Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

TOMATO AND TOMATO BY-PRODUCTS. HUMAN HEALTH BENEFITS OF LYCOPENE AND ITS APPLICATION TO MEAT PRODUCTS: A REVIEW

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Accepted author version posted online: 26 Mar 2013.

To cite this article: Critical Reviews in Food Science and Nutrition (2013): TOMATO AND TOMATO BY-PRODUCTS. HUMAN HEALTH BENEFITS OF LYCOPENE AND ITS APPLICATION TO MEAT PRODUCTS: A REVIEW, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2011.623799

To link to this article: http://dx.doi.org/10.1080/10408398.2011.623799

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ABSTRACT

During recent decades the food industry, consumers and regulatory authorities have developed a significant interest in functional foods because of their potential benefits for human health over and above their basic nutritional value. Tomato is the second most important vegetable crop in the world. The amount of the related wastes is estimated at up to 50 thousand tons per year, representing a serious disposal problem with a consequent negative impact on the environment. Tomato by-products contain a great variety of biologically active substances, principally lycopene, which have been demonstrated by *in vitro* and *in vivo* studies to possess antioxidant, hypolipidemic and anticarcinogenic activities. The aim of this review is to present an overview of the functional and physiological properties of the principal bioactive compound present in tomato and tomato by-products, lycopene, its addition to meat and meat products.

Keywords: Tomatoes, lycopene, health properties, meat, meat products

INTRODUCTION

The industrial transformation of vegetables and fruits generates large quantities of by-products rich in bioactive compounds that may well be suitable for other purposes (Viuda-Martos et al., 2009). The importance of natural food additives is increasing due to the more extensive use of natural compounds in foods, cosmetics and pharmaceuticals, following EU directives in favor of natural rather than synthetic additives. The recycling or re-usage of by-products that are accumulated during processing and are available in high amounts can reduce treatment costs (Vági et al., 2007).

Of all vegetables, the tomato (*Lycopersicon esculentum*) is both qualitatively and quantitatively one of the most important components of the Mediterranean Diet. The history of tomatoes, one of the most widely available vegetables today, is long. Tomatoes have been cultivated in Europe as a food source since the 16th century, although they used to be considered as poisonous in various areas and used for decorative purposes only (Salman et al., 2007). Tomatoes are mainly consumed as a raw staple food due to their desirable nutritional properties but they are also increasingly in many popular tomato products (Pérez-Conesa et al., 2009). More than 80% of tomatoes grown are consumed in the form of processed products such as juice, soup, concentrate, dry-concentrate, sauce, salsa, puree, dry-tomato, ketchup or paste (Kaur et al., 2008). The demand for any kind of processing step usually stems from a variety of origins to make products available out of season (such as canned tomatoes); to produce products

especially suited for home-consumption (such as tomato ketchup); for conversion into new food products with alternative/supplemented flavor and texture (such as sauces, soups); to provide better nutritional characteristics; and, to add value for extra income (Capanoglu et al., 2010).

The by-products obtained during tomato processing (Figure 1) are mainly from tomato pomace. Wet pomace contains 33% seed, 27% skin and 40% pulp, while dried pomace contains 44% seed and 56% pulp and skin (Sogi and Bawa, 1998). In fact, the management of tomato by-products is one of the most important sustainability-related issues faced by processing companies involved in agriculture today, due to the potential negative effects of undesirable materials discharged into the environment. If these products remain unused, they not only add to the problems of disposal but they also aggravate environmental pollution (Garcia et al., 2009). However the treatment of wastes is perceived as an expensive process, whose implementation impacts negatively on the economic viability/sustainability of commercial enterprises.

One way of avoiding this problem would be to re-use the tomato by-products obtained from the tomato industry to take advantage of the large quantity of potentially beneficial compounds they contain. Tomato by-products contain a variety of biologically active substances which mostly go to waste despite being a promising source of dietary fibers, proteins, carotenoids, tocopherols, polyphenols and other compounds (Vági et al., 2007; Lavelli and Torresani, 2011). Among these bioactive compounds polyphenols, carotenoids and vitamins have a wide range of physiological properties such as anti-inflammatory, anti-allergenic, antimicrobial, vasodilatory, anti-thrombotic, cardio-protective and antioxidant effects (Yang et al., 2008).

Carotenoids, particularly lycopene, represent the primary components of ripe fruit pigmentation in tomato pericarp and tomato products (Table 1) where they are responsible for

the characteristic color of ripe tomatoes, conferring deep red and orange colors, respectively (Liu et al., 2009) and the same compounds are also present in tomato by-products. Furthermore, the amount of lycopene and other carotenoids in tomatoes depends on several factors, including variety as well as fruit maturity at harvesting (Thompson et al., 2000). Similar to most fruit and vegetables, tomato creates a surplus during the production season and become insufficient during off-season (Liu et al., 2010). The all-*trans* isomer of lycopene, the most stable form, is most prevalent in fresh tomatoes. Nevertheless, it is liberated from the tissue matrix during processing and spontaneously undergoes isomerization and oxidation, which causes pigment degradation. A greater loss of lycopene occurs when various heat treatments such as blanching, sterilization and drying are applied (Bruno and Wetzel, 2004; Goula et al., 2006)

The use of functional foods (FF) for their potential impact on specific ongoing diseases or in their prevention is an emerging topic in the research area of food and nutrition. Changing consumer demands and increasing global competition are causing the food industry, in general, and the meat and meat product manufacturing sector in particular, to embrace new processing technologies and new ingredient systems, which is remarkable if one considers the traditional and historically long term approach to product and process development in the meat industry (Weiss et al., 2010).

At present animal are frequently given so called functional feeds enriched at bioactive compounds to improve their health, not necessarily in order to improve the meat quality. More research is needed to study any relationship between bioactive compounds and meat quality. One way of improving meat quality might be to add substances to the meat itself which will have a direct effect on human health.

The aim of this review is to present an overview of the functional and physiological properties of the principal bioactive compounds present in tomatoes and tomato by-products, especially lycopene, their addition to meat and meat products and their use as animal feed ingredient.

CAROTENOIDS

Carotenoids are a family of more than 600 substances that are synthesized by higher plants and algae. They are a class of natural pigments, familiar to all through the orange-red to yellow colors of many fruits, vegetables, and flowers as well as for the provitamin A activity which some of them possess (Ribayo-Mercado et al., 2000). They are characterized by a linear polyisoprene structure with conjugated double bonds, either as such (lycopene), or as derived by cyclisation of the two extremities, with oxidation (xanthophylls such as lutein and zeaxanthin) or without oxidation (carotenes). Carotenoid molecules, especially those without hydroxyl groups, are lipophilic (Noziere et al., 2006). The structures of some common carotenoids are shown in figure 2.

Carotenoids are thought to be responsible for the beneficial properties of fruits and vegetables in preventing human diseases. The principal carotenoids present in the diet and human body are β-carotene, α-carotene, lycopene, α-cryptoxanthine and lutein, which account for over 90% of all carotenoids (Gerster, 1997). Recent epidemiological and animal studies have indicated a direct relationship between a high dietary intake of carotenoids and a decreased risk of certain types of cancer, cardiovascular diseases, and age-related macular degeneration (Bhosale et al., 2004). The antioxidant properties of carotenoids have been suggested as being

the main mechanism by which they afford their beneficial effects. Indeed lycopene is ranked as the most potent among the following antioxidants: lycopene > α-tocopherol > α-carotene > β-cryptoxanthin > β-carotene > lutein (Heber and Lu, 2002). However, our knowledge regarding how the concentration, structure and ratios of specific carotenoids affect their activity and uptake in the human body is limited (Rubio-Diaz et al., 2010).

LYCOPENE

Lycopene is the red colored pigment abundantly found in red fruits and vegetables particularly in tomatoes and tomato products (Cadoni et al., 2000). Although used as a natural food colorant for many years, it is only recently that lycopene has attracted considerable attention as a pharmaceutical component (Shi et al., 1999; Choudhari and Ananthanarayan, 2007). It is one of the commonly used pigments and is highly accepted by the food industry as a food additive and also for its health benefits (Rao and Argawal, 1999). As a red colorant and antioxidant agent, the demand for lycopene is still increasing. According to Kong et al., (2010) total world consumption of lycopene was tripled to 15,000 metric tons in 2004 compared to 5,000 in 1995.

Lycopene is a lipid soluble antioxidant member of the carotenoid family of phytochemicals. It is synthesized by many plants and microorganisms to absorb light during photosynthesis and to protect them against photosensitization but it is not synthesized by animals and the human body (Paina and Russell, 1999; Rao et al., 2006). The extended conjugated double bond system of these compounds is an important feature in the carotenoids responsible for their attractive colors because it forms the light absorbing chromophore (Rodriguez-Amaya and Kimura, 2004).

