International Journal of Food Nutrition and Safety, 2012, 1(1): 15-31

Modern Scientific Press

International Journal of Food Nutrition and Safety **ISSN: 2165-896X**

Journal homepage: www.ModernScientificPress.com/Journals/ijfns.aspx *Florida, USA*

Review

Resources and Bioactivities of Lycopene

Fang Li [1], Xiang-Rong Xu [2], Sha Li [1], Gui-Fang Deng [1], Shan Wu [1], Hua-Bin Li [1,*]

[1] *Guangdong Provincial Key Laboratory of Food, Nutrition and Health, School of Public Health, Sun Yat-Sen University, Guangzhou 510080, China*

[2] *Key Laboratory of Marine Bio-resources Sustainable Utilization, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou 510301, China*

* Author to whom correspondence should be addressed; E-Mail: lihuabin@mail.sysu.edu.cn; Tel.: +86-20-87332391; Fax: +86-20-87330446.

Article history: Received 7 January 2012, Received in revised form 6 February 2012, Accepted 7 February 2012, Published 9 February 2012.

Abstract: Lycopene is a fat-soluble red-orange carotenoid, and could be found in many fruits and vegetables, such as tomato, carrot, watermelon and pink grapefruit. Unlike β-carotene, lycopene lacks a β-ionone ring and therefore has no pro-vitamin A activity. Interest in lycopene is growing because many studies showed that consumption of lycopene rich food is inversely associated with some diseases, such as cardiovascular disease and cancer. In this review, we provide an up-to-date coverage of lycopene with reference to resource, extraction, stability and bioactivities, and special attention is paid to its bioactivities, including antioxidant and free radical scavenging, anticancer, anti-atherosclerosis, cardiopretective, antiinflammatory, antimutigenic and antifungal activities.

Keywords: lycopene; resource; diet; bioactivity; antioxidant; anticancer.

1. Introduction

Lycopene is the carotenoid responsible for the red color of tomato. It was first discovered in tomato by Millardet in 1876, and later named lycopene by Schunck. The red pigment is abundant in red fruits and vegetables such as tomato, red carrot, watermelon, papaya, pink grapefruit, rosehips and guava.

Belonging to the hydrocarbon carotene class of carotenoids, lycopene is acyclic and contains 11 conjugated and two non-conjugated double bonds which make it highly reactive towards oxygen and free radicals, and this antioxidant activity probably contributes to its efficacy as a chemoprevention agent (van Breemen and Pajkovic, 2008). Unlike β-carotene, lycopene lacks a β-ionone ring and therefore has no pro-vitamin A activity (van Breemen and Pajkovic, 2008), which sets its biochemistry

apart from carotenes such as α-carotene and β-carotene. Lycopene β-cyclase (Lyc-B) is the key enzyme in the catalysis of linear lycopene to form cyclic β-carotene that is an important source of vitamin A in human and animal nutrition (Zhu et al., 2008). Lycopene might play an important role in the modulation of β-carotene, retinoid, and lipid metabolism (Zaripheh et al., 2006). The epidemiological, tissue culture, and animal studies provided convincing evidence supporting the role of lycopene in the prevention of some chronic diseases (Rao et al., 2006). In addition to antioxidant activity, in vitro experiments indicated other mechanisms of chemoprevention by lycopene including induction of apoptosis and antiproliferation in cancer cells, anti-metastatic activity, and the upregulation of the antioxidant response element leading to the synthesis of cytoprotective enzymes (van Breemen and Pajkovic, 2008). This review provides an up-to-date coverage of lycopene in regard to resource, extraction, stability and bioactivities, and special attention is paid to its bioactivities.

2. Resource, Extraction and Stability of Lycopene

Lycopene is a fat-soluble red-orange carotenoid found primarily in tomatoes and tomato-derived products, including tomato sauce, tomato paste, and ketchup, and other dietary sources, including dried apricots, guava, watermelon, papaya, and pink grapefruit (Rafi et al., 2007). Lycopene content of plant-derived products could be improved by suppressing the expression of Lcy gene and regulating biosynthetic enzyme in carotenoid pathway by RNAi (Wan et al., 2007). Lycopene is a substrate for carotene-9', 10'-monooxygenase (CMO2) and can be converted to apo-10'-carotenal (van Breemen and Pajkovic, 2008).

Lycopene cold be extracted from tomato skin with supercritical carbon dioxide, and the maximum yield was obtained at 40 MPa, 373 K, and 2.5 mL of CO_2/min. The chromatographic analysis indicated that lycopene was extracted from tomato skin with negligible degradation at the optimum conditions, and the amount extracted represented more than 94% of the total carotenoid in the sample (Topal et al., 2006). The mechanical and thermal treatments did not affect the lycopene content to any great extent (Tiback et al., 2009). The extraction temperature has the most effect on lycopene yield, and the yield at 60 □ was 14% greater than that obtained at 70 □ (Katherine et al., 2008).

Lycopene exists in nature as the all-trans form mostly (Fig. 1). Heat, light, oxygen, and different food matrices could be factors that have effects on isomerization and antioxidation of lycopene. Lycopene may isomerize to mono- or poly-cis forms on the condition of heat or oil or during dehydration. Reisomerization takes place during storage. After oxidation, the lycopene molecule split which causes color loss and flavor off. The effects of heat, oxygen, light, and oil on the stability of lycopene are uniform in much of the literature; nevertheless, controversy still exists on some details, such as the conditions causing the occurrence of isomerization, and the optimal moisture and temperature for storage (Xianquan et al., 2005).

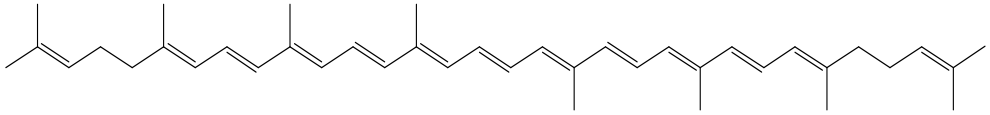

Figure 1. The chemical structure of the all *trans*-lycopene

In addition, the Observed Safe Level risk assessment method indicated the evidence of safety was strong at intakes up to 75 mg/d for lycopene (Shao and Hathcock, 2006).

