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Review

Lycopene as a guardian of redox signalling

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It has been suggested that lycopene, the major carotenoid found in tomato, exhibits health-beneficial effects by virtue of its antioxidant activity. However, recent literature suggests that lycopene can actually "perform" roles independent of such capacity and involving a direct modulation of redox signalling. Reactive oxygen species are known to act as second messengers in the modulation of cellular signalling leading to gene expression changes and pharmacological responses. Lycopene may control redox-sensitive molecular targets, affecting enzyme activities and expressions and modulating the activation of MAPKs and transcription factors, such as NF-κB and AP-1, Nrf2.

Key words: lycopene, antioxidant, ROS, redox signal, intracellular redox status

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INTRODUCTION

Lycopene is present in many fruits and vegetables, with tomatoes and processed tomato products being among the richest sources. Several recent studies suggest that dietary lycopene is able to reduce the risk of chronic diseases such as cancer (Giovannucci, 1999) and cardiovascular diseases (Rao, 2002) Although several mechanisms have been implicated in health-beneficial effects of lycopene, such as modulation of intercellular gap junction communication, hormones, immune system and metabolic pathways, the antioxidant properties of lycopene are thought to be primarily involved in its preventive effects in chronic diseases. Because of its high number of conjugated dienes, lycopene is one of the most potent antioxidants, with a singlet-oxygen-quenching ability twice as high as that of β-carotene and 10 times higher than that of α-tocopherol (Di Mascio *et al.,* 1989). Increased reactive oxygen species (ROS) levels result in oxidative stress that can damage DNA, proteins, and lipids and lead to early cell death. The evidence that lycopene is able to modulate ROS levels is demonstrated by several studies, showing that the carotenoid may chemically interact with ROS and undergo oxidation and may prevent ROS-induced cell damage (Palozza *et al.,* 2010a).

However, recently, a novel mechanism has been hypothesized by which lycopene may act as a beneficial agent in human health. The carotenoid has been reported to directly modulate several redox-sensitive signalling pathways altered in cancer (Palozza *et al.,* 2011a) and cardiovascular diseases (Palozza *et al.,* 2010b), being responsible for cell regulatory functions. The redox molecules regulated by lycopene involve antioxidant response elements (ARE), ROS-producyng enzymes, small-GTPases, mitogen-activated protein kinases (MAPK), nuclear factor-κB (NF-κB), activator protein-1 (AP-1), redox-sensitive proteins involved in cell growth, such as p53 and the Bcl-2 family proteins and the Ku proteins (Fig. 1). This review summarizes the background information about lycopene as a modulator of redox signal.

MODULATION OF ANTIOXIDANT RESPONSE ELEMENTS AND Nrf2

Several evidences suggest that lycopene can upregulate the antioxidant electrophile/antioxidant response element (EpRE/ARE) and the nuclear factor E2-related factor 2 (Nrf2), thereby stimulating the production of phase II detoxifying antioxidant enzymes that protect cells from reactive oxygen species and other electrophilic molecules (Ben-Dor *et al.,* 2005). Lycopene has been reported to upregulate the ARE system in HepG2 and MCF-7 cells through the Nrf2 nuclear transcription pathway (Ben-Dor *et al.,* 2005) and the expression of ARE-regulated proteins, including epoxide hydrolase 1 (EPHX1), superoxide dismutase-1 (SOD-1), catalase (CAT), and the metal binding protein transferrin (TF), in the androgen-sensitive human prostate cell line LNCaP (Goo *et al.,* 2007). Recently, enzymatic metabolites of lycopene have been also reported to be able to induce Nrf2-mediated expression of phase II detoxifying/antioxidant enzymes (Linnewiel *et al.,* 2009). In particular, apo-10'-lycopenoic acid, one of the products of lycopene cleaved by carotene 9',10'-oxygenase at its 9',10' double bond, induced heme oxygenase-1, NAD(P)H:quinone oxidoreductase 1, glutathione S-transferases, and glutamate-cysteine ligases and increased total intracellular glutathione levels in human bronchial epithelial cells. Such effects were accompanied by a suppression of endogenous ROS generation and H_2O_2-induced oxidative damage. Recently, lycopene has been also reported to mitigate the nephrotoxic effect of cisplatin in rat through Nrf2-mediated induction of