The lycopene molecule corresponds to isoprenoid polyenes ($C_{40}H_{56}$), which contain eight C_5-isoprene units, and have a central skeleton constituted of 22 carbon atoms, and two ends with an additional 9 carbon atoms each (Huang et al., 2008). As with other carotenoids, the double bonds in lycopene can undergo isomerization from *trans* to mono or *poly-cis* isomers by light, thermal energy, and chemical reactions (Rao et al., 2006) although it is naturally present in food products in the *all-trans* form, which is the most thermodynamically stable isomer (Chasse et al., 2001). Thus, red tomatoes typically contain 94% to 96% *all-trans*-lycopene, which is the thermodynamically most stable form (Porrini et al., 1998). In contrast, human plasma and tissues contain at least 50% *cis*-isomers, the most common isomeric lycopene forms being 5-*cis*-, 9-*cis*-, 13-*cis*- and 15-*cis*-lycopene (Singh and Goyal, 2008) (Figure 3).

Lycopene was found to be a more efficient antioxidant (singlet oxygen quencher) than β-carotene, α-carotene and α-tocopherol (Mascio et al., 1989). Increasingly, *in vivo* and *in vitro* clinical studies have reported that this compound can also be used as a nutraceutical due to its high antioxidant activity, reducing the risk of atherosclerosis and coronary heart disease (Nobre et al., 2009). Moreover, epidemiological studies have related the intake of lycopene with a lower risk of the incidence of certain types of cancer (Shi and Le Maguer, 2000).

EXTRACTION

The principal source used to extract lycopene is ripe tomatoes in which it represents 80-90% of the total pigment content (Shi and Maguer, 2000). The global production of lycopene in 2004 was 15,000 metric tons priced at 54 million dollars (Vita, 2007). Lycopene can be commonly obtained by chemical extraction, since it is soluble in organic solvents such as benzene, chloroform and methylene chloride (Ciurlia et al., 2009) and also industrially produced by

chemical synthesis. Since these processes involve the use of highly toxic chemical solvents (Ernst, 2002), interest has grown in the use of environmentally friendly processes for the industrial production of lycopene (Choudhari and Singhal, 2008).

Supercritical fluid extraction (SFE) has established itself as an alternative to traditional, poorly selective and questionable isolation processes using organic solvents, because of the relatively low critical temperature (Tc = 304.1 K), inertness, and non-toxicity of carbon dioxide (CO_2) (Felix-Valenzuela et al., 2001; Wang et al., 2001). Thus, studies to obtain lycopene by SFE are principally focused on optimizing SC-CO_2 fluid extraction conditions to obtain higher yields of lycopene by adjusting temperature, pressure, and flow rate and by adding a modifier or co-solvent (Yi et al., 2009).

Nobre et al., (2009) studied the extraction of *trans*-lycopene from tomato industrial wastes (skins and seeds) with SFE. These authors reported that the recovery of *trans*-lycopene depended on the content of the compound in the starting material and increased as the pressure and solvent flow rate increased, and with a decrease in particle size. Moreover, the highest *trans*-lycopene recovery, 93%, was obtained at 60 ºC, 300 bar, solvent flow-rate of 0.59 g/min, particle size of 0.36 mm and feed moisture content of 4.6%. Kaur et al., (2008) analyzed the lycopene extracted from tomato skin, obtaining a yield that varied from 0.639 to 1.98 mg/100 g. This wide range of extraction was due to the solvent/meal ratio, number of extractions, temperature, particle size and extraction time. The maximum lycopene yield was obtained by extracting tomato skin with a 30:1 v/w solvent/meal ratio, in four extractions at 50 ºC and with a 0.15 mm particle size and 8 min extraction time. Shi et al., (2009) investigated the SFE from tomato skins. The extraction yields increased both with temperature and pressure, the effect of temperature being more

significant than that of pressure. With pure CO_2, the lycopene yields varied (from 11.0 to 25.5 µg/g) with changes in temperature and pressure. The highest amount of lycopene was recovered at the highest pressure (35 MPa) and highest temperature (75 ºC). Vági et al., (2007) investigated the content of high value compounds such as carotenoids (lycopene, β-carotene) from industrial tomato waste extracted by SFE. The product obtained by supercritical CO_2 extraction (460 bar and 80 ºC) contained the highest concentration of carotenoids with 90.1% lycopene. Egydio et al., (2010) presented a new method to extract lycopene from tomato juice using supercritical CO_2 as solvent and without the need to dry the raw material. To conduct the extraction, the tomato juice was subjected to cycles of centrifugation followed by rinsing with absolute ethanol to partially remove the water present in the solid part of the juice. The extraction efficiency varied from 7.7% to 76.7% and only extraction temperature had a statically significant effect on the process.

Other methods for the extraction of lycopene not involving SFE include ultrasonic assisted extraction (UAE) and ultrasonic/microwave assisted extraction (UMAE). Thus, Zhang and Liu (2008) extracted lycopene from tomato paste using UAE and UMAE. The results showed that the optimal conditions for UMAE were 98W microwave power, 40 KHz ultrasonic processing, a solvent to tomato paste ratio of 10.6:1 (V/W) and extraction time of 367 s. With regard to UAE, the best conditions were: extracting temperature 86.4 ºC, ratio of solvents to tomato paste 8.0:1 (V/W) and extraction time of 29.1 min. Under these conditions the lycopene yield was 97.4% and 89.4% for UMAE and UAE, respectively.

BIOAVAILABILITY

Bioavailability refers to the fraction of the carotenoid ingested that becomes available for utilization in normal physiological functions or for storage in the human body (Castenmiller and West, 1998). Bioavailability is a critical feature in the assessment of the role of dietary components in human health (Granado-Lorencio et al., 2007). Interest in the bioavailability of vitamins and other phytochemicals has greatly increased because of the existence of undernourished populations and groups at risk of developing micronutrient deficiencies (as in the elderly) and the epidemiological evidence that points to protective effects against non-communicable diseases (such as cancer, cardiovascular disease, age-related eye diseases) (van den Berg et al., 2000).

Current knowledge on the bioavailability of lycopene in humans is limited due to the inability to distinguish newly administered lycopene from the body reserves of the same (Tang et al., 2005). The bioavailability of carotenoids appears to be dependent on several factors such as the species of carotenoid, linkages at molecular level, the amount of carotenoid, matrix, effectors, nutrient status, genetics, host-related factors and interactions among these variables (Castenmiller and West, 1998). In intact tomato cells, lycopene exists in a crystalline form and is located inside thylakoid membranes within the chromoplasts that is, encapsulated within cellular compartments (Ljubesic et al., 1991). Consequently, any release and subsequent absorption of lycopene from raw tomato is low. However, disrupting the tomato matrix by thermal and mechanical processing can significantly increase lycopene bioavailability (Fröhlich et al., 2006). Such treatments may increase the accessibility of the lycopene but could also help to disperse the liposoluble tomato constituents including lycopene in the food matrix (Richelle et al., 2002). In concentrated tomato extracts, the poorly soluble lycopene is predominantly crystallized, and the

crystalline form of carotenoids has been found to be one of the primary factors that reduce their bioavailability (Zhou et al., 1996).

The mechanism of lycopene absorption is similar to that of lipids and includes release from the physical matrix, emulsification, solubilization in mixed micelles, diffusion and permeation through the enterocyte membrane (Borel, 2003). The capacity of the digestive process to release carotenoids from the food matrix (namely, bioaccessibility) may be the first step for determining the bioavailability of carotenoids (Goñi et al., 2006). In general, the absorption of carotenoids depends on their bioavailability from the food matrix and their solubility in micelles (Boileau et al., 2002). Thus, Alshatwi et al., (2010) reported that lycopene beadlets present greater bioavailability than tomato powder. Many carotenoids are absorbed better in the presence of dietary fats and from heat processed foods than from unprocessed sources (Reboul et al., 2006). The nature of the isoforms of carotenoids also affects their bioavailability and absorption (Unlu et al., 2007). *Cis* isomers of lycopene make up more than 50% of the total lycopene in human serum and other tissues. This is in contrast with the food sources in which they originate; in tomatoes and tomato-based products, all-*trans* lycopene comprises 79% to 91% of total lycopene (Marković et al., 2006). *Cis* isomers of lycopene are more bioavailable than *trans*-lycopene, probably because the *cis* isomers are more soluble in bile acid micelles and may be preferentially incorporated into chylomicrons (Gartner et al., 1997; Boileau et al., 1999). Faisal et al., (2010) reported that the intestinal lymphatic route is the major uptake mechanism of lycopene from the gastrointestinal tract. Lycopene transport in intestinal lymph was closely associated with triglyceride transport in the lymph. Formulation strategies designed to promote intestinal

lymphatic uptake, such as lipid-based formulations containing long-chain fatty acids (LCFAs) or lecithin, may serve to enhance the oral bioavailability of lycopene.

