylbenz[a]anthracene; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione-s-transferase; IQ, 2-amino-3-methylimidazo[4,5-f]quinoline; LDL, low-density lipoprotein; Lyc, lycopene; MDA, malondialdehyde; NE, no effect; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; SOD, superoxide dismutase; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; vs., versus; wk, week;

Supplemental Table 2. Animal Studies examining the antioxidant potential of lycopene extracts.

Model	Source	Amount (mg/kg)	Admin	Groups	Duration	Outcomes
Male Wistar Rats [24]	Lyc-O-Mato	30, 100, 300	Diet	2 wk before Den	10 wk study Den given at wk 2	Only 300 ↓ hepatic DNA damage (comet) vs. Den alone.
Male Wistar Rats [25]	Lyc-O-Mato	5 BW	Gavage	Lyc Lyc + Dox	7 wk	↓ cardiomyocyte DNA damage (comet) vs. Dox alone.
Male Wistar rats [26]	LycoRed	1 BW	Intragastric	Lyc + Control ischemia-reperfusion (CIR)	31 d	↑ cardiac GSH, GPx , ↓ cardiac MDA vs. CIR. NE - cardiac SOD & CAT.
Male Wistar rats [27]	LycoRed	10 BW	i.p.	Lyc Lyc + Fe-NTA	5 d	↓ hepatic MDA & 8-oxoGuo vs. Fe-NTA alone.
Male Wistar rats [28]	LycoRed	2,4,6 BW Acute 0.5, 1, 1.5 BW Sub acute	Gavage	Acute - 24 hr before cisplatin Subacute - 72, 48, 24, 1 hr before cisplatin	Unknown	All treatments ↓ chromosomal damage vs. cisplatin alone.
Male Sprague-Dawley rats [29]	LycoRed	2.6 (Low) 7.8 (High)	Diet	Sedentary + Low Lyc Sedentary + High Lyc Exhaustive Exercise (EE) + Low Lyc EE + High Lyc	30 d	↓ plasma & muscle MDA levels in EE. NE - either dose in EE on erythrocyte & muscle GSH. NE - either dose in sedentary mice on plasma & muscle MDA, erythrocyte & muscle GSH.
Male Wistar rats [30]	LycoRed	200	Diet	Ferrum Lyc + Ferrum	10 d	↓ mucosa MDA, ↑ erythrocyte SOD vs. ferrum alone.
Male Wistar rats [31]	Lyc-O-Mato	1.25	Intragastric	Lyc Lyc + MNNG	5 d	↓ bone marrow micronucleated polychromatic erythrocytes & chromosomal aberrations vs. MNNG alone.

						NE - Lyc alone vs. control.
Male Fisher 344 Rats [32]	LycoRed	50	Diet	Lyc	10 wk	↑ lymphocyte pyrimidine & puridine oxidation. NE - lymphocyte DNA damage (Comet), hepatic GST, erythrocyte GPx, SOD, & CAT.
Male Wistar Rats [33]	Isolated from Blakeslea Trispora Fungus > 80% pure	10 BW 50 BW	Intragastric	10 mg/kg (Low) 50 mg/kg (High)	14 d	High ↑ plasma TAC & ascorbate-dependent lipid peroxidation vs. control. Both ↓ hepatic MDA & GST activity vs. control. NE - GPX, GR, CAT, NADPH-dependent lipid peroxidation.
Male Wistar Rats [34]	Lyc-O-Pen	70 BW Every other day	Gavage	Lyc + Den	8 wk	↓ DNA damage (Comet) vs. Den alone.
Male Syrian Hamsters [35]	Lyc-O-Mato	2.5 BW 3Xs/wk	Intragastric	Lyc Lyc + DMBA	14 wk	Lyc & Lyc + DMBA ↓ hepatic TBARS, ↑ GSH, GPx, GST, GR vs. control & DMBA alone, respectively.
Male Wistar Rats [36]	Lyc-O-Mato	2.5 BW 3Xs/wk	Intragastric	Lyc Lyc + MNNG	3 wk	NE of either group on plasma & erythrocyte TBARS, GSH, GPx, GST, & GR.
Male Syrian Hamster [37]	Lyc-O-Mato	2.5 BW 3Xs/wk	Orally	Lyc Lyc + DMBA	14 wk	Lyc & Lyc + DMBA ↓ buccal pouch mucosa TBARS, ↑ GSH, GPx, GST, GR vs. control & DMBA alone, respectively.
LacZ Mice [38]	Cognis Lycopene/tomato oleoresin	0.5 & 1 mmol/kg	Diet	0.5 mmol/kg (Low) 1 mmol/kg (High)	8 wk (benzopyrene) or 9 mo	High Lyc ↑lung and colon mutations in benzopyrene animals. NE spontaneous mutations by high or low Lyc.
Male Wistar Rats [39]	LycoRed	10 BW	i.p.	Lyc Lyc + Fe-NTA	5 d	↓ hepatic MDA & 8-oxoGuo vs. FE-NTA alone.

						NE - Lyc alone on hepatic MDA & 8-oxoGuo vs. control.
Female Wistar Rats [40]	LycoRed	1 BW 5 BW 50 BW 100 BW	Gavage	1 mg/kg BW 5 mg/kg BW 50 mg/kg BW 100 mg/kg BW	2 wk	5, 50 ↑ erythrocyte SOD, 5 ↑ GR & GPx, 100 ↑ GST vs. control. NE - protein oxidation (2-amino adipic seimaldehyde), plasma MDA, before or after PhiP administration
Broiler Chicks [41]	Tomato hexane extract	25 BW	Diet	Lyc Lyc + T-2 toxin	7,14, 21 d	↓ hepatic MDA, GPx, GST, ↑GSH vs. T-2 toxin alone. Lyc alone ↑ hepatic GST. NE - Lyc alone on hepatic MDA, GSH, GPx vs. control.

Abbreviation List: 8-oxoGuo, 8-oxo guanine; Admin, administration; BW, body weight; CAT, catalase; CIR, control. Ischemia-reprefusion; d, days; Den, diethylnitrosamine; Dox, doxorubicin; EE, exhaustive exercise; Fe-NTA, ferric nitrilotriacetate; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GST, glutathione-s-transferase; hr, hours; i.p., intraperitoneal injection; Lyc, lycopene; MDA, malondialdehyde; MNNG, N-methyl-N'-nitro-N-nitrosoguanidine; SOD, superoxide dismutase; TAC, total antioxidant capacity; vs., versus; wk, week.

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