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Abbreviations: AP-1, activator protein-1; CAT, catalase; COX-2, cyclooxygenase 2; EPHX1, epoxide hydrolase 1; EpRE/ARE, electrophile/antioxidant response element; ERK-1, extracellular signal-regulated kinase-1; ERK-2, extracellular signal-regulated kinase-2; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HO-1, heme oxygenase-1; IFN-γ, interferon-γ; iNOS, inducible nitric oxide synthase; IGFBP-3, Insulin-like growth factor-binding protein 3; IRF-1, interferon regulatory factor-1; JNK, Jun N-terminal kinase; LDL, low-density lipoprotein; LOX, lipoxygenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor-κB; NO, nitric oxide; Nrf2, nuclear factor E2-related factor 2; PDGF, platelet derived growth factor; ROS, reactive oxygen species; SOD-1, STAT-1-α, signal transducer and activator of transcription-1-α; superoxide dismutase-1; TF, transferring.

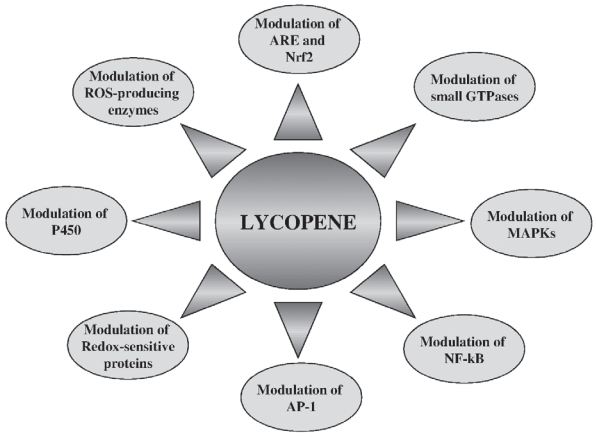

Figure 1. Redox molecules regulated by lycopene.

heme oxygenase-1 (HO-1) (Sahin *et al.,* 2010). However, recently, it has been reported that lycopene supplementation was not able to modulate the oxidant-responsive protein HO-1 in lymphocytes from healthy young men (Markovitch *et al.,* 2009).

MODULATION OF P450 EXPRESSION

Mammalian cytochromes P450 (P450) are a family of heme-thiolate enzymes involved in the oxidative metabolism of a variety of endogenous and exogenous lipophilic compounds. Poor coupling of the P450 catalytic cycle results in continuous production of ROS, which affects signalling pathways and other cellular functions (Zangar *et al.,* 2004). Several studies have reported the ability of carotenoids to induce enzyme activities associated with P450 family. In particular, Astorg and colleagues proposed that lycopene-induced modulation of the liver metabolizing enzyme, cytochrome P4502E1, was the underlying mechanism of protection against carcinogen-induced preneoplastic lesions in the rat liver (Astorg, *et al.,* 1997). Moreover, the administration of lycopene to rats was shown to induce liver CYP types 1A1/2, 2B1/2 and 3A in a dose-dependent manner [Breinholt *et al.,* 2000). Recently, both lycopene and β-carotene have been shown to activate the cytochrome P450 1A1 gene but only β-carotene was able to induce the retinol dehydrogenase gene in mice (Aung, *et al.,* 2009). The observations that P450 activity was induced at very low lycopene plasma levels suggests that modulation of drug metabolising enzymes by carotenoids may be relevant to humans.