Other factors that influence the absorption of carotenoids include the presence of dietary fiber, the health status of the person, and the physical form of the carotenoid (Erdman et al., 1986). Jain et al., (2009) reported that lycopene at a dose of 10 mg/kg, which is equivalent to two servings of tomatoes or tomato products per day is bioavailable, accumulates in tissues and is well tolerated by rats. O'Neill and Thurnham (1998) found 1.0 mg of lycopene was absorbed from a 38-mg dose contained in capsules (2.6%). In a human dietary intervention study, serum lycopene levels were shown to increase significantly after the consumption of tomato juice, spaghetti sauce and lycopene capsules for one week (Rao and Agarwal, 1998). Paetau et al., (1998) reported that lycopene in buccal mucosa cells significantly increased (<2-fold) after 4 wk of ingestion of oleoresin or lycopene beadlets to 4.95 and 3.75 mg/g protein, respectively, but was not significantly affected by tomato juice treatment. Rao and Shen (2002) analyzed the effect of ingesting low levels of lycopene (5 to 20 mg), which are more reflective of dietary intake, on its absorption and antioxidant properties. At these levels, serum lycopene levels increased significantly by 92% to 216%. Researchers have reported increases in lycopene in the blood of humans after ingesting lycopene or tomato products. Human subjects had a plasma increase of 0.47-0.58 μM after two weeks with 25 mg supplement/day of lycopene or tomato paste (Richelle et al., 2002).

LYCOPENE AS ANTIOXIDANT

Reactive oxygen species (ROS) are products of electron transport chains, enzymes, and redox cycling and their production may be enhanced by exposure to xenobiotics. Oxidative stress

occurs when ROS overwhelm the cellular defences, causing damage to proteins, membranes and DNA (Adams and Greeley, 2000) and is defined as a disruption of the pro-antioxidant balance, which leads to potential damage (Yonar and Sakin, 2011). Some studies reported that a lycopene-rich diet and lycopene supplementation provide protective effects against ROS products (Böhm et al., 2001; Sahin et al., 2006; Palozza et al., 2010a) because lycopene is reported as the most efficient singlet oxygen quencher in the carotenoids group, whose quenching ability is mainly dependent on the number of conjugated double bonds, and, to a lesser, influenced by the presence of cyclic or acyclic end groups (Stah and Sies, 1996). Experimental evidence also suggests that lycopene can quench singlet oxygen ($^1O_2$), scavenge free nitrogen dioxide ($NO^{\bullet}_2$), thiol ($RS^{\bullet}$) and sulfonyl ($RSO^{\bullet}_2$) radicals (Srinivasan et al., 2007). In addition, its chain structure with an extensive conjugated polyene system is important for its biological properties such as susceptibility to oxidative degradation (Shi et al., 2002). *In vitro, ex vivo*, and *in vivo* studies have been carried out to demonstrate the effects of lycopene against oxidative stress (Velmurugana et al., 2005; Türk et al., 2007; Salman et al., 2007). In this context, lipid, protein and DNA oxidation are closely related to oxidative stress (Kong et al., 2010).

In animals, Yonar and Sakin (2011) investigated the ameliorative properties of lycopene against the toxic effects of the insecticide deltamethrin (DM) by examining oxidative damage markers such as lipid peroxidation and the antioxidant defense system components in carp (*Cyprinus carpio*). These authors reported that treatment with oral administration of 10 mg/kg lycopene attenuated the DM-induced oxidative stress by significantly decreasing the levels of malondialdehyde. In addition, lycopene significantly increased the superoxide dismutase,

catalase, and glutathione peroxidase activities and the level of glutathione. Velmurugana et al., (2005) evaluated the protective effect of pretreatment with S-allylcysteine (SAC) and lycopene (0.125 mg/mL) against N-methyl-NV-nitro-N-nitrosoguanidine (MNNG)–induced genotoxicity and oxidative stress in male Swiss mice. The combination of SAC and lycopene exerted a greater protective effect against oxidative stress. This was associated with modulation of lipid peroxidation, as well as reduced levels of glutathione and the glutathione-dependent enzymes, glutathione peroxidase, glutathione S-transferase and glutathione reductase. Scolastici et al., (2007) investigated the antigenotoxic/antimutagenic effects of lycopene in Chinese hamster ovary cells (CHO) treated with hydrogen peroxide, methylmethanesulfonate (MMS), or 4-nitroquinoline-1-oxide (4-NQO). Lycopene (97%), at final concentrations of 10, 25, and 50 μM reduced the frequency of micronucleated cells induced by the three mutagens. However, this chemopreventive activity was dependent on the concentrations and treatment schedules used. Türk et al., (2007) conducted a study to investigate the possible protective effect of the administration of lycopene at a dose of 10 mg/kg against testicular and spermatozoal toxicity associated with the oxidative stress caused by cyclosporine A in male rats. Treatment with lycopene significantly inhibited the increase in testes malondialdehyde levels, and accentuated the reductions in glutathione, glutathione peroxidase and catalase activities of testicular tissue caused by cyclosporine A. The possible explanation for the protective effects of lycopene against the increase in cyclosporine A-induced lipid peroxidation is its ability to react with the free oxygen metabolites.

In humans, Zini et al., (2010) reported that preincubation of human spermatozoa with lycopene (5 μmol/L) offers protection against oxidative DNA damage *in vitro*. These data also

highlight the differential protective effects of lycopene on sperm motility and sperm DNA integrity. Palozza et al., (2010a) indicated that lycopene (0.5-2 μM) may act as a potential antiatherogenic agent by preventing 7-ketocholesterol-induced oxidative stress and apoptosis in human macrophages because it reduces the increase in ROS production and in 8-OHdG formation induced by oxysterol in a dose-dependent manner. Boosalis et al., (1996) demonstrated that the presence of an acute phase response was associated with a significant decrease of lycopene and other carotenoids in plasma, which may compromise the antioxidant status and increased oxidative stress and damage in elderly persons with inflammatory conditions.

Human foreskin fibroblasts (Hs68 cells) enriched with 10 and 20 μM lycopene were analyzed by Yeh and Hu (2000). The results showed that lycopene at 20 μM significantly decreased levels of TBARS induced by ferric nitrilotriacetate (Fe/NTA) but enhanced levels of TBARS induced by a lipid-soluble radical generator (2,2′-azobis[2,4-dimethylvaleronitrile]; AMVN). Both the antioxidant and pro-oxidant effects of lycopene tended to be dose-dependent. Srinivasan et al., (2009) evaluated the radioprotective effect of lycopene on γ-radiation-induced toxicity. Lycopene pretreatment (1, 5 and 10 μg/mL) significantly decreased the frequency of micronuclei, dicentric aberration and translocation compared with the γ-radiation control. The levels of thiobarbituric acid reactive substances and hydroperoxides also decreased and the activities of superoxide dismutase, catalase and glutathione peroxidase significantly increased as did GSH levels, compared with the γ-radiation control. In this way, lycopene's protective effects against oxidative stress were also illustrated when human skin was irradiated with UV light.

Lycopene was found to be preferentially destroyed compared with β-carotene, suggesting either a more active or a more protective role (Ribayo-Mercado et al., 1995).

LYCOPENE AND CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVDs) are among the most common causes of death and disability worldwide (Goyal and Yusuf, 2006). Risk assessment for the primary prevention of CVD and stroke should include regularly updated family history, smoking status, food intake and nutrition patterns, alcohol intake, physical activity, blood pressure, body mass index (BMI), waist circumference, pulse rate, fasting serum lipoprotein profile (or total and HDL cholesterol if fasting is unavailable), and fasting blood glucose level (Pearson et al., 2002).

Plasma low-density lipoprotein (LDL) is the major risk factor of CVD. Increased LDL oxidation is hypothesized to be causally associated with the increasing risk of atherosclerosis (Kong et al., 2010). Atherosclerosis is a chronic disease with a high health impact, since it contributes to more mortality and morbidity in the western world than any other disorder (Viuda-Martos et al., 2010). It is characterized by lesions called atheromas or fibro-fatty plaques that protrude into the lumen weaken the underlying media and undergo a series of complications as CVD progresses (Albertini et al., 2002).

A variety of epidemiological studies have suggested that the intake of lycopene-containing foods, as well as blood lycopene concentrations, are inversely related with the incidence of CVD (Arab and Steck, 2000; Sesso et al., 2004). Lycopene may protect against atherosclerosis, although the exact mechanism(s) is still unknown. The oxidative modification of LDL particles may play a role in the formation of foam cells, atherosclerotic lesions, and CVD (Witztum and Hörkkö, 1997). Lycopene has been demonstrated to inhibit ROS production *in vitro* and to

protect LDL from oxidation (Visioli et al., 2003). Agarwal and Rao (1998) reported that lycopene significantly reduces the levels of oxidized LDL (LDLox) in subjects consuming tomato sauce, tomato juice and lycopene oleoresin capsules. Balestrieri et al., (2004) found that lycopene, in association with α-tocopherol or tomato lipophilic extracts, enhances acyl-platelet-activating factor biosynthesis in endothelial cells during oxidative stress. The lipophilic compounds contained in tomato can prevent cardiovascular diseases by modulating the atherogenic processes in the vascular endothelium mediated by oxidized low-density lipoproteins (LDLs). Alshatwi et al., (2010) reported that tomato powder, a product rich in lycopene, lowered serum total cholesterol and triglycerides by one fifth, as well as decreased serum low-density lipoprotein cholesterol by more than one third of their respective levels in controls. In agreement with these results, Fuhrman et al., (1997) reported that dietary supplementation with tomato lycopene (60 mg/day) resulted in a significant reduction (14%) in the LDL cholesterol concentrations of six males after 3 months. For these authors the carotenoids may act as moderate hypocholesterolemic agents, besides having an inhibitory effect on macrophage 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase, the rate limiting enzyme in cholesterol synthesis.