3. Bioactivities of Lycopene

3.1. Antioxidant and Free Radical Scavenging Activities

Oxidative stress is now recognized as an important etiological factor in the causation of several chronic diseases including cancer, cardiovascular diseases, osteoporosis, and diabetes (Rao et al., 2006). Dietary antioxidant supplementation from fruits and vegetables might play a beneficial role in the prevention of chronic diseases (Suwannalert et al., 2007). Lycopene is verified to be a very efficient singlet oxygen quencher (Stahl et al., 2006), interacting with reactive oxygen species and mitigating their damaging effects (Waliszewski and Blasco, 2010). Lycopene administration exhibited protective effects on 3-NP induced mitochondrial dysfunctions and oxidative stress (Sandhir et al., 2010) and oxidative stress-induced cell death by preventing loss of DNA repair protein Ku70 (Seo et al., 2009). In a rat model, preincubation of spermatozoa with lycopene offered protection against oxidative DNA damage in vitro, the development of CP-induced lipid peroxidation in spermatogenic cells and CsA-induced oxidative stress in the testicular tissue and sperm quality (Turk et al., 2007 & 2010; Zini et al., 2010). Combined treatments of lycopene and CP tended to prevent the CP-induced testicular apoptosis, histopathological lesions and lipid peroxidation (Turk et al., 2011). Lycopene might reduce or prevent the side effects of chemotherapy due to its antioxidant and anti-inflammatory properties (Sahin et al., 2010). Lycopene has a significant contribution to the scavenging activity of methanolic mushroom extracts (Robaszkiewicz et al., 2010). Lycopene can also reduce oxidative stress and the levels of bone turnover markers in postmenopausal women, and may be beneficial in reducing the risk of osteoporosis (Rao et al., 2007). Lycopene administration could minimize the toxic effects of fluoride administration-induced oxidative stress by elevating levels of lipid peroxidation measured as malondialdehyde and total nitrate/nitrite in red blood cells, heart and brain tissues. The glutathione level was significantly decreased, and total anti-oxidant capacity and superoxide dismutase activity were increased in the examined tissues (Mansour and Tawfik, 2011). Lycopene could inhibit NASH-promoted hepatocarcinogenesis mainly as a result of reduced oxidative stress (Wang et al., 2010).

3.2. Antitumor Activities

Epidemiological and experimental studies provided supportive evidence that lycopene might act as a chemopreventive agent against many cancers, such as breast cancer, prostate cancer and colon cancer. Preclinical studies showed that lycopene had potently antitumor effects in vitro and in vivo, suggesting the potential preventive and therapeutic effects of lycopene (Seren et al., 2008).

Recent studies suggested that lycopene might possess specific biological activities on several important cellular signaling pathways and molecular targets. Lycopene was found to inhibit proliferation of cancer cells through arrest of tumor cell-cycle progression, IGF-1 (insulin-like growth factor 1) signaling transduction, and PDGF-BB (platelet-derived growth factor-BB)-induced cell

migration and apoptosis. Higher insulin-like growth factor I (IGF-I) concentrations in circulation were related to a greater risk of cancer, while lycopene supplementation might increase circulating IGFBP-1 and IGFBP-2 concentrations (Vrieling et al., 2007). Trapped of PDGF by lycopene compromised melanoma-induced fibroblast migration and attenuated signaling transduction in fibroblasts simulated by melanoma-derived conditioned medium, which suggested that lycopene might interfere with tumor stroma interactions (Wu et al., 2007). Lycopene could significantly inhibit DNA synthesis in a dose-dependent manner and androgen receptor gene element activity and expression (Zhang et al., 2010). Protection of lycopene against PAH-induced carcinogenesis in the breast was investigated in a cell culture model MCF-7. The results showed that lycopene inhibited recombinant CYP1A1 and CYP1B1 with estimated K(i)s in the micromolar range, and reduced the DMBA-induced ethoxyresorufin-O-deethylase activity by 20%, which illustrated that phase I enzyme inhibition and phase II enzyme induction were the underlying chemoprotective mechanisms of lycopene against PAH-induced toxicity (Wang and Leung, 2010). Human breast (MCF-7) and endometrial (ECC-1) cancer cells were synchronized in G0/G1 phase by serum deprivation followed by stimulation with IGF-I. Cell treatment with lycopene and atRA inhibited IGF-I-stimulated cell cycle progression from G_1 to S phase and decreased retinoblastoma protein phosphorylation which were associated with a reduction in cyclin D1 and p21 (CIP1/WAF1) level, but ectopic expression of cyclin D_1 could overcome cell cycle inhibition caused by lycopene and atRA (Nahum et al., 2006). Attenuation of cyclin D_l levels and atRA is an important mechanism for the reduction of the mitogenic action of IGF-I. Lycopene inhibited the growth of ER-positive MCF-7 cells through the inhibition of the cell cycle progression, and depressed the growth of the ER-negative MDA-MB-231 cells with the G_1 phase cell cycle-arrest and induced apoptosis (Wang and Zhang, 2007).

An increasing number of preclinical data, epidemiological evidence and clinical trials indicated potential roles of lycopene in the prevention and treatment of different prostate conditions such as hyperplasia, inflammation, and cancer (Magri et al., 2008). Lycopene emerged as a primary candidate for dietary intervention of prostate cancer (Zaripheh and Erdman, 2005) in cell proliferation which was further supported by a large randomized study of lycopene supplementation in malignant prostate disease, which might be associated with attenuation of proliferating cell nuclear antigen expression and interference of the insulin-like growth factor 1 signaling by increasing plasma insulin-like growth factor-binding protein-3 levels (Zhang et al., 2010). Several signaling pathways were identified in prostate cancer development, and the inhibition of VEGF by lycopene suggested that the antitumor mechanisms of lycopene also involve anti-angiogenesis (Yang et al., 2011). Lycopene could inhibit the proliferation of androgen-dependent prostate LNCaP cancer cells through the activation of the peroxisome proliferator-activated receptor gamma-liver X receptor alpha-ATP-binding cassette transporter 1 ($ABCA_1$) pathway, leading to reduced cellular total cholesterol levels (Yang et al., 2011). Lycopene could induce apoptosis of human prostate cancer cell line PC-3 by changing the cell cycle distribution and downregulating the expression of cyclin D_1 and bcl-2 and upregulating the expression of bax and then restraining cell proliferation (Wang and Zhang, 2007). Lycopene had activities in prostate cancer patients with prostate-specific antigen (PSA) relapse disease and might delay progression of both hormone-refractory and hormone-sensitive prostate cancer (Vaishampayan et al., 2007). Infection is a risk factor for prostate cancer, endogenous production of reactive oxygen species

during inflammation might lead to oxidative DNA damage, which could be mutagenic, if unrepaired. Androgen signaling, cytokine (IL-6, IL-4) and growth factor signaling (e.g. IGF and Wnt/beta-catenin) cross-talk via PI3K/Akt, MAPK, and Jak/STAT pathways was identified as major controllers of prostate growth. During disease progression, and after androgen ablation therapy, the remaining operational pathways were upregulated to compensate for the lost growth signal, and finally induced androgen-independent prostate cancer. Lycopene modulated several of the aforementioned pathways, providing a promising rationale for prostate cancer risk reduction. In many experiments, lycopene reduced inflammatory signals, prevented oxidative DNA damage, modulated the expression or activity of IGF axis members, Wnt/beta-catenin and androgen signaling, and enhanced gap junctional communication. Influence of lycopene on these pathways likely contributed to the cell growth inhibition and apoptosis induction. A substantial part of the effects of lycopene could be explained by its antioxidant action, and other mechanisms might also be involved (Wertz, 2009). Lycopene consumption inhibited IGF-I and androgen signaling in rat prostate cancer perhaps by attenuating IGF-I's effects on serine phosphorylation of Akt and GSK3beta and tyrosine phosphorylation of GSK3 (Liu et al., 2008). Prospective and retrospective epidemiological studies indicated an inverse relationship between lycopene intake and prostate cancer risk. Lycopene could inhibit the progression of benign prostate hyperplasia (BPH) and was an effective chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia (HGPIN) (Mohanty et al., 2005; Schwarz et al., 2008).