MODULATION OF ROS-PRODUCING ENZYMES

Activated macrophages and neutrophils can produce large amounts of superoxide anion and its derivatives *via* the phagocytic isoform of NAD(P)H oxidase. Increasing evidence suggests that lycopene is able to reduce the levels of ROS through changes in NAD(P)H oxidase expression. Lycopene and β-carotene depletion for 3 weeks increased PMN-H_2O_2 content after PMA activation, able to stimulate NADPH activation, while supplementation for 5 weeks restored basal H_2O_2 generation (Walrand *et al.,* 2205). Moreover, lycopene was able to decrease oxysterol-induced inflammation (Palozza *et al.,* 2011b) and ROS production (Palozza *et al.,* 2010c) in THP-1 cells through a decreased expression of NOX-4, one of the homologues of NADPH oxidase.

Lycopene has been also reported to counteract the effects of iNOS by inhibiting nitric oxide (NO) production and/or by decreasing iNOS at protein and mRNA levels. In particular, it has been shown that treatment with lycopene inhibited lipopolysaccharide (LPS)-stimulated NO production in RAW 264.7 macrophage cells (Rafi *et al.,* 2007) and decreased LPS-induced iNOS. Moreover, it has been recently reported that dietary supplementation of lycopene-rich foods conferred a strong *in vivo* protection of human lymphocytes, against $NO_2^{\bullet}$ radical (by electron transfer) and $^1O_2$ (by energy transfer) (Böhm *et al.,* 2001).

The effect of lycopene and other natural antioxidants, such as quercetin and tyrosol, on inducible nitric oxide synthase (iNOS) and cyclooxygenase-*2* (COX-2) gene expression have been studied in RAW 264.7 macrophages stimulated by gliadin in association with interferon-γ (IFN-γ) (De Stefano *et al.,* 2007). The IFN-γ plus gliadin combination treatment was capable of enhancing iNOS and COX-2 gene expression and NF-ϰB, interferon regulatory factor-1 (IRF-1) and signal transducer and activator of transcription-1-α (STAT-1-α) activation induced by ROS generation. Lycopene, quercetin and tyrosol inhibited all these effects, suggesting that they may decrease iNOS and COX-2 gene expression, acting as non toxic agents for the control of pro-inflammatory genes.

In an interesting study, lycopene and all-*trans*-lycopene-16,16'-diol lycophyll, a derivate of lycopene have been suggested to modify the enzymatic function of 5-LOX (Hazai *et al.,* 2006).

MODULATION OF SMALL-GTPASES

Numerous observations have suggested a role for the Ras superfamily of small GTPase in redox regulation and ROS have been reported as important downstream effectors for Ras protein. We recently demonstrated that lycopene was able to modify Ras activation by decreasing its pharnesylation and by inducing its translocation from the membrane to the cytoplasm in cancer cells (Palozza *et al.,* 2010d) as well as in stimulated macrophages (Palozza *et al.,* 2011c). The changes in Ras activation were strictly related to an inhibition of the expression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by the carotenoid and were accompanied by decreased ROS production and MAPK/NF-ϰB activation.

MODULATION OF MAPK CASCADES

Numerous studies show that MAPKs are strongly activated by ROS and that lycopene, alone or in combination with other natural products, modulate MAPK phosphorylation (Sarkar *et al.,* 2009). Lycopene was reported to attenuate the phenotypic and functional maturation of murine bone marrow-dendritic cells, especially in lipopolysaccharide (LPS)-induced DC maturation, by down-regulating the expression of costimulatory molecules (CD80 and CD86) and major histocompatibility complex type II molecules and by inhibiting the activation of MAPK and NF-ϰB (Kim *et al.,* 2004). The carotenoid was also able to inhibit platelet derived growth factor (PDGF)-BB-induced signalling and migration in human fibroblasts by inhibiting the activation

of extracellular signal-regulated kinase (ERK)1/2, p38, and jun N-terminal kinase (JNK) (Chan *et al.,* 2009). In recent studies from our laboratory, lycopene suppressed both MAPK phosphorylation and NF-κB activation in oxysterol-stimulated macrophages as well as in prostatic cancer cells (Palozza *et al.,* 2010c).