Ried and Fakler (2011) reported that lycopene taken in doses of ≥25 mg daily is effective in reducing LDL cholesterol by about 10%, which is comparable with the effect of low doses of statins in patient with slightly elevated cholesterol levels. Ghaffari and Ghiasvand (2006) reported that lycopene suppressed the formation of TBARS and LDL-copper complex in a dose-dependent manner. Lycopene, at concentrations of 10 µM, 50 µM and 100 µM reduced the susceptibility of LDL to oxidative modification by approximately 31, 67 and 71%, respectively.

Safari (2007) demonstrated that the incubation of plasma with lycopene prolonged, dose-dependently, the lag time before the initiation of oxidation reaction. This author concluded that lycopene protects LDL from copper-induced oxidation reactions significantly decreasing the susceptibility of LDL to oxidative modification

Recently, other mechanisms that have been evoked include: prevention of endothelial injury; the modulation of lipid metabolism through a control of cholesterol synthesis and oxysterol toxic activities; the reduction of inflammatory response through changes in cytokine production; the inhibition of smooth muscle cell proliferation through regulation of molecular pathways involved in cell proliferation and apoptosis (Palozza et al., 2010b). Available evidence suggests that intimal wall thickness and the risk of myocardial infarction are reduced in persons with higher adipose tissue concentrations of lycopene (Arab and Steck, 2000). Similarly, Kohlmeier et al., (1997) found that men with the highest concentrations of lycopene in adipose tissue were 48% less likely to develop CVD compared with men with the lowest lycopene concentrations. Sesso et al., (2004) indicated an apparent association between increasing quartiles of plasma lycopene and a lower risk of CVD in middle-aged and elderly women, which appeared to be independent of overall lifestyle and clinical, and dietary risk factors. Women with concentrations of plasma lycopene greater than 16.5 μg/dL had a 34% reduction in the possibility of CVD compared with those in the lowest quartile after multivariate adjustment. Rissanen et al., (2000) reported that low levels of plasma lycopene were associated with a 17.8% increase in the intima-media thickness of the common carotid artery wall that may produces early atherosclerosis. Gianetti et al., (2002) concluded that the inverse relationship of plasma lycopene with maximum carotid intima-media thicknesses is compatible with a protective role of this natural dietary antioxidant

in atherosclerosis, although the mechanism of protection does not apparently involve a decrease in endothelial activation, as measured through soluble adhesion molecules. Martin et al., (2000) reported that lycopene appears to be effective in reducing both human aortic endothelial cells adhesion to monocytes and expression of adhesion molecules on the cell surface. These results suggest an important role for lycopene in attenuating atherogenesis. The same study showed that lycopene administration decreased serum vascular cell adhesion molecule-1, monocyte chemoattractant protein-1 and interleukin-8 levels of rats significantly, and inhibited the high expression of inflammatory agents.

LYCOPENE AND CANCER

Cancer is the second leading cause of death worldwide (Desai et al., 2008). Nutritional factors have been suggested to play an important role in the prevention of chronic diseases, such as cancers. For example, it has been shown that diets rich in fruits and vegetables are associated with a lower risk of various cancers (Skuladottir et al., 2006). Several epidemiology studies strongly suggest that the consumption of foods containing high concentrations of lycopene such as tomatoes or tomato products reduces the risk for certain types of cancer (Giovannucci et al., 2002; Jian et al., 2005). Over the last decade numerous epidemiological (Table 2), experimental and tissue culture (Table 3) studies and reviews have been published which describe an association between lycopene supplementation or a tomato-rich diet and decreased positive markers of cancer (Ansari and Gupta, 2004; Mohanty et al., 2005; Fornelli et al., 2007; Schwenke et al., 2009; Dias et al., 2010; Wang and Leung 2010). The inverse relation between lycopene intake and cancer risk might be ascribed to (i) lycopene as an antioxidant, (ii) increased cell–cell communication, (iii) reduced mutagenesis, (iv) inhibited tumor cell proliferation, and

(v) improved antitumor immune responses (Clinton, 1998). Sharoni et al., (2000) informed that the mechanism of lycopene function in cancer cells involves interference in the mitogenic pathway of IGF-I and a slowdown of cell cycle progression. Mein et al., (2008) suggest that lycopene metabolites may possess specific biological activities for several important cellular signaling pathways and molecular targets.

Tang et al., (2008) found that lycopene inhibited cell proliferation in human colon cancer HT-29 cells with an IC_{50} value of 10 μM. For these authors, the mechanism of action of lycopene is based on suppressing Akt activation and non-phosphorylated β-catenin protein level in human colon cancer cells and increasing the phosphorylated form of β-catenin proteins. These effects were also associated with reduced promoter activity and protein expression of cyclin D1. Furthermore, lycopene significantly increased nuclear cyclin-dependent kinase inhibitor $p27^{kip}$ abundance and inhibited phosphorylation of the retinoblastoma tumor suppressor protein. El-Rouby (2011) indicated that lycopene can exert protective effects against 4-NQO-induced tongue carcinogenesis through a reduction in cell proliferation and enhanced cellular adhesion, suggesting a new mechanism for the anti-invasive effect of lycopene. Livny et al., (2002) reported that lycopene inhibited the proliferation of the human oral cancer cell line (KB-1) in the G1 phase to approximately 10% of control cell numbers. Park et al., (2005) investigated the effect of lycopene on DNA damage and cell growth inhibition in the Hep3B human hepatoma cell line. When a final lycopene concentration of 0.1-50 μM was added to cells, lycopene inhibited cell growth in a dose-dependent manner. Cell growth was inhibited by 20% at 0.2 μM lycopene and by 40% at 50 μM lycopene. Lycopene-treated cells showed less DNA damage than placebo-treated cells. Scolastici et al., (2007) investigated the antimutagenic effects of lycopene

in hamster ovary cells treated with three mutagens. Lycopene (97%) was tested at final concentrations of 10, 25, and 50 μM. The data showed that lycopene reduced the frequency of micronucleated cells induced by the 3 mutagens. However, this chemopreventive activity was concentration-dependent. Chiang et al., (2007) found that lycopene inhibited platelet-derived growth factor (PDGF) induced human Hs68 skin fibroblast migration on gelatin and collagen. Further analysis showed that lycopene inhibited PDGF-BB-induced signaling in human Hs68 and primary cultured skin fibroblasts. The PDGF-BB-induced phosphorylation of PDGF receptor β, extracellular signal-regulated kinase 1/2, p38, and c-Jun N-terminal kinase was attenuated by lycopene in a concentration-dependent manner, whereas the total expression of each protein was not affected. Hantz et al., (2005) reported that lycopene at 0.3–3.0 μM induced apoptosis in a concentration-dependent manner in the androgen sensitive human prostate cancer cell line LNCaP. Specific indicators of apoptosis were observed in the LNCaP cells, including decreased mitochondrial function, a reduction of the mitochondrial transmembrane potential, the release of mitochondrial cytochrome C, and increased annexin V binding. Ivanov et al., (2007) found that both a 3% tomato preparation and 38% lycopene purified from tomato extract possessed antiproliferative activity in both androgen-responsive and independent prostate cancer cells as a result of the down-regulation of insulin-like growth factor-1 receptor expression and signal transduction, resulting in decreased expression of cyclin/cdk complexes critical for the phosphorylation of retinoblastoma. In this way van Breemen and Pajkovic (2008) indicating an inverse relationship between lycopene intake and prostate cancer risk. *In vitro* and *in vivo* experiments showed that oral lycopene is bioavailable, accumulates in prostate tissue and is localized in the nucleus of prostate epithelial cells. Obermuller-Jevic et al., (2003) showed that,

at a physiological concentration of 0.3 mM/L, lycopene inhibits the growth of non-neoplastic human prostate epithelial cells *in vitro*, through cell cycle arrest which may have significant implications for the prevention of benign prostate hyperplasia, a risk factor for prostate cancer.