S-allylcysteine and lycopene alone significantly suppressed the development of gastric cancer, S-allylcysteine (SAC) and lycopene in combination might interact synergistically with high efficacy and lessened toxicity against gastric cancer (Velmurugan and Nagini, 2005). One of the possible mechanisms accounted for their synergistic chemopreventive activity against gastric cancer might be the induction of apoptosis by SAC and lycopene combination (Velmurugan et al., 2005). Upregulation of antioxidant and immunity by lycopene treatment might be responsible for the anticancer effect in gastric carcinoma (Luo and Wu, 2011). Inhibition of phase 1 metabolism and metabolic activation as well as induction of phase 2 detoxification enzyme activity were the potential mechanisms for the chemopreventive effects of lycopene (Tang et al., 2007). The inhibition of Hep3B cell growth also demonstrated the antitumor properties of lycopene (Park et al., 2005).

The inhibitory effects of lycopene on cell proliferation of human colon cancer HT-29 cells were associated with the downregulation of the PI-3K/Akt/mTOR signaling pathway and downstream targeted molecules, and could act as a chemopreventive agent against the growth and progression of colorectal cancer in a mouse xenograft model (Tang et al., 2008, 2009 & 2011). Tomato digestate and purified β-carotene had the same cell growth inhibition by an arrest of cell cycle progression at the G_0/G_1 and G_2/M phase, downregulating cyclin D_1, Bcl-2 and Bcl-xl expression and inducing apoptosis (Palozza et al., 2009). Lycopene could act as a chemopreventive agent to suppress MMP-7 expression and leptin-mediated cell invasion in human colon cancer HT-29 cells and effectively inhibit the phosphorylation of Akt, glycogen synthase kinase-3beta and ERK 1/2 proteins. The molecular mechanisms of lycopene were in part through decreasing nuclear levels of AP-1 and β-catenin proteins (Lin et al., 2011). Dietary micronutrients with antioxidant properties might play a role in reducing colorectal cancer risk (Kune and Watson, 2006).

In vitro, animal and clinical studies suggested that lycopene might attenuate the liver injury and possibly prevent the development of hepatic cellular cancer (Seren et al., 2008). Effects of lycopene on tumor cells and the apoptotic rate depended on its dosage and on the type of the malignant cells (Salman et al., 2007). Lycopene supplements might have potential therapeutic benefits in the adjuvant management of high-grade gliomas and osteosarcomas (Puri et al., 2010; Wakshlag and Balkman, 2010). Lycopene inhibited HMG-CoA reductase expression and cell growth and inactivated Ras in prostate PC-3, colon HCT-116 and HT-29 and lung BEN cancer cells (Palozza et al., 2010). Dietary lycopene with melatonin provided antioxidant defense with strong chemopreventive activity against DMBA-induced mammary tumors (Moselhy and Al, 2008). Pretreatment with lycopene offered protection against γ-radiation induced cellular damage and could be developed as an effective radioprotector during radiotherapy (Srinivasan et al., 2007 & 2009). In middle-aged men, the higher circulating concentrations of lycopene might contribute to the lower risk of cancers, with the exception of prostate cancer (Karppi et al., 2009).

3.3. Anti-atherosclerosis Activities

Atherosclerosis is a chronic disease with a high health impact, it was considered to be a chronic inflammatory response of the arterial wall initiated by an injury to the endothelium, including endothelial injury, lipoproteins accumulation, blood monocytes recruitment and consequent transformation in foam cells, release of factors from activated macrophages, platelets or vascular cells that cause migration of smooth muscle cells from media into the intima. Lycopene was demonstrated to inhibit ROS production in vitro, protect LDL from oxidation to prevent endothelial injury, modulate lipid metabolism through a control of cholesterol synthesis and oxysterol toxic activities, reduce inflammatory response through changes in cytokine production and inhibit smooth muscle cell proliferation through regulation of molecular pathways involved in cell proliferation and apoptosis (Palozza et al., 2010). Diabetes mellitus is characterized by oxidative stress, which in turn induces endothelial dysfunction. As a potent antioxidant compound, chronic lycopene treatment might be useful in preventing diabetic vascular complications associated with endothelial dysfunction (Zhu et al., 2011)**.** A study on healthy women showed an inverse relationship between arterial stiffness and circulating lycopene. Brachial-ankle pulse wave velocity inversely correlated with serum lycopene after adjustment for the confounders, blood pressure, insulin resistance, and oxidative stress ($r = -0.136$, $P < 0.05$). Oxidative stress markers also significantly correlated with baPWV as well as serum lycopene. When serum lycopene was lower than median level (≤ 0.0294 mmol/L), baPWV was significantly higher in metabolic syndrome subjects than that in non-metabolic syndrome subjects (1436 ± 41 vs 1367 ± 23 cm/s) after adjustment for age, body mass index, smoking, drinking, and oxidative stress ($P = 0.041$) (Yeo et al., 2011). Lycopene was observed to block the endothelial cell proliferation in a dose-dependent manner and significantly decreased tube formation, capillary-like tube lengths, and endothelial cell migration (Sahin et al., 2011). Higher serum levels of lycopene might play a protective role against cardiovascular diseases, especially carotid atherosclerosis (Riccioni et al., 2011). The LDL-oxidization plays a key role in the pathogenesis of atherosclerosis and cardiovascular diseases through the initiation of plaque formation process. Lycopene showed an antioxidant effect in reducing oxidative markers stress and LDL-oxidization process in both

epidemiological studies and supplementation human trials (Riccioni et al., 2008). Lycopene might act as a potential antiatherogenic agent by preventing 7-KC-induced oxidative stress and apoptosis in human macrophages (Palozza et al., 2010). It also played a potential role in attenuating foam cell formation and preventing atherosclerosis by a cascade mechanism involving inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, RhoA inactivation and subsequent inhibition of NF-kappa B nuclear binding and increase in PPAR gamma and liver X receptor alpha activities and enhancement of ABCA1 and cav-1 expressions (Palozza et al., 2011a & b). Lycopene reduced macrophage foam cell formation and modified LDL by decreasing lipid synthesis and downregulating the activity and expression of SR-A accompanied by impaired secretion of the anti-inflammatory cytokine IL-10. Lycopene decreased scavenger receptor activity by approximately 30% assessed by the uptake of acLDL, reduced the relative abundance of mRNA transcripts for scavenger receptor A in THP-1 macrophages treated with aggLDL and inhibited IL-10 secretion by up to 74% regardless of the presence of nLDL or aggLDL but did not affect IL-1beta or TNF-alpha release (Napolitano et al., 2007).