MODULATION OF NF-κB AND AP-1 ACTIVATIONS

NF-κB is the first eukaryotic transcription factor shown to respond directly to oxidative stress (Schrek *et al.,* 1991). At least two mechanisms contribute to this effect. The first one involves ROS-mediated enhancement of IkB degradation and the second one the oxidative enhancement of upstream signal cascades. It has been found that lycopene inhibited the binding activity of NF-κB and the expression of NF-κB target gene MMP-9, leading to the inhibition of the invasion of human hepatoma cells (Huang, *et al.,* 2007). Such inhibition was mediated by the downregulation of IκB phosphorylation, NF-κB expression, and NF-κB p65 subunit translocation from cytosol to nucleus (Hung *et al.,* 2008). LPS stimulation has been known to activate the MAPK and NF-κB signal pathways. Pre-treatment with lycopene markedly inhibited the LPS-induced up-regulation of p-ERK, p-p38, p-JNK, and NF-κB (Kim *et al.,* 2004). Moreover, tomato lycopene extract prevented LPS-induced pro-inflammatory gene expression by blocking NF-κB signalling (Joo *et al.,* 2009).

Many different oxidative stress-inducing stimuli, including smoking exposure, lead to AP-1 activation, with consequent alteration in cell proliferation, differentiation and apoptosis. It has been reported that lycopene is able to inhibit AP-1 signalling in mammary cancer cells (Karas *et al.,* 2000).

MODULATION OF CELL CYCLE- AND APOPTOSIS-REDOX-SENSITIVE PROTEINS

p53 is known to respond to stress signals responsible for oncogenic alterations (Xu *et al.,* 1999). Smoke-elevated p53 was markedly attenuated by lycopene, supplemented to ferrets. The carotenoid also prevented smoke-induced changes in p21Waf1/Cip1, Bax-1, cleaved caspase 3, cyclin D1, and PCNA. Lycopene also counteracted tar-induced p53 increase and DNA damage in cultured fibroblasts (Palozza *et al.,* 2005) and attenuated H_2O_2-induced p53 and caspase-3 mRNA in endothelial cells (Tang *et al.,* 2009).

The cancer-preventive effect of lycopene mediated by its ability to induce apoptosis has been comprehensively studied (Palozza *et al.,* 2004). Zhang *et al.* (2003) have found that not the lycopene itself, but its auto-oxidant product induces apoptosis in HL-60 cells. Although many mechanisms have been suggested by which lycopene may control apoptosis, one of the most interesting is the carotenoid ability to modulate Bcl-2, a protein whose antiapoptotic effects has been, at least partially, explained by its antioxidant properties (Palozza *et al.,* 2004).

The Ku proteins are involved in multiple cellular pathways, including DNA repair, telomere maintenance and Bax-mediated apoptosis. Recently, lycopene has been reported to reduce the levels of H_2O_2, to arrest cell cycle progression and to inhibit Ku-DNA binding activity, and Ku70 levels in Pancreatic Acinar AR42J cells (Seo *et al.,* 2009).