A diet supplemented with lycopene suppresses spontaneous mammary tumor development in SHN virgin mice, the mechanism of which is related in the thymidylate synthetase activity in the mammary gland and serum prolactin and free fatty acid levels (Nagasawa et al., 1995). Wang and Leung (2010) reported that ethoxyresorufin-*O*-deethylase activity in MCF-7 cells was reduced by about 20% following lycopene administration. Kinetic studies performed on human recombinant cytochrome P450-1 showed that lycopene effectively inhibited the cytochrome P450-1 enzymes at 2 mmol/L, whereas lycopene also reduced cytochrome P450-1A1 mRNA abundance at 5 mmol/L. Tang et al., (2009) suggested that lycopene and eicosapentaenoic acid (ω-3 fatty acid) synergistically inhibit the growth of human colon cancer HT-29 cells even at low concentration. The inhibitory effects of lycopene and eicosapentaenoic acid on cell proliferation in human colon cancer HT-29 cells were, in part, associated with the down-regulation of the phosphatidylinositol 3-kinase /Akt/mTOR-signaling pathway.

In contrast, Burgess et al., (2008) demonstrated that the exposure of cells grown (cancerous and non-cancerous) in a culture medium to lycopene (0.0001 to 10 μM) will not always affect cell proliferation when the concentration of lycopene is not dramatically higher than the normal physiological range found in human. Similarly, Kirsh et al., (2006) did not support the hypothesis that greater lycopene/tomato product consumption offers protection against prostate cancer.

LYCOPENE AND OTHER HUMAN DISEASES

The main emphasis on the role of lycopene in human health has been in the areas of oxidative stress, cancer and CVD. However, lycopene may confer a multitude of other health-promoting effects in the body, although more conclusive studies are needed to confirm these effects, because the literature contains very few references to substantiate these claims.

Type 2 diabetes: The association of lycopene with the risk of type 2 diabetes has not been much studied. In a study carried out in a population considered to be at high risk of type 2, Ylönen et al., (2003) found that the dietary intake of α- and β-carotene and of lycopene had beneficial associations with glucose metabolism in men. An inverse association with fasting plasma glucose concentrations was observed for the former, and an inverse association with insulin resistance was observed for the latter. Li et al., (2010) investigated whether the serum levels of lycopene differed between type 2 diabetic patients with and without diabetic retinopathy. In the diabetic group, subjects with proliferative diabetic retinopathy had significantly lower lycopene levels than subjects without diabetic retinopathy or with non-proliferative diabetic retinopathy, suggesting that lycopene may be helpful for the diagnosis, severity, and therapeutic evaluation of diabetic. Ford et al., (1999) reported a significantly linear decrease in β-carotene and lycopene in persons with impaired glucose tolerance and in persons with newly diagnosed diabetes compared with persons with normal glucose concentrations, after adjustment for confounding factors. Akinnuga et al., (2010) carried out a study to investigate whether both ripe and unripe tomatoes have a hypoglycemic effect in a chronic disease such as diabetes mellitus in albino Wistar rats. These authors reported that both high-lycopene ripe tomato and high-tomatine unripe tomato have hypoglycemic effects on diabetic mellitus after a short period of dietary intake, suggesting that consumers may benefit by not only eating high-

lycopene ripe tomatoes, but also high-tomatine unripe tomatoes. On the other hand, Wang et al., (2006) found little evidence to support an association between baseline plasma lycopene and other carotenoid levels with the risk of type 2 diabetes after adjustment for multiple risk factors.

Bone health: Osteoporosis is a condition characterized by low bone mass and deterioration of bone tissue which ultimately leads to bone fragility and increased fracture risk. Osteoporosis results from unbalanced bone remodeling (inadequate activity of bone-forming osteoblasts and/or excessive activity of bone-resorptive osteoclasts) (Yang et al., 2008). Recently, lycopene research has begun to explore the potential for this antioxidant carotenoid to work against the onset of bone disease (Dillingham and Rao 2009). For example, Sahni et al., (2009) reported that there is an association between total carotenoid intake and lycopene intake, and also fracture risk which supports the hypothesis that these nutrients may be protective against fractures as well as non-vertebral osteoporotic fracture in older adults. Rao et al., (2007) showed that there was a correlation between lycopene intake and the bone turnover markers BAP and N-telopeptide (NTx) in postmenopausal women. These authors claimed that serum lycopene levels are negatively associated with the bone turnover marker NTx and suggest that higher lycopene consumption is associated with reduced bone resorption in postmenopausal women. In this way, Mackinnon et al., (2011) reported that after 30 days of dietary lycopene restriction, there were significant increases (20.6%) in the bone resorption marker NTx, which could lead to a long-term increased risk of fracture. Brown and Josse (2002) suggest that a longer restriction period may be detrimental to bone health, particularly in groups of postmenopausal women who are already at high risk for osteoporosis.

MEAT PRODUCTS ENRICHED WITH TOMATO BY-PRODUCTS

There are initiatives by food scientists to recycle lycopene-rich by-products as food ingredients. The direct addition of tomato peel to foods such as meat products could be a cheaper solution than the isolation of lycopene (Calvo et al., 2007). Since tomato peel is rich in lycopene, the direct addition of peel to food products could be an easy way to use this by-product to obtain new products enriched in lycopene (Calvo et al., 2008). Indeed, adding tomato, tomato products or lycopene to processed meat could lead to products with health benefits. However a prerequisite for physiological action of many bioactives are: (i) sufficient quantities of the components must be present in the food systems (ii) the compounds must remain physically and chemically stable throughout production, storage and consumption (Schmidl and Labuza, 2000) and (iii) upon consumption the products must pass through the human digestive system in a physical form that allows the compounds to be optimally absorbed in the intestinal tract (Weiss et al., 2010). Such bioactive compounds must be bioavailable and bioaccesible.

The determination of carotenoid bioavailability is complicated because of the many dietary and physiological factors that can affect it. Food-related factors involved include the amount and structure of the carotenoid, the nature of the food matrix, physical state and intracellular location of the carotenoid, particle size of the food, food preparation or processing method, competition/interaction with other carotenoids and the intake of other food constituents (for example, fat increases while fiber decreases bioavailability) (van het Hof et al., 2000; Yeum and Russell, 2002; Yonekura and Nagao, 2007).

Several authors have studied the use of tomato products or lycopene in meat products (Figure 3). Among those who have Garcia et al., (2009) studied the addition of different amounts of dry tomato peel (0-6.0% w/w) to raw and cooked hamburgers. These authors reported that the

addition of lycopene to hamburgers at 4.5% showed good overall acceptability and presented a final lycopene content of 4.9 mg/100 g cooked hamburger. The addition of dry tomato peel increased the color characteristics (a* and b*) of raw and cooked hamburgers, decreased the pH values significantly in a concentration-dependent manner, and modified all the textural properties probably because of the presence of fiber. The hardness values of cooked samples were significantly higher in products containing 6% dry tomato peel than in a control batch.

Selgas et al., (2009) analyzed the safety and shelf-life of raw hamburgers containing 30, 45 and 60 g/kg dry tomato peel as a source of lycopene, vacuum-packed and irradiated with 2 or 4 kGy. These authors reported that after irradiation with 4 kGy and 17 days of storage, the lycopene concentration fell to 15% of the initial value. Even with this decrease, hamburgers containing 6% dry tomato peel had a final lycopene concentration of 7.14 mg per 100 g of hamburger, an amount very close to the recommended daily intake for a healthy diet. Indeed, dry tomato peel masks the brownish color characteristic of irradiated meat, and 6% dry tomato peel imparts to the hamburger a similar redness (a*), independently of the dose of radiation applied. The sensory characteristics were influenced by irradiation, but the higher lycopene concentration (6 g/kg) masked these changes sufficiently to ensure an acceptable color and odor in the final product after the storage period.

Østerlie and Lerfall (2005) analyzed the addition of sun-dried tomatoes and tomato paste to minced meat. The resulting product did not exceed the limit for good microbiological quality (NFSA, 1992) during storage (14 d), while the control sample passed the limit after five days. The pH values decreased significantly in samples with added tomatoes, and presented a lycopene content of nearly 32.6-38 mg/kg. The addition also reduced rancidity.

Deba et al., (2007) analyzed frankfurters (18% fat) produced with two levels of sodium nitrite, 0 and 150 mg/kg (0.015%), and seven levels (0%,2%,6%,8%,12% and 16%) of tomato paste with 12% soluble solids. As regards color these authors reported that the higher the tomato paste level the lower the values for lightness (L*) and hue (H*) values and the higher the redness (a*), yellowness (b*) and chroma (C*) values. Similar results have been reported by Condogan (2002) for beef patties produced with the addition of 5%, 10% and 15% tomato paste. The higher the tomato paste level the higher the preference of consumers for frankfurters based on their color. Therefore, the incorporation of tomato paste had a positive effect on the red color of frankfurters. Treatments involving 12% tomato paste led to lower pH and residual nitrite values, and higher thiobarbituric acid values (TBA). Condogan (2002) found that in beef patties, produced without sodium nitrite, treatment with 5%, 10% or 15% tomato paste led to lower TBA values than the control, due to the antioxidative activity of lycopene present in the tomato paste.