3.4. Cardioprotective Activities

Cardiovascular diseases (CVDs) result from the sub-endothelial accumulation of inflammatory cells and smooth muscle cells. Cardiovascular disease is associated with oxidative stress, inflammatory processes, and vascular dysfunction. Chronic inflammation and proatherogenic lipids are important risk factors of cardiovascular disease. A meta-analysis showed that lycopene taken in doses ≥ 25 mg daily effectively reduced LDL cholesterol by about 10% which was comparable to the effect of low doses of statins in patient with mildly elevated cholesterol levels (Ried and Fakler, 2011). A study in female transgenic mice showed that dietary supplementation of anti-inflammatory dietary mixture containing resveratrol, lycopene, catechin, vitamins E and C, and fish oil would improve lipid oxidation and inflammatory risk factors of CVD and strongly reduced atherosclerotic lesion development (Verschuren et al., 2011). Lycopene could inhibit PDGF-BB-induced cell proliferation and migration in rat A10 and aortic SMCs, the action mechanism of which was that lycopene was capable of binding PDGF-BB and inhibiting its interaction with SMC, which was quite different from those previously developed PDGFR-beta antagonists (Lo et al., 2007). In a rat model, treatment with the combination of vitamin E and lycopene in isoproterenol induced myocardial infarction for 30 days showed significantly cardioprotective effect compared to the individual treatment and ISO treated groups on biochemical and histopathological alteration (Upaganlawar et al., 2010). Lycopene could prevent cardiovascular diseases partly by decreasing the oxidative injury of endothelial cells induced by H_2O_2, attenuating the expression of p53 and caspase-3 mRNA in injured cells, and diminishing the apoptosis of injured cells (Tang et al., 2009). However, a prospective, nested, case-control study of 499 cases indicated that higher plasma lycopene concentrations were not associated with the risk of CVD of older men (Sesso et al., 2005).

3.5. Antiinflammation Activities

Lycopene has a potential role in suppressing rhinovirus induced airway inflammation (Saedisomeolia et al., 2009). Animal experiments showed that lycopene brought anti-inflammatory activity

into play by inhibiting iNOS proteins and mRNA expressions in mouse macrophage cell lines (Rafi et al., 2007). Lycopene supplementation was reported to significantly improve the changes associated with cisplatin nephrotoxicity primely through Nrf2/HO-1 signaling pathway and reduce inflammation by inhibiting NF-kappaB (Sahin et al., 2010). High dietary intake of lycopene showed protective effects against acute pancreatitis by protecting the pancreatic tissues from oxidative damage induced by cerulein, and this effect possibly involved the inhibition of neutrophil infiltration, lipid peroxidation, the NF-kappaB activation and the inflammatory cytokines expression through reduction in intracellular levels of ROS in pancreatic acinar cells (Kang et al., 2011; Ozkan et al., 2011). Lycopene prevented CSE-induced IL-8 production through a mechanism involving an inactivation of NF-κB which was accompanied by an activation of PPAR gamma signaling and an inhibition of redox signaling. These findings provided novel data on new molecular mechanisms by which lycopene regulated cigarette smoke-driven inflammation in human macrophages (Simone et al., 2011).

3.6. Antimutagenic Activities

Lycopene is an effective agent for preventing chemically-induced DNA and chromosome damage. The chemopreventive action of lycopene was examined on DNA damage and clastogenic or aneugenic effects of H_2O_2 and n-nitrosodiethylamine in the metabolically competent human hepatoma cell line and Chinese Hamster Ovary Cells. The results indicated that lycopene significantly reduced the genotoxicity and mutagenicity of H_2O_2 in all of the conditions tested (Scolastici et al., 2007 & 2008). In an animal experiment, lycopenen proved to be useful in reducing some of the toxic effects associated with certain classes of chemotherapeutic agents compared with the animals treated only with cDDP. After submitted to acute and subacute treatments with different lycopene doses, cDDP-treated animals showed a significant reduction ($p < 0.01$) in the number of abnormal metaphases, and the protective effects might be attributed to its antioxidant activity. The antimutagenic effects of lycopene were connected with the chemoprotective role in the prevention of carcinogenesis (Polivkova et al., 2010).

3.7. Other Bioactivities

In addition to the activities introduced above, there are still other effects involved in the bioactivities of lycopene, and some bioactivities of lycopene are summarized in Table 1. Lycopene has some protective effects on red blood cells, fibrinolytic activity promotion and aortic lesions decrease in hyperlipidemic rats by regulating the blood lipid and improving antioxidation (Xu et al., 2011; Zeng et al., 2009). Rat experiments showed that lycopene treatment might prevent the toxicity of cardiac and renal function impaired by adriamycin (Yilmaz et al., 2006). Lycopene induced a prolonged sustainment of gap junctional communication between an oocyte and the cumulus cells during porcine IVM culture, which was an effective cytoplasmic maturation of porcine IVM oocytes (Watanabe et al., 2010). Dietary supplementation or adequate intake of lycopene- and vitamin A-rich foods might be beneficial in asthmatic subjects (Riccioni et al., 2007). Consumption of adequate levels of lycopene might be useful to prevent heavy metal induced LPO and body weight loss (Rencuzogullari and Erdogan, 2007). Lycopene protected against TMT-induced neurotoxicity on hippocampal neurons by

inhibiting the mitochondrial apoptotic pathway (Qu et al., 2011). Pretreatment with lycopene efficiently attenuated Abeta(25-35)-induced neurotoxicity by improving cell viability and decreasing apoptotic rate, inhibited the reactive oxygen species generation and mitochondrial membrane potential depolarization caused by Abeta(25-35), restored the levels of proapoptotic Bax, antiapoptotic Bcl-2, and inhibited caspase-3 activation (Qu et al., 2011). Lycopene could also exert protective effects against cigarette smoke condensate (Palozza et al., 2005). In addition, lycopene exerted potently antifungal activity on the serum-induced mycelia of *Candida albicans*. It caused significant destruction of the membrane integrity and inhibited the normal budding process (Sung et al., 2007).

Table 1. Bioactivities of Lycopene

Bioactivity	**Reference**
antioxidant and scavenging free radical	Mansour and Tawfik, 2011; Robaszkiewicz et al., 2010; Sandhir et al., 2010; Seo et al., 2009; Turk et al., 2007, 2010 & 2011; Waliszewski and Blasco, 2010; Wang et al., 2010; Zini et al., 2010
chemopreventive agent against breast cancer, prostate cancer, colon cancer, and gastric cancer	Magri et al., 2008; Nahum et al., 2006; Seren et al., 2008; Tang et al., 2008, 2009 & 2011; Vaishampayan et al., 2007; Velmurugan and Nagini, 2005; Vrieling et al., 2007; Wang and Leung, 2010; Wang and Zhang, 2007; Zhang et al., 2010
protecting against γ-radiation	Srinivasan et al., 2007 & 2009
anti-atherosclerosis	Napolitano et al., 2007; Palozza et al., 2010; Yeo et al., 2011; Zhu et al., 2011
cardioprotective	Lo et al., 2007;Ried and Fakler, 2011; Tang et al., 2009; Upaganlawar et al., 2010; Verschuren et al., 2011
antiinflammation	Kang et al., 2011; Ozkan et al., 2011; Rafi et al., 2007; Saedisomeolia et al., 2009; Sahin et al., 2010; Simone et al., 2011
antimutagenic	Polivkova et al., 2010; Scolastici et al., 2007 & 2008
promoting fibrinolytic activity	Xu et al., 2011
decreasing aortic lesions	Zeng et al., 2009
beneficial for asthmatic	Riccioni et al., 2007
preventing harm induced by heavy metal	Rencuzogullari and Erdogan, 2007
protecting against TMT-induced neurotoxicity	Qu et al., 2011
protecting against cigarette smoke condensate	Palozza et al., 2005
protecting on bone health in older adults	Sahni et al., 2009
beneficial for oral diseases	Lu et al., 2011
antinociceptive	Kuhad et al., 2008
antifungal	Sung et al., 2007