FROM EXPERIMENTAL TO HUMAN STUDIES: EVIDENCE FOR A REDOX ACTIVITY OF LYCOPENE

Some human studies are being conducted to evaluate the influence of lycopene and/or tomato products on the modulation of markers of oxidative stress and on changes in redox signalling. Devaraj *et al.* (2007) examined the antioxidant potential of 8 weeks of lycopene supplementation (6.5, 15, 30 mg/d) following a 2 week washout period in healthy subjects. None of the lycopene doses had an effect on LDL oxidation rate, plasma lipid peroxidation markers, and urinary F2-isoprostanes. However, the 30 mg/d dose did decrease lymphocyte DNA damage and urinary 8-OHdG concentrations compared to baseline. 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 (Neyestani *et al.,* 2007). Zhao *et al.* (2006) 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. On the other hand, a significant prevention of the H_2O_2-induced DNA damage was observed in lycopene-enriched lymphocytes from healthy volunteers supplemented with 15 mg/day lycopene for 1 week (Torbergsen *et al.,* 2000). Moreover, in patients with localized prostate adenocarcinoma, consumption of lycopene-rich tomato sauce-based diet lead to a decrease in the oxidative DNA damage (Chen *et al.,* 2001). An increase in serum lycopene after supplementation has been also reported to reduce lymphocyte DNA comet tail length in healthy men (Kim *et al.,* 2010). Tomato paste rich in lycopene protects against cutaneous photodamage in humans, by reducing mitochondrial DNA (mtDNA) damage (Rizwan *et al.,* 2011). In addition, the consumption of commercial tomato juice increased plasma lycopene levels and the intrinsic resistance of LDL to oxidation in patients with diabetes (Upritchard *et al.,* 2000).

A recent study shows a significant up-regulation of IGFBP-3 and Bax/Bcl-2 ratio and down-regulation of cyclin-D1, p53, and Nrf-2 in cells incubated with sera from men who consumed red tomato paste (Talvas *et al.,* 2010). Moreover, cell incubation with sera from men who consumed purified lycopene led to significant up-regulation of IGFBP-3, c-fos, and uPAR (Talvas *et al.,* 2010).

It is widely recognized that most of the inflammatory cytokines are produced by a mechanism involving activation of redox-sensitive molecules, including MAPKs and NF-κB. In a recent review, we reported (Palozza *et al.,* 2010a) that lycopene decreases pro-inflammatory cytokine levels in human subjects (Riso *et al.,* 2006; Upritchard *et al.,* 2000; Watzl *et al.,* 2000).

Although these promising results, some other studies did not show an *in vivo* antioxidant role of lycopene and/or tomato products (for a review, see Erdman *et al.,* 2009). Therefore, when considering the data as a whole, there is an overall shortage of supportive evidence and more well designed studies are needed to further clarify this potential mechanism in humans.

CONCLUSIONS

This review summarizes the available evidence for a redox role of lycopene in biological environments. The

carotenoid can modulate redox signalling, by controlling antioxidant response elements and Nrf2, ROS-producing enzymes, MAPKs, transcription factors, such as NF-κB and AP-1, and redox proteins involved in cell growth. Despite these promising reports, it is difficult at the moment to directly relate available experimental data to human pathophysiology. More well designed human studies and controlled clinical intervention trials are needed to further clarify the redox role of lycopene *in vivo*. Such studies should take into consideration subject selection, specific markers of analysis, metabolism and isomerization of lycopene, interaction with other antioxidants.

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REFERENCES

Astorg P, Gradelet S, Berges R Suschetet M (1997) Dietary lycopene decreases the initiation of liver preneoplastic foci by diethylnitrosamine in the rat. *Nutr Cancer* **29**: 60–68.

Aung HH, Vasu VT, Valacchi G, Corbacho AM, Kota RS, Lim Y, Obermueller-Jevic UC, Packer L, Carroll E, Cross CE, Gohil K (2009) Effects of dietary carotenoids on mouse lung genomic profiles and their modulatory effects on short-term cigarette smoke exposures. *Genes Nutr* **4**: 23–39.

Ben-Dor A, Steiner M, Gheber L, Danilenko M, Dubi N, Linnewiel K, Zick A, Sharoni Y, Levy J (2005) Carotenoids activate the antioxidant response element transcription system. *Mol Cancer Ther* **4**: 177–186.

Böhm F, Edge R, Burke M, Truscott TG (2001) Dietary uptake of lycopene protects human cells from singlet oxygen and nitrogen dioxide — ROS components from cigarette smoke. *Photochem Photobiol B* **64**: 176–178.

