JFBE 5(1): 24-33, 2022

Journal of Food and Bioprocess Engineering

Journal homepage: https://jfabe.ut.ac.ir

Review article

Health impacts and functional properties of lycopenes: A Review

Ali Motamedzadegan, Azita Nemati*

Department of Food Science and Technology, Faculty of Agricultural Engineering, Sari Agricultural Sciences and Natural Resources University, Km 9 Farah Abad Road, Sari, Iran

A B S T R A C T

There is now a growing awareness of a healthy lifestyle in the community and people are looking for useful products in their diet. Functional foods are therefore of great importance to health. Lycopene is a carotenoid that causes the red color in fruits and vegetables. Lycopene is one of the most effective antioxidants among the carotenoids. Lycopene is synthesized by some plants and microorganisms and is the predominant carotenoid found in human serum, and as a pharmaceutical supplement, it protects important cell biomolecules - such as DNA, proteins and fats - from the oxidation and destruction of their radicals. It plays an important role in reducing the risk of cardiovascular diseases as well as treating metabolic syndrome, liver disease and cancers. In this article, the characteristics of lycopene and its effect on human health and treatment of diseases are reviewed.

Keywords: Antioxidant; Cancer; Carotenoid; Lycopene; Tomato

Received 22 December 2021; Revised 24 April 2022; Accepted 24 April 2022

1. Introduction

Maintaining the balance of oxidants and antioxidants in the cellular and intracellular environment is essential for optimal metabolism and human health. The mechanism of energy acquisition is based on the oxidative metabolism of macronutrients of dietary nutrients, but through this process, reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can damage lipids, proteins, and DNA, are produced.

There are mechanisms and enzymatic networks to counter excess ROS or RNS that protect the body against the imbalance caused by these oxidants, which is so far called oxidative stress. The enzymatic network provides human body's main defense against oxidative stress and it stops the production of ROS and RNS and their damage to macromolecules such as DNA (Grabowska et al., 2019; Li et al., 2012; Siva et al., 2011; Bhuvaneswari & Nagini, 2005).

Small molecules such as carotenoids, vitamins, and some minerals act as a part of the enzymes and are involved in antioxidant defense, or they themselves are directly involved in stopping or shutting down ROS and RNS. Inhibition of singlet oxygen or peroxide radical by carotenoids results in energy transfer to the environment or self-destruction of the carotenoids. Therefore, in order to maintain the antioxidant property of carotenoids, they must be sufficiently present in specific ROS and RNS sites (Bhuvaneswari & Nagini, 2005).

More than 600 carotenoid compounds are known, the most famous of which are α-carotene, β-carotene, lutein, lycopene and zeaxanthin. Some contain retinol precursors and convert to vitamin A in the human body. Some carotenoids, such as lycopene, lack vitamin A activity, and their biological effects on the body can be linked to antioxidant effects, effects on immune, binding and inducer system (Hedayati et al., 2018).

Carotenoid bioavailability is related to various factors such as carotenoid species, molecular bonds, carotenoid content, influential factors, nutrients, genetics, host-related factors and the interaction between these variables (Ciriminna et al., 2016). Lycopene is the main carotenoid pigment found naturally in tomatoes. Its name is derived from the tomato's species classification, Solanum lycopersicum (formerly Lycopersicon esculentum) (Motamedzadegan & Shahiri, 2018).

The lycopene content varies in different parts of tomatoes; the amount of lycopene in the tomato skin is much higher than that in tomato pulp and core (Toor & Savage, 2005; Motamedzadegan & Shahiri, 2018).

Factors such as variety, maturity, growth, and storage environmental conditions affect the amount of lycopene and tomato antioxidants, such a way that the amount of lycopene in red ripe tomatoes is approximately 300 times more than unripe tomatoes,

---

*Corresponding author.

E-mail address: azita.nemati@yahoo.com (A. Nemati).

https://doi.org/10.22059/jfabe.2022.336045.1104

and the lycopene content in greenhouse tomatoes is lower than that in farm tomatoes (Strazzullo et al., 2007; Sahin et al., 2018).

Lycopene plays an important role in reducing cancer and cardiovascular disease due to its antioxidant role, which prevents plaque formation and blood clots and heart attacks. Cellular enzymes such as glutathione s- transferase, superoxide dismutase or quinone reductase are activated by lycopene and this is another way to protect the cell from reactive oxygen. The health effects of lycopene on humans have been repeatedly studied (Borguini, & Torres, 2009).