Lycopene played a protective role on bone health in older adults (Sahni et al., 2009), and daily consumption of lycopene significantly increased antioxidant capacity and decreased oxidative stress and the bone resorption marker N-telopeptide (NTx). Lycopene acted as an antioxidant to decrease bone resorption makers in postmenopausal women and may be beneficial in reducing the risk of osteoporosis (Mackinnon et al., 2011). The studies showed that lycopene might have beneficial effects in the management of some premalignant lesions in the oral cavity including oral submucous fibrosis and oral leukoplakia and might be an adjunct in the prevention and therapy of oral cancer (Lu et al., 2011). Lycopene might prevent smoke exposure-induced changes in p53, p53 phosphorylation, p53 target genes, p21 (Waf_1/Cip_1), Bax-1, cleaved caspase 3, cyclin D_1, and PCNA in a dose-dependent fashion, and decreased cell proliferation and apoptosis in the gastric mucosa of ferrets (Liu et al., 2006). Lycopene could be used as a first line of therapy in the initial management of oral submucous fibrosis (Kumar et al., 2007). Lycopene also inhibited the TNF-alpha and NO release in a dose dependent manner, indicating an antinociceptive activity of lycopene and a potential to attenuate diabetic neuropathic pain (Kuhad et al., 2008).

4. Conclusions and Prospects

Lycopene is the red pigment that plays an important role in plants, animals and humans. The resource, extraction, stability and bioactivities as well as action mechanisms of lycopene have been summarized. The consumption of lycopene rich foods can help to prevent degenerative diseases. Many bioactivities of lycopene have been found, such as antioxidant and free radical scavenging capacities, anticancer capacities, anti-atherosclerosis capacities, cardiopretective capacities, antiinflammation, antimutigenic capacities, and antifungal capacities. In the future, bioavailability, recommended intake, the action mechanism towards diseases, interaction with other compounds and the metabolites activities should be further studied. In addition, more widely pharmacological studies should be carried out to find out new pharmacodynamic effects.

Acknowledgments

This research was supported by the Hundred-Talents Scheme of Chinese Academy of Sciences, and the Hundred-Talents Scheme of Sun Yat-Sen University.

References

Kang, M., Park, K. S., Seo, J. Y., and Kim, H. (2011). Lycopene inhibits IL-6 expression in cerulein-stimulated pancreatic acinar cells. *Genes. Nutr.*, **6**: 117-123.

Karppi, J., Kurl, S., Nurmi, T., Rissanen, T. H., Pukkala, E., and Nyyssönen, K. (2009). Serum lycopene and the risk of cancer: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study. *Ann. Epidemiol.*, **19**: 512-518.

Katherine, L. S., Edgar, C. C., Jerry, W. K., Luke, R. H., and Julie, C. D. (2008). Extraction conditions affecting supercritical fluid extraction (SFE) of lycopene from watermelon. *Bioresour. Technol.*, **99**: 7835-7841.

Kuhad, A., Sharma, S., and Chopra, K. (2008). Lycopene attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. *Eur. J. Pain*, **12**: 624-632.

Kumar, A., Bagewadi, A., Keluskar, V., and Singh, M. (2007). Efficacy of lycopene in the management of oral submucous fibrosis. Oral Surg. Oral Med. Oral Pathol. *Oral Radiol. Endod.*, **103**: 207-213.

Kune, G., and Watson, L. (2006). Colorectal cancer protective effects and the dietary micronutrients folate, methionine, vitamins B6, B12, C, E, selenium, and lycopene. *Nutr. Cancer*, **56**: 11-21.

Lin, M. C., Wang, F. Y., Kuo, Y. H., and Tang, F. Y. (2011). Cancer chemopreventive effects of lycopene: suppression of MMP-7 expression and cell invasion in human colon cancer cells. *J. Agric. Food Chem.*, **59**: 11304-11318.

Liu, C., Russell, R. M., and Wang, X. D. (2006). Lycopene supplementation prevents smoke-induced changes in p53, p53 phosphorylation, cell proliferation, and apoptosis in the gastric mucosa of ferrets. *J. Nutr.*, **136**: 106-111.

Liu, X. X., Allen, J. D., Arnold, J. T., and Blackman, M. R. (2008). Lycopene inhibits IGF-I signal transduction and growth in normal prostate epithelial cells by decreasing DHT-modulated IGF-I production in co-cultured reactive stromal cells. *Carcinogenesis*, **29**: 816-823.

Lo, H. M., Hung, C. F., Tseng, Y. L., Chen, B. H., Jian, J. S., and Wu, W. B. (2007). Lycopene binds PDGF-BB and inhibits PDGF-BB-induced intracellular signaling transduction pathway in rat smooth muscle cells. *Biochem. Pharmacol.*, **74**: 54-63.

Lu, R., Dan, H. X., Wu, R. Q., Meng, W. X., Liu, N., Jin, X., Zhou, M., Zeng, X., and Zhou, G. (2011). Lycopene: features and potential significance in the oral cancer and precancerous lesions. *J. Oral Pathol. Med.*, **40**: 361-368.

Luo, C., and Wu, X. G. (2011). Lycopene Enhances Antioxidant Enzyme Activities and Immunity Function in N-Methyl-N'-nitro-N-nitrosoguanidine-Induced Gastric Cancer Rats. *Int. J. Mol. Sci.*,**12**: 3340-3351.

Mackinnon, E. S., Rao, A. V., and Rao, L. G. (2011). Dietary restriction of lycopene for a period of one month resulted in significantly increased biomarkers of oxidative stress and bone resorption in postmenopausal women. *J. Nutr. Health Aging*, **15**: 133-138.

Magri, V., Trinchieri, A., Perletti, G., and Marras, E. (2008). Activity of Serenoa repens, lycopene and selenium on prostatic disease: evidences and hypotheses. *Arch. Ital. Urol. Androl.*, **80**: 65-78.

Maresca, J. A., Graham, J. E., Wu, M., Eisen, J. A., and Bryant, D. A. (2007). Identification of a fourth family of lycopene cyclases in photosynthetic bacteria. *Proc. Natl. Acad. Sci. USA*, **104**: 11784-11789.

Meydan, D., Gursel, B., Bilgici, B., Can, B., and Ozbek, N. (2011). Protective effect of lycopene against radiation-induced hepatic toxicity in rats. *J. Int. Med. Res.*, **39**: 1239-1252.

Mohanty, N. K., Saxena, S., Singh, U. P., Goyal, N. K., and Arora, R. P. (2005). Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. *Urol. Oncol.*, **23**: 383-385.

Moselhy, S. S., and Al Mslmani, M. A. B. (2008). Chemopreventive effect of lycopene alone or with melatonin against the genesis of oxidative stress and mammary tumors induced by 7,12 dimethyl(a)benzanthracene in sprague dawely female rats. *Mol. Cell Biochem.*, **319**: 175-180.