Breinholt V, Lauridsen ST, Daneshvar B, Jakobsen J (2000) Dose-response effects of lycopene on selected drug-metabolizing and antioxidant enzymes in the rat. *Cancer Lett* **154**: 201–210.

Chan CM, Fang JY, Lin HH, Yang CY, Hung C (2009). Lycopene inhibits PDGF-BB-induced retinal pigment epithelial cell migration by suppression of PI3K Akt and MAPK pathways. *Biochem Biophys Res Commun* **388**: 172–176.

Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, van Breemen R, Ashton D, Bowen PE (2001). Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *J Natl Cancer Inst* **93**: 1872–1879.

De Stefano D, Maiuri MC, Simeon V, Grassia G, Soscia A, Cinelli MP, Carnuccio R (2007) Lycopene, quercetin and tyrosol prevent macrophage activation induced by gliadin and IFN-γ. *Eur J Pharmacol* **566**: 192–199.

Devaraj S, Mathur S, Basu A, Aung HH, Vasu VT, Meyers S, Jialal I. (2008) A dose-response study on the effects of purified lycopene supplementation on biomarkers of oxidative stress. *J Am Coll Nutr* **27**: 267–273.

Di Mascio P, Kaiser S, Sies H (1989) Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys* **274**: 532–538.

Erdman JW Jr, Ford NA, Lindshield BL (2009) Are the health attributes of lycopene related to its antioxidant function? *Arch Biochem Biophys* **483**: 229–235.

Giovannucci E (1999) Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. *J Natl Cancer Inst* **91**: 317–331.

Goo YA, Li Z, Pajkovic N, Shaffer S, Taylor G, Chen J, Campbell D, Arnstein L, Goodlett DR, van Breemen RB (2007) Systematic investigation of lycopene effects in LNCaP cells by use of novel large-scale proteomic analysis software. *Proteomics Clin App* **1**: 513–523.

Hazai E, Bikádi Z, Zsila F, Lockwood SF (2006) Molecular modeling of the non-covalent binding of the dietary tomato carotenoids lycopene and lycophyll, and selected oxidative metabolites with 5-lipoxygenase. *Bioorg Med Chem* **14**: 6859–6867.

Huang CS, Fan YE, Lin CY, Hu, ML (2007) Lycopene inhibits matrix metalloproteinase-9 expression and down-regulates the binding activity of nuclear factor-kappa B and stimulatory protein-1. *J Nutr Biochem* **18**: 449–456.

Hung CF, Huang TF, Chen BH, Shieh JM, Wu PH, Wu WB (2008) Lycopene inhibits TNF-alpha-induced endothelial ICAM-1 expression and monocyte-endothelial adhesion. *Eur J Pharmacol* **586**: 275–282.

Joo YE, Karrasch T, Mühlbauer M, Allard B, Narula A, Herfarth HH, Jobin C (2009) Tomato lycopene extract prevents lipopolysaccharide-induced NF-kappaB signaling but worsens dextran sulfate sodium-induced colitis in NF-kappaB^{EGFP} mice. *PLoS One* **4**: 4562–4573.

Karas M, Amir H, Fishman D, Danilenko M, Segal S, Nahun A, Koifman A, Giat Y, Levy J, Sharoni Y (2000) Lycopene interferes with cell cycle progression and insuline-growth factor I signalling in mammary cancer cells. *Nutr Cancer* **36**: 101–111.

Kim GY, Kim J.H, Ahn SC, Lee HJ, Moon DO, Lee CM, Park YM (2004) Lycopene suppresses the lipopolysaccharide-induced phenotypic and functional maturation of murine dendritic cells through inhibition of mitogen-activated protein kinases and nuclear factor-κB. *Immunology* **113**: 203–211.

Kim JY, Paik JK, Kim OY, Park HW, Lee JH, Jang Y, Lee JH (2010) Effects of lycopene supplementation on oxidative stress and markers of endothelial function in healthy men. *Atherosclerosis* **215**: 189–195.