2. History

Schunck (1903) reported that the red substance extracted from tomatoes was easily recognizable from carotene, and he evaluated it for appearance, crystalline form, solubility, and adsorption, and named it “lycopene”, which is derived from the scientific name of tomato (*Solanum lycopersicum*). Its other name, solanorubin, was suggested by the French chemist, who stated that this substance is crystalline and is insoluble in water and soluble in hot alcohol and carbon disulfide, chloroform and benzene. Production of natural lycopene in Israel began in 1990 (Ciriminna et al., 2016).

Table 1. Physical properties of lycopene (Kong et al., 2010; El- Raey et al., 2013).

Molecularformula	$C_{40}H_{56}$
Molecular weight	536.85 Da
Melting point	172-175 °C
Crystal form	Long red needles separate form a mixture of carbon disulfide and ethanol
Powder form	Dark reddish –brown
Solubility	Soluble in chloroform, hexane,benzene, carbon disulfide, acetone, petroleum ether and oil
Stability	Sensitive to light, oxygen, high temperature, acids, catalyst and metal ions

Table 2. Lycopene levels in human tissues (Boileau et al., 2002; Rao et al., 2006; Stahl et al., 2006; Bramley et al., 2000).

Species & Tissue	Lycopene concentration (nm lycopene/g tissue)	Species & Tissue	Lycopene concentration (nm lycopene/g tissue)
Liver	1.28-5.72	Skin	0.42
Adrenal	1.90-21.60	Stomach	0.2
Prostate	0.8	Testes	4.34-21.36
Lung	0.22-0.57	Adipose	0.2-1.3
Breast	0.78	Brainstem	Not detectable
Colon	0.31	Spleen	Not available
Kidney	0.15-0.62	Heart	Not available
Ovary	0.3	Pancrease	0.7

3. Lycopene

The production of these natural pigments, which are not produced in humans' or animals' bodies, is estimated to be around 100 million tons per year, in which algae and leaves have the highest share (Otles & Cagindi, 2008).

Its molecular formula is $C_{40}H_{56}$ and is available in long needle crystals. It's a cyclic isomer from beta-carotene and lacks vitamin A activity. The hydrocarbon chain is straight and unsaturated and consists of two unbound double bonds and 11 conjugated double bonds. Due to its high molecular weight and the lack of polar groups, it is insoluble in water but soluble in non-polar organic solvents. Its molecular weight is 536.9 g/mol and its melting point is 173°C (Table 1) (Shi & Memaguer, 2000). Chemical reactions, light and heat processes may cause cis-trans isomerization. Commonly, distinguished forms of lycopene are 15-cis, 13-cis, 9-cis, 5-cis and trans forms. Lycopene is present in human plasma as 50% cis isomer and 50% trans. High levels of cis-isomer have been reported in serum and prostate (Table 2). The inhibitory constants of lycopene are more than twice that of β-carotene and 10-times higher than α-tocopherol. Lycopene is soluble in organic solvents such as chloroform, hexane, benzene, and methylene chloride and poorly soluble in ethanol and methanol and insoluble in water (Strazzullo et al., 2007; Camare et al., 2013).

Table 3. Plant material sources of lycopene (mg/kg) (Agrwal et al., 2000; Grabowska et al., 2019).

Fruits	Amount (mg/100g)
Guava fresh, pink	5.4
Tomato fresh, red	3.1-7.7
Grapefruit fresh, pink	3.36
Watermelon fresh, red	4.1
Papaya fresh, red	2-5.3
Carrot	0.65
Roseship	0.68
Pumpkin	0.38
Sweet potato	0.02
Apricot	0.01
Persimmon	0.158-0.359
Mango	0.072-0.082
Wild cherry	0.01

Lycopene and carotenoids are 40-carbon and synthesized from acetyl coenzyme A. It is converted into a six-carbon compound called mevalonic acid, which is a precursor of terpenes. By adding phosphorus to the mevalonate structure, it is converted to a 5-carbon molecule called isopentenyl pyrophosphate (IPP). The 20-carbon geranylgeranyl pyrophosphate (GGPP, C20) is then formed by the binding of four IPPs. The binding of two GGPP molecules by their terminal portion produces the 40-carbon and colorless Phytoene molecule, which contains three conjugated double bonds and six non-conjugated double bonds. Phytoene converts to lycopene by dehydrating and increasing the number of double bonds in a few steps (Mantzouridou & Tsimidou, 2008; Wang et al., 2012).