Eyiler and Oztan (2011) analyzed the chemical properties including the nitrosomyoglobin content, lycopene content and the oxidation level, and the sensory properties of frankfurters which had been produced by both reducing the nitrite level and adding tomato powder. The pH of the frankfurters produced with tomato powder was reduced, compared with samples which did not contain tomato powder. The addition of 2 g tomato powder/100 g decreased the level of oxidation; however, 4 g tomato powder /100 g caused a slight increase compared with the samples which did not contain tomato powder. According to this result it can be stated that tomato powder retards the oxidation reaction. According to sensorial evaluations, tomato powder also improved consumer acceptability. The addition of tomato powder increased the internal and external color scores, and frankfurters were found to be more acceptable by the panelists. The

nitrosomyoglobin (NOMb) content of the samples was decreased with the decreased level of nitrite, and this, in turn, contributed to the decreased level of redness (a*).

Yilmaz et al., (2002) analyzed low-fat (5.9–10.3% fat) cooked sausages made with tomato juice, finding that they had a lower pH, total aerobic count and nitrite content, but were firmer than the control sausage. Calvo et al., (2008) carried out a study analyzing the addition of tomato peel, at different concentrations (0%, 0.6%, 0.9% and 1.2%) to dry fermented sausages. A slight loss of lycopene was detected after 21 days of ripening, while lycopene levels remained at between 0.26 and 0.58 per 100 g of sausage. The sensory and textural properties and overall acceptability of all the sausages were good, indicating that tomato peel could be added to dry fermented sausages to produce a meat product enriched in lycopene. The pH values of dry sausage were not affected by the addition of tomato peel, while all the color parameters were affected by the addition of it.

Mercadante et al., (2010) analyzed the oxidative stability of sausages containing added natural pigments and stored under refrigeration; these authors reported that the addition of lycopene (10%) produced significant reductions in redness, although it did not exert any antioxidant effect. Sanchez-Escalante et al., (2003) analyzed the stabilization of color and odor of beef patties using lycopene-rich tomato as a source of antioxidants, which they found exerted a significant antioxidative effect on the beef patties, depending on the lycopene concentration. These tomato products delayed meat deterioration to a varying extent, so that the shelf life of treated beef patties ranged between 8 and 12 days.

TOMATO BY-PRODUCTS AS INGREDIENTS OF ANIMAL FEED

The use of local crop residues and agroindustrial by-products as feedstuffs is a common practice to improve small ruminant production in arid zones (Ben Salem and Znaidi, 2008). Livestock and poultry are considered important carriers of health functional compounds if they are fed with diets containing optimal amounts of nutraceuticals. These compounds are retained in animal tissues and transferred to animal products such as meat, eggs and milk. For this reason, it is necessary to identify the main tomato by-products (solids and waste water) and quantify the tomato by-products produced by industries and carry out a complete chemical and nutritional functional characterization of these by-products.

Tomato pomace which represents 0.05-0.10 % of the original weight of tomatoes and is a mixture of tomato peels, crushed and whole seeds and a small amount of pulp that remain after the processing of tomatoes for juice, paste and/or ketchup, has been evaluated for use as poultry feed (Mansoori et al., 2008) and for small ruminants (Denek and Can, 2006). Wet tomato by-product can be ensiled with corn plants and the resulting silage has been seen to support good milk production in dairy cows (Weiss et al., 1997). However, studies carried out to evaluate the nutritive value of by-products from tomato production are scarce.

Sahin et al., (2006) evaluated the effects of dietary lycopene supplementation on performance, carcass characteristics, biomarkers of oxidative stress (malondialdehyde (MDA) and homocysteine), and concentrations of vitamins C, E, A, cholesterol, triglyceride, and glucose in Japanese quails (*Coturnix coturnix*). Lycopene supplementation (50, 100 or 200 mg of lycopene/kg of diet) linearly increased feed intake, live weight gain, feed efficiency and cold carcass weight and yield. Indeed, supplementation with lycopene increased the high-density lipoprotein (HDL) concentration, whereas, the very-high-density lipoprotein (VLDL) and low-

density lipoprotein (LDL) concentrations fell with lycopene supplementation. In another experiment, Sahin et al., (2008) analyzed lycopene-enriched egg production in quails and their effects on the antioxidant status of humans upon their consumption. The authors analyzed diets containing lycopene (0, 100, and 200 mg lycopene per kilogram) which were seen to increase feed intake and egg production in quails. Egg yolk color improved, whereas the egg yolk malondialdehyde (MDA) content fell with increasing levels of lycopene. Botsoglou et al., (2004) analyzed the effect of dietary dried tomato pulp on the oxidative stability of Japanese quail meat. For this, quails (*Coturnix coturnix*) were fed with a basal diet that served as control or a basal diet containing 5 or 10% of dried tomato pulp which contained lycopene (281 mg/kg of dry weight) and β-carotene (24.3 mg/kg of dry weight). As regards lipid oxidation, the malondialdehyde (MDA) values in raw meat increased after 6 and 9 days of refrigerated storage. The increase was higher for the 10% dried tomato pulp group and lower for the 5% dried tomato pulp. An analogous oxidation profile was observed for cooked meat after 3, 6, and 9 days of storage. These results suggested that the inclusion of dried tomato pulp in feed at a level of 50 g/kg has an antioxidant effect, whereas addition at 10% exerts a prooxidant effect. Mean fatty acid analysis showed that the 10% dried tomato pulp group had a higher content of total polyunsaturated fatty acids and a higher unsaturated/saturated fatty acid ratio compared with the control.

Mansoori et al., (2007) carried out an investigation to assess the possibility of using single dietary sources as alternatives to feed deprivation for the induction of molt in commercial laying hens analyzing, for 12 weeks, post-molt production parameters such as number of eggs produced per hen per day, egg weight, shell weight, yolk color and Haugh unit. These authors reported that

hens provided with tomato pomace showed lower weight loss than feed-deprived hens at the end of the molting period. Hens consuming tomato pomace exhibited post-molt levels of egg production over a 12 week period that were superior to those of hens molted by feed withdrawal. Knoblich et al., (2005) analyzed the ability of hens to transfer tomato by-product carotenoids from feed to the egg yolk, finding than when peel and seed by-products were included at 75 g/kg in hen diets, the lycopene content of dry egg yolk was approximately 0.9 µg/g. Approximately 100 mg/kg of the lycopene in the peel by-product and approximately 700 mg/kg in the seed by-product was transferred from the feed to the yolk. Ševčikova et al., (2008) conducted an experiment to determine the effect of lycopene concentration (0, 50 and 100 mg/kg) on the lipid profile and quality of meat of broiler chicken meat. The higher content of HDL cholesterol in plasma was recorded in groups supplemented with 50 mg lycopene, followed by groups with 100 mg lycopene. The concentrations of LDL cholesterol showed an opposite trend. Thus, the lycopene supplement had a positive effect on the lipid profile of blood plasma of broiler chickens.

CONCLUSIONS

Tomatoes and tomato by-products and their main phytonutrient, lycopene, are widely used by the food industry as colorants, although their nutritional and functional properties make them also suitable for other purposes, such as the enhancement of functional foods. However, despite the widely demonstrated beneficial effects of lycopene on several diseases, including cancers and cardiovascular diseases, more mechanistic studies and randomized controlled trials of large

sample size are necessary to further confirm these effects. Hopefully, lycopene will be confirmed as suitable for use in the routine management of these diseases.

ACKNOWLEDGEMENTS

We are grateful to "Caja Murcia" for the research scholarship awarded to one of the authors (MVM) and the project CYTED-IBEROFUN codec: 110AC0386.

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TABLES

Table 1. Lycopene content in different tomatoes and tomato products

Product	Lycopene content (mg/100 g)	Reference
Tomato peel	55.70	Calvo et al., (2008)

Tomato pomace	28.64	Huang et al., (2008)
Tomato puree	27.39	Yildiz and Baysal, (2007)
Tomato paste	26.18	Østerlie and Lerfall (2005)
Fresh tomatoes from Italy	23.29	Ilahy et al., (2011)
Fresh tomatoes from Croatia	11.19	Marković et al., (2006)
Hot-break tomato puree	10-14.5	Perez-Conesa et al., (2009)
Ketchup	8.30	Bicanic et al., (2005)
Fresh tomatoes from Spain	8.05	Odriozola-Serrano et al., (2008)
Fresh tomatoes from Mexico	7.92	Galicia et al., (2008)
Fresh tomatoes from Turkey	7.30	Capanoglu et al., (2008)
Tomato juice	7.13	Odriozola-Serrano et al., (2009)
Instant foods containing tomato powder	5.6 to 35.9	Lugasi et al., (2003)
Raw tomato puree	5-8	Perez-Conesa et al., (2009)
Fresh tomatoes from France	3.70	Georgé et al., (2011)
Fresh tomatoes from U.S.A.	2.57	Campbell et al., (2004)
Ketchup	1.9-26.2	Lugasi et al., (2003)
Tomato powder	1.44	Liu et al., (2010)
Baby foods	0.425	Jiwan et al., (2010)

Table 2. Overview of *in vivo* clinical trials.