Nahum, A., Zeller, L., Danilenko, M., Prall, O. W. J., Watts, C. K. W., Sutherland, R. L ., Levy, J., and Sharoni, Y. (2006). Lycopene inhibition of IGF-induced cancer cell growth depends on the level of cyclin D1. *Eur. J. Nutr.*, **45**: 275-282.

Napolitano, M., De Pascale, C., Wheeler-Jones, C., Botham, K. M., and Bravo, E. (2007). Effects of lycopene on the induction of foam cell formation by modified LDL. *Am. J. Physiol. Endocrinol. Metab.*, **293**: 1820-1827.

Palozza, P., Sheriff, A., Serini, S., Boninsegna, A., Maggiano, N., Ranelletti, F. O., Calviello, G., and 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., Bellovino, D., Simone, R., Boninsegna, A., Cellini, F., Monastra, G., and Gaetani, S. (2009). Effect of beta-carotene-rich tomato lycopene beta-cyclase (tlcy-b) on cell growth inhibition in HT-29 colon adenocarcinoma cells. *Br. J. Nutr.*, **102**: 207-214.

Palozza, P., Colangelo, M., Simone, R., Catalano, A., Boninsegna, A., Lanza, P., Monego, G., and Ranelletti, F. O. (2010). 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. E., and Catalano, A. (2010). 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., Bohm, V., Frohlich, K., Mele, M. C., Monego, G., and Ranelletti, F. O. (2010). Lycopene prevents 7-ketocholesterol-induced oxidative stress, cell cycle arrest and apoptosis in human macrophages. *J. Nutr. Biochem.*, **21**: 34-46.

Palozza, P., Simone, R., Catalano, A., Monego, G., Barini, A., Mele, M. C., Parrone, N., Trombino, S., Picci, N., and Ranelletti, F. O. (2011a). Lycopene prevention of oxysterol-induced proinflammatory cytokine cascade in human macrophages: inhibition of NF-kappaB nuclear binding and increase in PPARgamma expression. *J. Nutr. Biochem.*, **22**: 259-268.

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

Park, Y. O., Hwang, E. S., and Moon, T. W. (2005). The effect of lycopene on cell growth and oxidative DNA damage of Hep3B human hepatoma cells. *Biofactors*, **23**: 129-139.

Polivkova, Z., Smerak, P., Demova, H., and Houska, M. (2010). Antimutagenic effects of lycopene and tomato puree. *J. Med. Food*, **13**: 1443-1450.

Puri, T., Goyal, S., Julka, P. K., Nair, O., Sharma, D. N., and Rath, G. K. (2010). Lycopene in treatment of high-grade gliomas: a pilot study. *Neurol. India*, **58**: 20-23.

Qu, M. Y., Li, L., Chen, C. H., Li, M., Pei, L. P., Chu, F., Yang, J., Yu, Z. P., Wang, D. G., and Zhou, Z. (2011). Protective effects of lycopene against amyloid beta-induced neurotoxicity in cultured rat cortical neurons. *Neurosci. Lett.*, **505**: 286-290.

Qu, M. Y., Zhou, Z., Chen, C. H., Li, M., Pei, L. P., Chu, F., Yang, J., Wang, Y., Li, L., Liu, C., Zhang, L., Zhang, G. B., Yu, Z. P., and Wang, D. G. (2011). Lycopene protects against trimethyltin-

induced neurotoxicity in primary cultured rat hippocampal neurons by inhibiting the mitochondrial apoptotic pathway. *Neurochem. Int.*, **59**: 1095-1103.

Rafi, M. M., Yadav, P. N., and Reyes, M. (2007). Lycopene inhibits LPS-induced proinflammatory mediator inducible nitric oxide synthase in mouse macrophage cells. *J. Food Sci.*, **72**: S069-074.

Rao, A. V., Ray, M. R., and Rao, L. G. (2006). Lycopene. *Adv. Food Nutr. Res.*, **51**: 99-164.

Rao, L. G., Mackinnon, E. S., Josse, R. G., Murray, T. M., Strauss, A., and Rao, A. V. (2007). Lycopene consumption decreases oxidative stress and bone resorption markers in postmenopausal women. *Osteoporos Int.*, **18**: 109-115.

Rencuzogullari, N., and Erdogan, S. (2007). Oral administration of lycopene reverses cadmium-suppressed body weight loss and lipid peroxidation in rats. *Biol. Trace Elem. Res.*, **118**: 175-183.

Riccioni, G., Mancini, B., Di llio, E., Bucciarelli, T., and D'Orazio, N. (2008). Protective effect of lycopene in cardiovascular disease. *Eur. Rev. Med. Pharmacol. Sci.*, **12**: 183-190.

Riccioni, G., Scotti, L., Di llio, E., Bucciarelli, V., Ballone, E., De Girolamo, M., D'Orazio, N., Martini, F., Aceto, A., and Bucciarelli, T. (2011). Lycopene and preclinical carotid atherosclerosis. *J. Biol. Regul. Homeost. Agents*, **25**: 435-441.

Riccioni, G., Bucciarelli, T., Mancini, B., Di llio, C., Della Vecchia, R., and D'Orazio, N. (2007). Plasma lycopene and antioxidant vitamins in asthma: the PLAVA study. *J. Asthma*, **44**: 429-432.

Ried, K. and Fakler, P. (2011). Protective effect of lycopene on serum cholesterol and blood pressure: Meta-analyses of intervention trials. *Maturitas*, **68**: 299-310.

Robaszkiewicz, A., Bartosz, G., Lawrynowicz, M., and Soszynski, M. (2010). The Role of Polyphenols, beta-Carotene, and Lycopene in the Antioxidative Action of the Extracts of Dried, Edible Mushrooms. *J. Nutr. Metab.*, Article ID: 173274.

Saedisomeolia, A., Wood, L. G., Garg, M. L., Gibson, P. G., and Wark, P. A. B. (2009). Lycopene enrichment of cultured airway epithelial cells decreases the inflammation induced by rhinovirus infection and lipopolysaccharide. *J. Nutr. Biochem.*, **20**: 577-585.

Sahin, K., Tuzcu, M., Sahin, N., Ali, S., and 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.

Sahin, K., Sahin, N., and Kucuk, O. (2010). Lycopene and chemotherapy toxicity. *Nutr. Cancer*, **62**: 988-995.

Sahni, S., Hannan, M. T., Blumberg, J., Cupples, L. A., Kiel, D. P., and Tucker, K. L. (2009). Protective effect of total carotenoid and lycopene intake on the risk of hip fracture: a 17-year follow-up from the Framingham Osteoporosis Study. *J. Bone Miner. Res.*, **24**: 1086-1094.

Salman, H., Bergman, M., Djaldetti, M., and Bessler, H. (2007). Lycopene affects proliferation and apoptosis of four malignant cell lines. *Biomed. Pharmacother.*, **61**: 366-369.

Sandhir, R., Mehrotra, A., and Kamboj, S. S. (2010). Lycopene prevents 3-nitropropionic acid-induced mitochondrial oxidative stress and dysfunctions in nervous system. *Neurochem. Int.*, **57**: 579-587.