The content of lycopene varies according to the ripening and species of tomatoes and is evaluated based on the soluble solids content. Analyzing the data on lycopene has indicated that lycopene is resistant to processing and storage. Lycopene may change due to high pressure, oxygen and low water activity. It acts in synergy with other compounds, and recent research has shown that eating tomato products has a greater effect on cancer treatment than lycopene alone (Zukinik et al., 2012). Tomatoes are a good source of vitamin C, vitamin A, and a variety of carotenoids including beta-carotene (Table 3) (Motamedzadegan & Shahiri, 2018).

Biodegradation of lycopene not only creates attractive color in food products, but also increases their nutritional value. The main cause of lycopene degradation in dehydrated tomatoes is the isomerization and oxidation process (Verma et al., 2015).

Table 4. Epidemiological studies involving lycopene, lycopene containing foods and chronic diseases.

Disease	Major conclusion	Reference
Prostate cancer	Intake of tomato products inversely associated with prostate cancer.	Fraser et al. (2020)
Digestive tract cancer	Reduced risk with high tomato intake.	Sharma et al. (2021)
Bladder cancer	Serum lycopene associate with decreased risk.	Xu et al. (2021)
Skin cancer	Decrease in skin lycopene on exposure to light.	Koul et al. (2019)
Breast cancer	Serum lycopene associated with decreased risk.	Vansconcelos et al. (2020)
Cervical cancer	Lycopene level showed inverse risk.	Akteb et al. (2021)
Cardiovascular disease	Adipose tissue lycopene associated with lower risk, low serum lycopene with increased mortality.	Saini et al. (2020)
Lung cancer	Lycopene could provide potential benefits against smoke carcinogen-induced pulmonary and hepatic injury.	Eheng et al. (2020) Aizawa et al. (2016)
Liver cancer	Lycopene Inhibits Human Liver Adenocarcinoma SK-Hep-1 Cells Metastasis by Down Regulation of NADPH Oxidase 4 Protein Expression.	Jhou et al. (2017)
Kidney cancer	Lycopene may play a role in the prevention of Renal cell carcinoma.	Sahin et al.(2015)
Colon cancer	Nanoemulsion carrying gold nanoparticles and lycopene inhibit colon cancer cell growth.	Chen et al. (2015)
Pancreatic cancer	Carotenoids, such as lycopene, alpha-and beta-carotene, reduce pancreatic cancer risk.	Huang et al. (2016)
Ovarian cancer	Lycopene supplementation significantly reduced the overall ovarian tumor through antioxidant and anti-inflammatory mechanisms.	Li et al. (2014)
Male infertility	Antioxidants resulted in a lower percentage of sperm with damaged DNA than that of the control.	Bucak et al. (2014)
Hepatic steatosis	Lycopene reduced steatosis by increasing mesenteric adipose tissue fatty acid utilization.	Ip et al. (2014)
Oral submucous fibrosis	Lycopene and injection betamethasone hold good promise in the treatment of this disease.	Goel et al. (2015)
Osteoporosis	Antioxidant-rich foods as a useful tool in bone health promotion and osteoporosis prevention.	Zhang et al. (2016)
Femoral head Cartilage defects	Higher carotenoids intake and vegetable consumption were associated with reduced risk of hip cartilage defects and bone marrow lesions.	Wang et al. (2016)
Down syndrome and Alzheimers disease	Lycopene-rich foods may prevent or delay oxidative stressmediated neuronal impairment in the pathologic conditions.	Lim et al.(2017)

Table 5. Overview of in vivo clinical trials.