Clinical status	Ingredient	Lycopene Dose (mg/day)	Time (days)	Effect	Reference

40 patients with high-grade prostate intraepithelial neoplasia (HGPIN)	Lycopene	8	365	lycopene can delay or prevent HGPIN from developing into occult prostate cancer	Mohanty et al., (2005)
Patients diagnosed with prostate adenocarcinoma	Tomato sauce pasta		21	Oxidative DNA damage in leukocytes and prostate tissues was significantly diminished the latter mainly in the tumor cell nuclei. Blood prostate-specific antigen was also decreased	Stacewicz-Sapuntzakis and Bowen (2005)
26 patients with prostate cancer	Capsules	30	21	Decreased tumor growth; decreased plasma PSA levels; decreased plasma IGF-1 levels	Kucuk et al., (2001)
30 healthy men	Red tomato paste	16	21	Circulating lycopene concentrati	Talvas et al., (2011)

				on increased. Short-term intake of tomatoes induces changes in the concentrations of serum components that modulate potential cancer-related gene expression in LNCaP cells	
32 patients with localized prostate adenocarcinoma	Tomato sauce pasta	30	21	Decreased leukocyte and prostate tissue oxidative DNA damage and decreased serum prostate-specific antigen	Chen et al., (2001)
46 patients with androgen-independent prostate cancer	Lycopene-rich tomato supplement	30	---	Lycopene not appear effective for androgen-independent prostate cancer	Jatoi et al., (2007)
36 men with	Lycopene	15, 30,	365	No serum	Clark et al.,

biochemically relapsed prostate cancer		45, 60, 90, and 120		prostate-specific antigen responses were observed, and 37% of patients had prostate-specific antigen	(2006)
11 healthy females	25 g of tomato puree	7	14	Lycopene concentrations in human lymphocytes increased by 44% and lymphocyte DNA resistance to oxidative damage increased by 50%.	Porrini and Riso, (2000)
12 healthy subjects	100 g raw tomatoes, 60 g tomato sauce, 15 g tomato paste	8	21	Decreased DNA oxidative damage with no effects on lymphocyte MDA levels	Riso et al., (2004)
20 healthy albino rats	Lycopene	2.5 mg/kg	224	A decreased percentage of proliferating cell	El-Rouby, (2011)

				nuclear antigen-positive nuclei was associated with lycopene treatment. Proliferating cells were mainly confined to the basal and parabasal epithelial cell layers. Increased E-cadherin and β-catenin immune expression	
Mice injected with human hepatoma SK-Hep-1 cells	Lycopene	1 or 20 mg/kg	84	High-lycopene supplementation lowered the mean number of tumors from 14 to 3 and decreased tumor cross-sectional areas by 62%. High-lycopene supplementation also	Huang et al., (2007)

		decreased the positive rate of proliferating cellular nuclear antigen.	

Table 3. Overview of experimental and tissue culture studies

Cell-Lines	Lycopene Dose	Effect	Reference
Human colon carcinoma (HuCC), B chronic lymphocytic leukemia (EHEB), human erythroleukemia (K562) and Raji cells	1.0, 2.0 and 4.0 mM	Lycopene exerted a significant dose-dependent effect on the proliferation capacity of K562, Raji and HuCC lines. Increased apoptotic rate was found after incubation of HuCC cells with 2.0 and 4.0 mM of lycopene	Salman et al., (2007)

		and in Raji cells following incubation with 2.0 mM.	
Human mammary cancer cell lines (MCF-7 and MDA-MB-231), and a fibrocystic breast cell line (MCF-10a)	10 mM	Modified gene expression was observed in various molecular pathways, such as apoptosis, cell communication, MAPK and cell cycle as well as xenobiotic metabolism, fatty acid biosynthesis and gap junctional intercellular communication.	Chalabi et al., (2007)
LNCaP human prostate cancer cells	5 μM	Lycopene increased G_2/M-phase of the cell cycle from 13 to 28% and decreased S-phase cells from 45 to 29%. Apoptosis was observed in the late stages during 24 and 48 h treatment	Hwang and Bowen, (2005a)
Human breast tumour cell line (MCF-7)	0.125 to 100 μM	Lycopene stimulated the functionality of gap junction intercellular communication (GJIC) at concentrations of 1 μM and this effect was dose-dependent.	Fornelli et al., (2007)
Human breast tumour cell lines	10 μM	Increase of *BRCA1* and *BRCA2*	Chalabi et al., (2004)

(MCF-7, HBL-100, MDA-MB-231)		(oncosuppressor genes) mRNA in the oestrogen receptor (ER)-positive cell lines (MCF-7 and HBL-100), and a decrease (MDA-MB-231) or no change (MCF-10a) in the ER-negative cell lines		
Hep3B human hepatoma cell line	0.1–50 μM	Lycopene inhibited cell growth in a dose-dependent manner. Cell growth was inhibited 20% at 0.2 μM lycopene and 40% at 50 μM lycopene after 24 h incubation. Lycopene-treated cells showed less DNA damage than did placebo-treated cells	Park et al., (2005)	
LNCaP human prostate cancer cell culture systems	0.1-50 μM	Lycopene significantly reduced LNCaP cancer cell survival which can only be partially explained by increased DNA damage at high lycopene concentrations (> 5 μM). Low concentrations of lycopene acted as a lipid antioxidant but did not protect DNA.	Hwang and Bowen, (2005b)	
H-Ras-transformed	0.1-20 μM	Lycopene significantly	Koh et al., (2010)	

MCF10A human breast epithelial cells (H-RasMCF10A) and MDA-MB-231 human breast cancer cells		inhibited invasion and migration as well as proliferation of H-Ras MCF10A and MDA-MB-231 cells. The activations of ERKs and Akt were inhibited by lycopene in H-Ras MCF10A cells, suggesting that the ERKs and Akt signaling pathways may be involved in lycopene-induced anti-proliferative and/or anti-invasive/migratory effects in these cells.	
Prostate cancer cell lines (RWPE-1; 22Rv1; PC-3, LNCaP)	10 nM	All the malignant cell lines exhibited lower expression of monoclonal antibodies ($\alpha 2\beta 1$) with the addition of lycopene to culture media. However lycopene had no effect on cell line growth tested.	Bureyko et al., (2009)

FIGURES

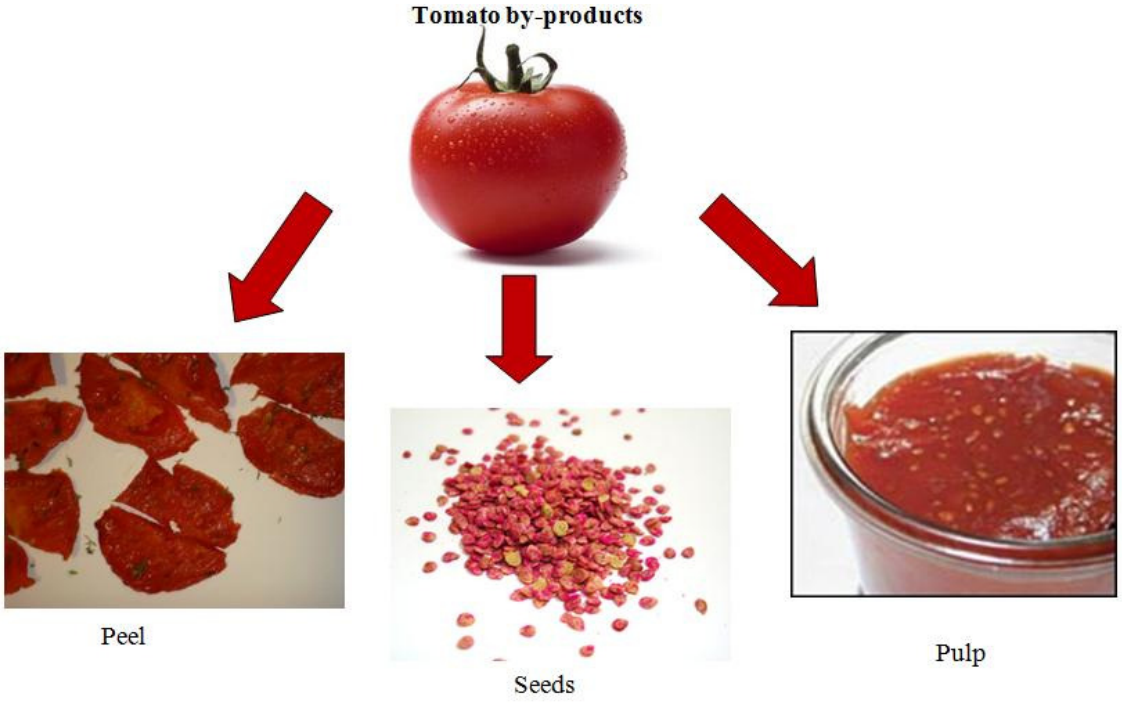

Figure 1. The main by-products during tomato processing.