Linnewiel K, Ernst H, Caris-Veyrat C, Ben-Dor A, Kampf A, Salman H, Danilenko M, Levy J, Sharoni Y (2009) Structure activity relationship of carotenoid derivatives in activation of the electrophile/antioxidant response element transcription system. *Free Radic Biol Med* **47**: 659–667.

Markovitch D, Tyrrell RM, Tauler P, Frystyk J, Stokes K, Thompson D (2009) Lycopene supplementation (passata sauce) reduces apoptosis but does not affect oxidant-responsive heme oxygenase-1 in human lymphocytes. *Nutrition* **25**: 668–675.

Neyestani TR, Shariatzadeh N, Gharavi A, Kalayi A, Khalaji N.(2007) Physiological dose of lycopene suppressed oxidative stress and enhanced serum levels of immunoglobulin M in patients with Type 2 diabetes mellitus: a possible role in the prevention of long-term complications. *J Endocrinol Invest* **30**: 833–838.

Palozza P, Serini S, Di Nicuolo F, Calviello G (2004) Modulation of Apoptotic Signalling by Carotenoids in Cancer Cells. *Arch Biochem Biophys* **430**: 104–109.

Palozza P, Sheriff A, Serini S, Boninsegna A, Maggiano N, Ranelletti FO, Calviello G, Cittadini A (2005) Lycopene induces apoptosis in immortalized fibroblasts exposed to tobacco smoke condensate through arresting cell cycle and down-regulating cyclin D1 pAKT and pBad. *Apoptosis* **10**: 1445–1456.

Palozza P, Parrone N, Catalano A, Simone R (2010a) Tomato lycopene and inflammatory cascade: basic interactions and clinical implications. *Curr Med Chem* **17**: 2547–2563.

Palozza P, Parrone N, Simone R, Catalano A (2010b) Lycopene in atherosclerosis prevention: an integrated scheme of the potential mechanisms of action from cell culture studies. *Arch Biochem Biophys* **504**: 26–33.

Palozza P, Simone R, Catalano A, Boninsegna A, Böhm V, Fröhlich K, Mele MC, Monego G, Ranelletti FO (2010c) Lycopene prevents 7-ketocholesterol-induced oxidative stress, cell cycle arrest and apoptosis in human macrophages. *J Nutr Biochem* **21**: 34–46.

Palozza P, Colangelo M, Simone R, Catalano A, Boninsegna A, Lanza P, Monego G, Ranelletti FO (2010d) Lycopene induces cell growth inhibition by altering mevalonate pathway and Ras signaling in cancer cell lines. *Carcinogenesis* **31**: 1813–1821.

Palozza P, Parrone N, Simone R, Catalano A (2011a) Role of lycopene in the control of ROS-mediated cell growth: implications in cancer prevention. *Curr Med Chem* **18**: 1846–1860.

Palozza P, Simone R, Catalano A, Monego G, Barini A, Mele MC, Parrone N, Trombino S, Picci N, Ranelletti FO (2011b) Lycopene prevention of oxysterol-induced proinflammatory cytokine cascade in human macrophages: inhibition of NF-κB nuclear binding and increase in PPARγ expression. *J Nutr Biochem* **22**: 259–268.

Palozza P, Simone R, Catalano A, Parrone N, Monego G, Ranelletti FO (2011c) Lycopene regulation of cholesterol synthesis and efflux in human macrophages. *J Nutr Biochem* **22**: 971–978.

Rafi MM, Yadav PN, Reyes M (2007) Lycopene inhibits LPS-induced proinflammatory mediator inducible nitric oxide synthase in mouse macrophage cells. *J Food Sci* **72**: S069–S074.

Rao AV (2002) Lycopene, tomatoes, and the prevention of coronary heart disease. *Exp Biol Med (Maywood)* **227**: 908–913.

Riso P, Visioli F, Grande S, Guarnieri S, Gardana C, Simonetti P, Porrini M (2006) Effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. *J Agric Food Chem* **54**: 2563–2566.