Schwarz, S., Obermuller-Jevic, U. C., Hellmis, E., Koch, W., Jacobi, G., and Biesalski, H. K. (2008). Lycopene inhibits disease progression in patients with benign prostate hyperplasia. *J. Nutr.*, **138**: 49-53.

Scolastici, C., Alves de Lima, R. O., Barbisan, L. F., Ferreira, A. L., Ribeiro, D. A., and Salvadori, D. M. F. (2007). Lycopene activity against chemically induced DNA damage in Chinese hamster ovary cells. *Toxicol. In Vitro*, **21**: 840-845.

Scolastici, C., de Lima, R. O. A., Barbisan, L. F., Ferreira, A. L. A., Ribeiro, D. A., and Salvadori, D. M. F. (2008). Antigenotoxicity and antimutagenicity of lycopene in HepG2 cell line evaluated by the comet assay and micronucleus test. *Toxicol. In Vitro*, **22**: 510-514.

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

Seren, S., Mutchnick, M., Hutchinson, D., Harmanci, O., Bayraktar, Y., Mutchnick, S., Sahin, K., and Kucuk, O. (2008). Potential role of lycopene in the treatment of hepatitis C and prevention of hepatocellular carcinoma. *Nutr. Cancer*, **60**: 729-735.

Seren, S., Lieberman, R., Bayraktar, U. D., Heath, E., Sahin, K., Andic, F., and Kucuk, O. (2008). Lycopene in cancer prevention and treatment. *Am. J. Ther.*, **15**: 66-81.

Sesso, H. D., Buring, J. E., Norkus, E. P., and Gaziano, J. M. (2005). Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in men. *Am. J. Clin. Nutr.*, **81**: 990-997.

Shao, A., and Hathcock, J. N. (2006). Risk assessment for the carotenoids lutein and lycopene. *Regul. Toxicol. Pharmacol.*, **45**: 289-298.

Simone, R. E., Russo, M., Catalano, A., Monego, G., Froehlich, K., Boehm, V., and Palozza, P. (2011). Lycopene inhibits NF-kB-mediated IL-8 expression and changes redox and PPARgamma signalling in cigarette smoke-stimulated macrophages. *Plos. One*, **6**: No. 19652.

Srinivasan, M., Sudheer, A. R., Pillai, K. R., Kumar, P. R., Sudhakaran, P. R., and Menon, V. P. (2007). Lycopene as a natural protector against gamma-radiation induced DNA damage, lipid peroxidation and antioxidant status in primary culture of isolated rat hepatocytes in vitro. *Biochim. Biophys. Acta.*, **1770**: 659-665.

Srinivasan, M., Devipriya, N., Kalpana, K. B., and Menon, V. P. (2009). Lycopene: An antioxidant and radioprotector against gamma-radiation-induced cellular damages in cultured human lymphocytes. *Toxicology*, **262**: 43-49.

Stahl, W., Heinrich, U., Aust, O., Tronnier, H., and Sies, H. (2006). Lycopene-rich products and dietary photoprotection. *Photochem. Photobiol. Sci.*, **5**: 238-242.

Sung, W. S., Lee, I. S., and Lee, D. G. (2007). Damage to the cytoplasmic membrane and cell death caused by lycopene in *Candida albicans*. *J. Microbiol. Biotechnol.*, **17**: 1797-1804.

Suwannalert, P., Boonsiri, P., Khampitak, T., Khampitak, K., Sriboonlue, P., and Yongvanit, P. (2007). The levels of lycopene, alpha-tocopherol and a marker of oxidative stress in healthy northeast Thai elderly. *Asia Pac. J. Clin. Nutr.* **16** (Suppl. 1): 27-30.

Tang, F. Y., Shih, C. J., Cheng, L. H., Ho, H. J., Chen, H. J. (2008). Lycopene inhibits growth of human colon cancer cells via suppression of the Akt signaling pathway. *Mol. Nutr. Food Res.*, **52**: 646-654.

Tang, F. Y., Cho, H. J., Pai, M. H., and Chen, Y. H. (2009). Concomitant supplementation of lycopene and eicosapentaenoic acid inhibits the proliferation of human colon cancer cells. *J. Nutr. Biochem.*, **20**: 426-434.

Tang, F. Y., Pai, M. H., and Wang, X. D. (2011). Consumption of lycopene inhibits the growth and progression of colon cancer in a mouse xenograft model. *J. Agric. Food Chem.,* **59**: 9011-9021.

Tang, L. L., Guan, H. X., Ding, X. L., and Wang, H. S. (2007). Modulation of aflatoxin toxicity and biomarkers by lycopene in F344 rats. *Toxicol. Appl. Pharmacol.*, **219**: 10-17.

Tang, X. Y., Yang, X. D., Peng Y. F., and Lin, J. H. (2009). Protective effects of lycopene against H2O2-induced oxidative injury and apoptosis in human endothelial cells. *Cardiovasc. Drugs Ther.*, **23**: 439-448.

Tiback, E. A., Svelander, C. A., Colle, I. J. P., Altskar, A. I., Alminger, M. A. G., Hendrickx, M. E. G ., Ahrne, L. M., and Langton, M. I. B. C. (2009). Mechanical and thermal pretreatments of crushed tomatoes: effects on consistency and in vitro accessibility of lycopene. *J. Food Sci.*, **74**: 386-395.

Topal, U., Sasaki, M., Goto, M., and Hayakawa, K. (2006). Extraction of lycopene from tomato skin with supercritical carbon dioxide: effect of operating conditions and solubility analysis. *J. Agric. Food Chem.,* **54**: 5604-5610.

Turk, G., Atessahin, A., Sonmez, M., Yuce, A., and Ceribasi, A. O. (2007). Lycopene protects against cyclosporine A-induced testicular toxicity in rats. *Theriogenology*, **67**: 778-785.

Turk, G., Ceribasi, A. O., Sakin, F., Sonmez, M., and Atessahin, A. (2010). Antiperoxidative and anti-apoptotic effects of lycopene and ellagic acid on cyclophosphamide-induced testicular lipid peroxidation and apoptosis. *Reprod. Fertil. Dev.*, **22**: 587-596.

Turk, G., Ceribasi, A. O., Sahna, E., and Atessahin, A. (2011). Lycopene and ellagic acid prevent testicular apoptosis induced by cisplatin. *Phytomedicine*, **18**: 356-361.

Upaganlawar, A., Gandhi, H., and Balaraman, R. (2010). Effect of vitamin E alone and in combination with lycopene on biochemical and histopathological alterations in isoproterenol-induced myocardial infarction in rats. *J. Pharmacol. Pharmacother.*, **1**: 24-31.

Vaishampayan, U., Hussain, M., Banerjee, M., Seren, S., Sarkar, F. H., Fontana, J., Forman, J. D., Cher, M. L., Powell, I., Pontes, J. E., and Kucuk, O. (2007). Lycopene and soy isoflavones in the treatment of prostate cancer. *Nutr. Cancer*, **59**: 1-7.

van Breemen, R. B., and Pajkovic, N. (2008). Multitargeted therapy of cancer by lycopene. *Cancer Lett.*, **269**: 339-351.