Lycopene Dose (mg/day)	Effect	Reference
8	Lycopene can delay or prevent high grade prostate intraepithelial neoplasia from developing into occult prostate cancer.	Flipcikova et al. (2015)
1-20	High lycopene supplementation lowered the mean number of tumors from 14 to 3 and decreased tumor cross sectional areas by 62%.	Huang et al. (2007)
7	Lycopene concentrations in human lymphocytes by 44% and lymphocyte DNA resistance to oxidative damage increased by 50%.	Porrini et al. (2000)
10	The level of myringosclerosis was significantly lower in lycopene- treated groups compared to the control group.	Sahin et al. (2015)
4	Lycopene significantly attenuated learning and memory impairments and prevented the reduction in dendritic spine density.	Wang et al. (2016)
10	The efficacy of lycopene in amelioration of thyroid gland structures as well as DNA damage.	Abdul-Hamid et al. (2013)
50	High dietary intake of tomatoes may have protective effects against acute pancreatitis.	Ozkan et al. (2012)
5-20	Lycopene reverses neurochemical deficts, oxidative stress, apoptosis and physiological abnormalities in mice.	Prema et al. (2012)

The ambient temperature affects the lycopene content in tomatoes. A 31% decrease in the amount of lycopene is observed in summer compared to other seasons, because the optimum temperature for fruit growth is 16°C to 26°C. Lycopene converts to beta-carotene at temperatures above 35°C. Growth conditions, improvers and microorganisms of soil can increase lycopene content up to 36% (Verma et al., 2015).

Diagnosis of lycopene in the food is done by HPLC or by direct spectrophotometry, which is a rapid and standard diagnosis method. A number of researchers have used chromatography and UV sense for this purpose.

Given the increasing value of this substance, other ways for its production, such as the production of carotenoids in plants and algae or their fermentation by microorganisms, have been considered. Microorganisms such as *Streptomyces chrestomyceticus*, *Phycomyces blakesleeanus* and *Blakeslea trispora* have been identified (Matthaus et al., 2014).

Table 6. Effect of HHP processing on lycopene content.

Product	Description	References
Tomato puree	100-600 MPa for 12 min at 20° Chigh pressure affected the total lycopene content and the percentage of the presumptive 13-cis isomer both in lycopene solution and tomato puree. At higher storage temperature, the loss of total lycopene and percentage of 13-cis isomer was greater. The highest stability of lycopene was found when tomato puree was pressurized at 500 Mpa and stored at 4°C.	Qiu et al. (2006)
Tomato puree	50- 400 MPa, 25°C, 15 min. High pressure was explored as one of the hurdles along with citric acid and NaCl for the manufacture of minimally processed tomato products with optimal sensory and microbiological characteristics. The inactivation of polyphenoloxidase, peroxidase and pectinmethyl esterase increased with combined treatments at high values for pressure and additive concentration.	Sanchez- Moreno et al. (2003)
Tomato puree	700 MPa Natural flora of the tomato puree was reduced below detectable limits. high pressure resulted in higher reduction in spore count of meatballs inoculated with Bacillus stearothermophilus spores added to the tomato puree, as compared to conventional sterilization, without significant loss of lycopene.	Svelander et al.(2011)
Carrot & Tomato	HPH did not notably affect the retention of carotenes or ascorbic acid but significantly increased both the release and micellar incorporation of α and β-carotene in carrot emulsions. butbioaccessibility of lycopene from tomato was not increased. HPH is an interesting opinion for increasing the bioaccessibility of carotenes but theresuls will depend on both food and type of carotene.	Svelander et al.(2011)
Tomato paste	100-600 MPa for 1, 30 min. High pressure processing did not destroy the molecular structure of lycopene. The extraction yield of lycopene obtained by high pressure processing for 1 min was higher than that obtained with solvent extraction for 30 min.	Kit et al. (2009)
Tomato pulps	Cold and hot- break tomato pulps have been treated by processing with different operating pressures and times. An increase in cis-lycopene concentration was found after HPCD treatment. For the cold-break tomato pulp, HPCD had a significant positive effect on the lycopene isomerization.	Zhao et al. (2019)

Table 7. Lycopene pathway from ingestion to incorporation into tissue (Preedy et al., 2008).

1) Lycopene is solubilized in the lumen of the small intestine by bile salts and fat.
2) Soluble lycopene is taken up by enterocytes in the intestinal wall.
3) Lycopene is delivered into lymphatics as chylomicrons.
4) Chylomicrons enter the circulation and are hydrolyzed, producing chylomicron remnants.
5) Remnants are taken up mainly by hepatocytes.
6) With hepatocytes, lycopene is incorporated into lipoproteins.
7) Low density and very low density lipoproteins enter the circulation.
8) Lycopene incorporated mostly in low density lipoproteins enters various tissues

Table 8. Lycopene content of common tomato products (Perveen et al., 2015; Nguyen et al., 1998; Boileau et al., 2002).