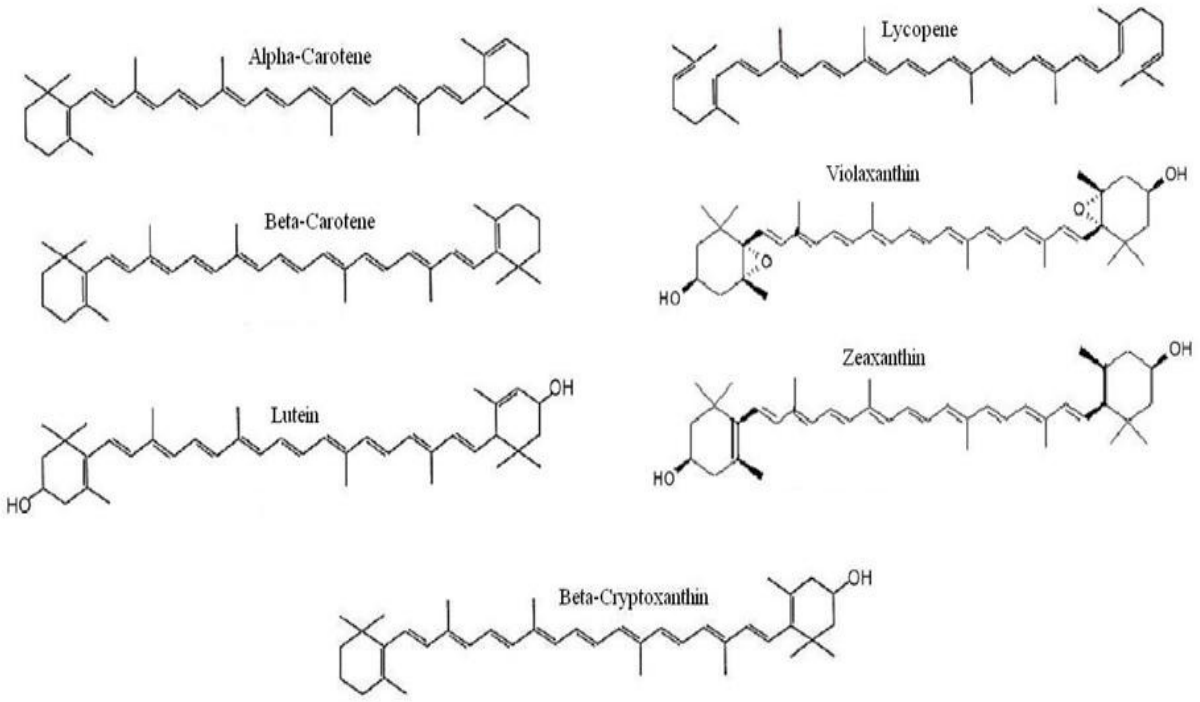

Figure 2. Structure of some major dietary carotenoids.

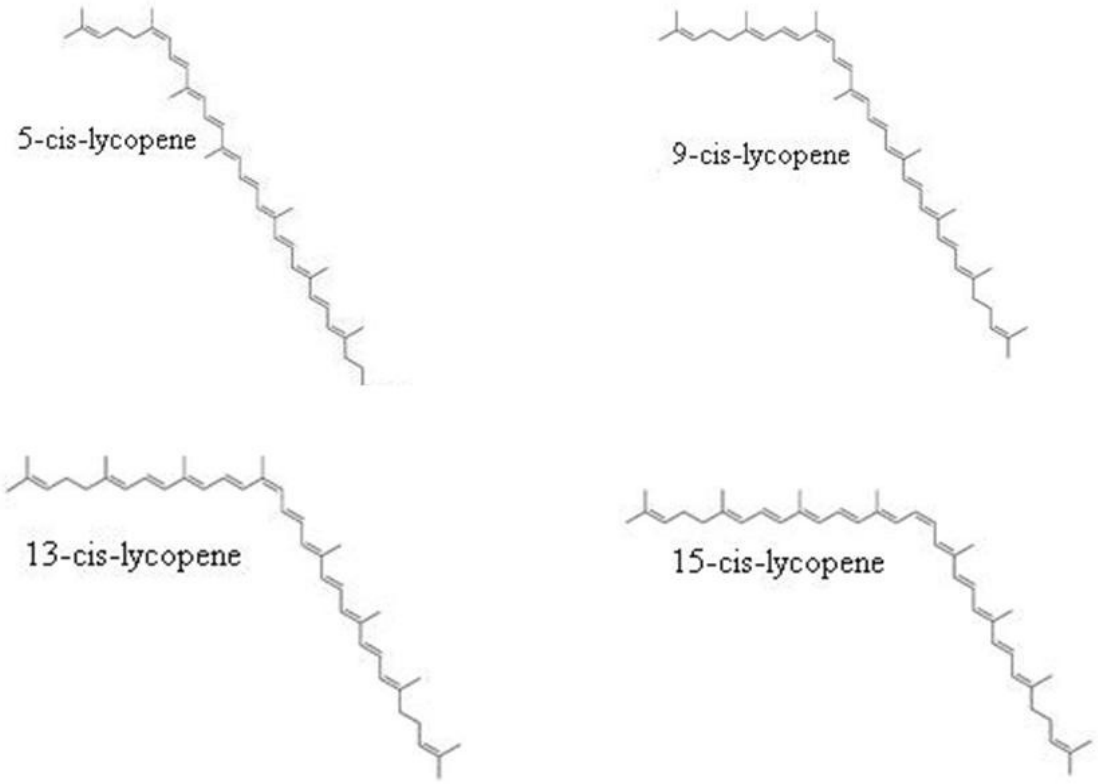

Figure 3. The most common isomeric lycopene forms

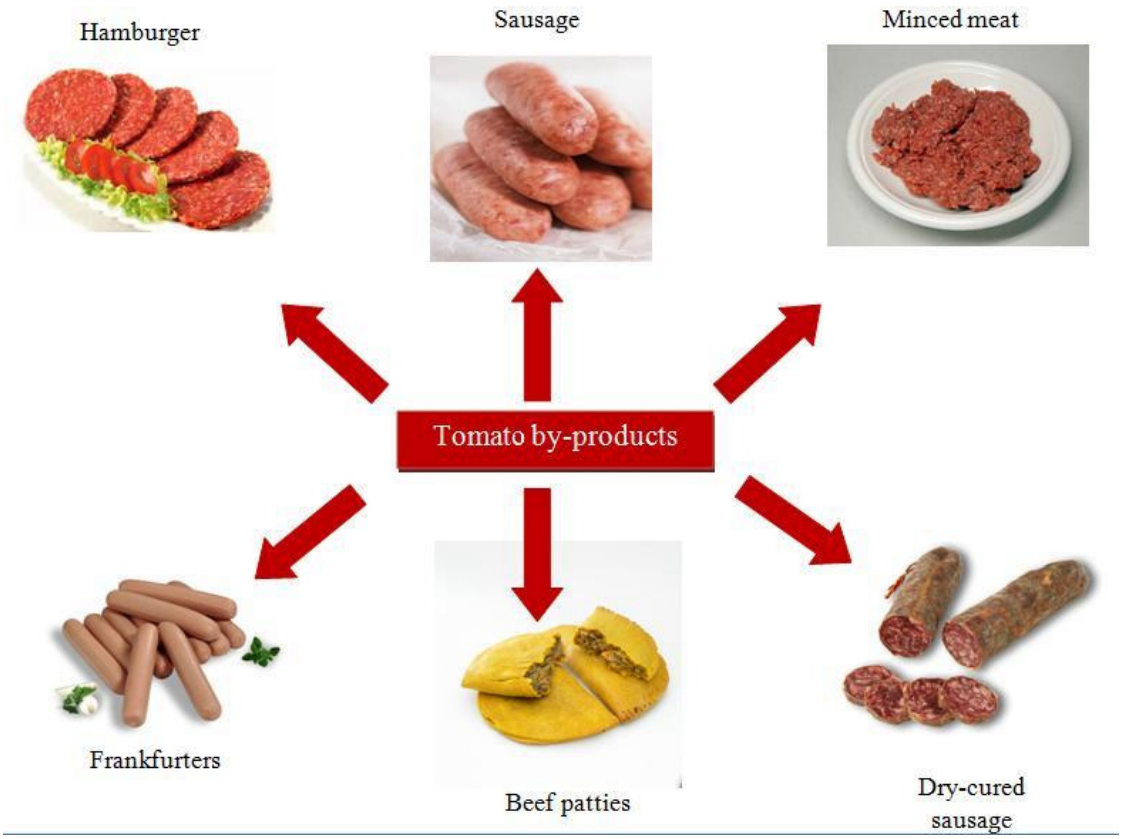

Figure 4. Application of tomato by-products to meat products.