Velmurugan, B., Mani, A., and Nagini, S. (2005). Combination of S-allylcysteine and lycopene induces apoptosis by modulating Bcl-2, Bax, Bim and caspases during experimental gastric carcinogenesis. *Eur. J. Cancer Prev.*, **14**: 387-393.

Velmurugan, B., and Nagini, S. (2005). Combination chemoprevention of experimental gastric carcinogenesis by s-allylcysteine and lycopene: modulatory effects on glutathione redox cycle antioxidants. *J. Med. Food*, **8**: 494-501.

Verschuren, L., Wielinga, P. Y., van Duyvenvoorde, W., Tijani, S., Toet, K., van Ommen, B., Kooistra, T., and Kleemann, R. (2011). A dietary mixture containing fish oil, resveratrol, lycopene, catechins, and vitamins E and C reduces atherosclerosis in transgenic mice. *J. Nutr.*, **141**: 863-869.

Vrieling, A., Voskuil, D. W., Bonfrer, J. M., Korse, C. M., van Doorn, J., Cats, A., Depla, A. C., Timmer, R., Witteman, B. J., van Leeuwen, F. E., van't Veer, L. J., Rookus, M. A., and Kampman, E. (2007). Lycopene supplementation elevates circulating insulin-like growth factor binding

protein-1 and -2 concentrations in persons at greater risk of colorectal cancer. *Am. J. Clin. Nutr.*, **86**: 1456-1462.

Wakshlag, J. J., and Balkman, C. E. (2010). Effects of lycopene on proliferation and death of canine osteosarcoma cells. *Am. J. Vet. Res.*, **71**: 1362-1370.

Waliszewski, K. N., and Blasco, G. (2010). Nutraceutical properties of lycopene. *Salud Publica Mex.*, **52**: 254-265.

Wan, Q., Zhang, X. G., and Song, M. (2007). Fruit-specific RNAi-mediated Lcy gene enhances content of lycopene in tomatoes silencing. *Chin. J. Biotechnol.*, **23**: 429-433.

Wang, A. H., and Zhang, L. S. (2007). Effect of lycopene on the proliferation of MCF-7 and MDA-MB-231 cells. *J. Sichuan Univ. Med. Sci. Edit.*, **38**: 958-960.

Wang, A., and Zhang, L. (2007). Effect of lycopene on proliferation and cell cycle of hormone refractory prostate cancer PC-3 cell line. *J. Hyg. Res.*, **36**: 575-578.

Wang, H., and Leung, L. K. (2010). The carotenoid lycopene differentially regulates phase I and II enzymes in dimethylbenz[a]anthracene-induced MCF-7 cells. *Nutrition*, **26**: 1181-1187.

Wang, L., Liu, S., Manson, J. E., Gaziano, J. M., Buring, J. E., and Sesso, H. D. (2006). The consumption of lycopene and tomato-based food products is not associated with the risk of type 2 diabetes in women. *J. Nutr.* **136**: 620-625.

Wang, Y., Ausman, L. M., Greenberg, A. S., Russell, R. M., and Wang, X. D. (2010). Dietary lycopene and tomato extract supplementations inhibit nonalcoholic steatohepatitis-promoted hepatocarcinogenesis in rats. *Int. J. Cancer*, **126**: 1788-1796.

Watanabe, H., Okawara, S., Bhuiyan, M. M. U., and Fukui, Y. (2010). Effect of lycopene on cytoplasmic maturation of porcine oocytes in vitro. *Reprod. Domest. Anim.*, **45**: 838-845.

Wertz, K. (2009). Lycopene effects contributing to prostate health. *Nutr. Cancer*, **61**: 775-783.

Wu, W. B., Chiang, H. S., Fang, J. Y., and Hung, C. F. (2007). Inhibitory effect of lycopene on PDGF-BB-induced signalling and migration in human dermal fibroblasts: a possible target for cancer. *Biochem. Soc. Trans.*, **35**: 1377-1378.

Xianquan, S., Shi, J., Kakuda, Y., and Yueming J. (2005). Stability of lycopene during food processing and storage. *J. Med. Food*, **8**: 413-422.

Xu, X. l., Zhu, M., and Hu, M. Y. (2011). Effects of lycopene on blood cells and fibrinolytic activity in hyperlipidemic rats. *J. Hyg. Res.*, **40**: 620-623.

Yang, C. M., Lu, Y. L., Chen, H. Y., and Hu, M. L. (2012). Lycopene and the LXRalpha agonist T0901317 synergistically inhibit the proliferation of androgen-independent prostate cancer cells via the PPARgamma-LXRalpha-ABCA1 pathway. *J. Nutr. Biochem.*, (In Press).

Yang, C. M., Yen, Y. T., and Huang, C. S. (2011). Growth inhibitory efficacy of lycopene and beta-carotene against androgen-independent prostate tumor cells xenografted in nude mice. *Mol. Nutr. Food Res.*, **55**: 606-612.

Yeo, H. Y., Kim, O. Y., Lim, H. H., Kim, J. Y., and Lee, J. H. (2011). Association of serum lycopene and brachial-ankle pulse wave velocity with metabolic syndrome. *Metabolism*, **60**: 537-543.

Yilmaz, S., Atessahin, A., Sahna, E., Karahan, I., and Ozer, S. (2006). Protective effect of lycopene on adriamycin-induced cardiotoxicity and nephrotoxicity. *Toxicology*, **218**: 164-171.

Zaripheh, S., and Erdman, J. J. (2005). The biodistribution of a single oral dose of [14C]-lycopene in rats prefed either a control or lycopene-enriched diet. *J. Nutr.*, **135**: 2212-2218.

Zaripheh, S., Nara, T. Y., Nakamura, M. T., and Erdman, J. W. Jr. (2006). Dietary lycopene downregulates carotenoid 15,15'-monooxygenase and PPAR-gamma in selected rat tissues. *J. Nutr.*, **136**: 932-938.

Zeng, Y. C., Hu, M. Y., Qu, S. L., and Zhou, G. Y. (2009). Effects of lycopene on blood lipid and red blood cell of rat with hypercholesterolemia, *Chin. J. Preven. Med.*, **43**: 1064-1068.

Zhang, X., Wang, Q., Neil, B., and Chen, X. (2010). Effect of lycopene on androgen receptor and prostate-specific antigen velocity. *Chin. Med. J. (Engl.)*, **123**: 2231-2236.

Zhu, J., Wang, C. G., and Xu, Y. G. (2011). Lycopene attenuates endothelial dysfunction in streptozotocin-induced diabetic rats by reducing oxidative stress. *Pharm. Biol.*, **49**: 1144-1149.

Zhu, Y. H., Jiang, J. G., and Chen, Q. (2008). Characterization of cDNA of lycopene beta-cyclase responsible for a high level of beta-carotene accumulation in Dunaliella salina. Biochem. *Cell. Biol.*, **86**: 285-292.

Zini, A., Gabriel, M. S., and Libman, J. (2010). Lycopene supplementation in vitro can protect human sperm deoxyribonucleic acid from oxidative damage. *Fertil. Steril.*, **94**: 1033-1036.