Food	Lycopene (mg/100g)	Food	Lycopene (mg/100g)
Raw tomato	9.25	Peeled tomato	149.89
Tomato paste	55.43	Tomato juice (hot-braek)	161.23
Tomato sauce	17.96	Spaghetti sauce	1.95
Tomato puree	16.60	Pizza sauce	1.1
Tomato Juice	10.76	Chili sauce	1
Tomato soup (condensed)	7.99	Tomato ketchup	3.53
Canned whole tomato	11.21	Barbecue sauce	0.2
Ketchup	13.44	Clam cocktail	0.2
Tomato powder (spray-dried)	126.49	Bloody mary mix	0.38

4. Health impacts of lycopene

Various chronic diseases can be caused by oxidative damage as a result of reactive oxygen species (ROS). Lycopene is an effective inhibitor against free radicals and singlet oxygen species and plays an important role in the protection of various diseases. Therefore, the biochemical properties of lycopene make it capable of protecting the cell from damage caused by reactive oxygen species. These reactions may be due to chronic inflammation, light, and temperature or normal metabolic processes. The antioxidant property of lycopene may prevent atherogenesis and cancer by protecting DNA, low-density lipids and lipoproteins and proteins (Table 4) (Grabowska et al., 2019).

Salimi et al. (2018) investigated the impact of tomatoes and lycopenes on cancer. Numerous studies have shown an inverse relationship between plasma lycopene levels and cancer. He obtained strong evidence regarding the impact of lycopene on reducing the risk of prostate, gastric, and lung cancers. Lycopene also plays a role in reducing the risk of other cancers, such as the pancreas, esophagus, colon, uterus, and breast (Table 5) (Salimi et al., 2018).

5. Lycopene extraction

The extraction of lycopene from tomatoes should be carried out under controlled environmental conditions in order to minimize oxidative reactions and isomer formation. The usual method is to extract lycopene by organic solvent. A combination of polar and non-polar solvents in various ratios, 1:2 acetone-chloroform ratio, and 50:25:25 ratios of hexane-acetone-ethanol, ethylene acetate, benzene, ethyl ether and petroleum ether is used to extract lycopene.

Organic solvents are not suitable for lycopene extraction, because they extract all the hydrophobic compounds present in tomatoes. Lycopene extractors use less toxic organic solvents such as ethanol and ethyl acetate. However, in European countries, solvents such as dichloromethane, acetone, hexane, ethyl acetate, methanol, and ethanol can be used to extract lycopene as a food coloring. To control isomerization and oxidation reactions, antioxidants such as butylated hydroxytoluene should be used in extraction solvents (Fritsch et al., 2017).

In enzymatic method, the level of extracted compound degradation is low and its stability is higher than some other methods, but due to the high cost of enzymes and the necessity of purification procedures, this method is also limited. But the pigment extracted from the enzyme is much more stable than the pigment extracted from the solvent (Choksi & Joshi, 2007).

Solvent extraction is not economically feasible. The raw material for solvent extraction method must contain a high concentration of lycopene in order to be economically justifiable to extract. This method has disadvantages such as high cost, safety issues, and dissemination of volatile organic compounds to the environment. Therefore, using synthetic methods is recommended to reduce the solvent content and obtain high efficiency (Han & Qun, 2007; Zuknik et al., 2012).

Supercritical fluids are suitable in lycopene extraction in industrial scale. Due to the use of inert carbon dioxide gas and the possibility of using relatively low temperatures, usually higher purity is obtained. Lower processing time and cost are the other benefits of supercritical fluids extraction (Ciriminna et al., 2015).

The benefits of ultrasonic and microwave methods include reduced extraction time, energy-saving and increased efficiency. Therefore, combining the ultrasonic and microwave methods will bring more benefits (Ciriminna et al., 2015).

The effect of the high-pressure process on the increase of lycopene content is probably due to the weakening of the cell wall and the bonding forces between lycopene and the tissue network. High pressure also results in the release of other antioxidants including ascorbic acid and phenolic compounds in tomatoes, and these active compounds provide a good protection that protects lycopene from degradation (Table 6) (Choudhari & Ananthanarayan, 2007).