Rizwan M, Rodriguez-Blanco I, Harbottle A, Birch-Machin MA, Watson RE, Rhodes LE (2011) Tomato paste rich in lycopene protects against cutaneous photodamage in humans *in vivo*: a randomized controlled trial *Br J Dermatol* **164**: 154–162.

Sahin K, Tuzcu M, Sahin N, Ali S, Kucuk O (2010) Nrf2/HO-1 signaling pathway may be the prime target for chemoprevention of cisplatin-induced nephrotoxicity by lycopene. *Food Chem Toxicol* **48**: 2670–2674.

Sarkar FH, Li Y, Wang Z, Kong D (2009) Cellular signaling perturbation by natural products. *Cell Signal* **21**: 1541–1547.

Schrek R, Bauerle PA (1991) Reactive oxygen intermediates as apparently widely used messengers in the activation of NF-κB transcription factor and HIV-1. *Trends Cell Biol* **1**: 39–42.

Seo Y, Masamune A, Shimosegawa T, Kim H (2009) Protective effect of lycopene on oxidative stress-induced cell death of pancreatic acinar cells jeong. *Ann N Y Acad Sci* **1171**: 570–575.

Talvas J, Caris-Veyrat C, Guy L, Rambeau M, Lyan B, Minet-Quinard R, Lobaccaro JM, Vasson MP, Georgé S, Mazur A, Rock E (2010) Differential effects of lycopene consumed in tomato paste and lycopene in the form of a purified extract on target genes of cancer prostatic cells. *Am J Clin Nutr* **91**: 1716–1724.

Tang XY, Yang XD, Peng YF, Lin JH (2009) Protective effects of lycopene against H_2O_2-induced oxidative injury and apoptosis in human endothelial cells. *Cardiovasc Drugs Ther* **23**: 439–448.

Torbergsen AC, Collins AR (2000) Recovery of human lymphocytes from oxidative DNA damage; the apparent enhancement of DNA repair by carotenoids is probably simply an antioxidant effect. *Eur J Nutr* **39**: 80–85.

Upritchard JE, Sutherland WH, Mann JI (2000) Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. *Diabetes Care* **23**: 733–738.

Walrand S, Farges MC, Dehaese O, Cardinault N, Minet-Quinard R, Grolier P, Bouteloup-Demange C, Ribalta J, Winklhofer-Roob BM, Rock E, Vasson MP (2005) *In vivo* and *in vitro* evidences that carotenoids could modulate the neutrophil respiratory burst during dietary manipulation. *Eur J Nutr* **44**: 114–120.

Watzl B, Bub A, Blockhaus M, Herbert BM, Lührmann PM, Neuhäuser-Berthold M, Rechkemmer G (2000) Prolonged tomato juice consumption has no effect on cell-mediated immunity of well-nourished elderly men and women. *J Nutr* **130**: 1719–1723.

Xu A, Wu LJ, Santella RM, Hei TK (1999) Role of oxyradicals in mutagenicity and DNA damage induced by crocidolite asbestos in mammalian cells. *Cancer Res* **59**: 5922–5926.

Zangar RC, Davydov DR, Verma S (2004) Mechanisms that regulate production of reactive oxygen species by cytochrome P450. *Toxicol Appl Pharmacol* **199**: 316–331.

Zhang H, Kotake-Nara E, Ono H, Nagao A (2003) A novel cleavage product formed by autoxidation of lycopene induces apoptosis in HL-60 cells. *Free Radic Biol Med* **35**: 1653–1663.

Zhao X, Aldini G, Johnson EJ, Rasmussen H, Kraemer K, Woolf H, Musaeus N, Krinsky NI, Russell RM, Yeum KJ (2006) Modification of lymphocyte DNA damage by carotenoid supplementation in postmenopausal women. *Am J Clin Nutr* **83**: 163–169.