6. Lycopene metabolism

The digestion of carotenoids begins in the stomach, and pepsin enzymes initially release lycopene from the dietary matrix to make gastric lipase easier to hydrolyze. Lycopene is absorbed by bile acids. The presence of fat stimulates the production of bile acids, resulting in better absorption of lycopene. Due to the solubility of lycopene in fat, an amount of 5 grams fat per meal is necessary to increase the absorption of lycopene. After being separated from the food matrix and dissolved in the fat phase of the gastric mucosa, lycopene is absorbed into the intestinal membrane through the active release and transmitted to the liver. Lycopene is transmitted to the plasma by low and very low lipoproteins and is transferred to different parts of the body. The serum lycopene level is 50-900 nM/L and there is no significant difference between men and women in this respect. Lycopene levels depend on a variety of factors, including age. It is also reduced by alcohol consumption up to 25% (Table 7) (Camara et al., 2013).

7. Production by micro-organisms

Nowadays, synthetic carotenoids provide much of the commercial carotenoids needed, but their application in the food, pharmaceutical, and health industries has limitations such as the potential for toxicity, and that is why the use of microbial resources for the production of carotenoids is increasing.

Due to the increasing demand for natural carotenoids, the production of carotenoids from microbial sources has attracted the attention of many researchers. Since lycopene produced in microbial fermentation is mixed with other carotenoids and is low in amount, a variety of growth mediums, metabolic stimuli and inhibitors, mutagenic, environmental and genetic factors are used in order to increase the production of lycopene and to obtain a product purer than the product resulted from the microbial fermentation. Lycopene cyclase enzyme inhibitors such as pyridine, imidazole, piperidine, and creatine can increase the lycopene extraction yield. As a result, this increase happens because of the prevention of conversion of lycopene to carotene. The difference between the synthesis of carotenoids in plants and in microorganisms is that the microorganisms are able to convert phytoeneinto lycopene at once, and therefore the rate of synthesis of lycopene in them is much higher than in plants (Khodaiyan et al., 2008).

8. Lycopene bioavailability

Lycopene is poorly absorbed in its natural trans form as it is in raw tomatoes. Lycopene bioavailability in raw tomatoes is very low and is about 0.1 to 3%. Many studies have shown that the thermal processes on various tomato products such as tomato sauce and tomato paste induce trans isomerization to cis and increase its bioavailability (Camare et al., 2013). The highest rate of lycopene loss occurs when different thermal processes such as blanching, sterilization, and drying are used, which is due to the short cis isomer length, the high solubility of the cis isomer in the mixed micelles, and thus, the less tendency of the cis isomers to accumulate (Table 8) (Reboul et al., 2006; Camare et al., 2013).

It has also been reported that a slight increase in plasma lycopene levels is observed after unheated tomato juice consumption. However, plasma lycopene levels increase after 24 to 48 hours when the heated tomato juice is consumed with oil. The absorption of lycopene and its bioavailability depend on the fat content of the meal and the heat process applied. In the gastrointestinal tract, fats break down into fatty acids and monoglycerol, thereby increasing the solubility of carotenoids. Lipid nano-carriers increase the absorption of lycopene in the intestine by four times (Sahin et al., 2015).

The cis isomers are more accessible than trans isomers because they are soluble in bile acids and are easier to embed in chylomicrons. Fat stimulates the production of bile acids, resulting in better absorption of lycopene. Thermodynamically, the lower the relative bond energy is, the more stable it would be. Therefore, the stabilities of the isomers of lycopene are different. The 5-cis isomer with -0.539 KCal/mol bond energy and the 11-cis isomer with 6.053 Kcal/mol bond energy are the most unstable isomers of lycopene (Table 9) (Camare et al., 2013).

Table 9. Influence of processing on lycopene isomerization in foods (Boileau et al., 2002).

Lycopene source	Percent trans
Fresh tomato	100
Vac-dried	89.9
Air-dried	84.4
Fresh tomato	95.8
Fresh tomato, heated 200°C for 45 min	89.3
Tomato paste	92.6
Tomato paste, heated 70°C for 3 h	83.4

The intestinal lymphatic route has been reported to be the major mechanism of lycopene absorption by the gastrointestinal tract. Lycopene is transmitted to the intestinal lymph by triglycerides. Long-chain fatty acids or lecithin increase the availability of lycopene. Another important factor in the absorption of carotenoids is the presence of dietary fiber. Due to the hydrophobicity of lycopene and the presence of high lipoprotein receptors in adipose tissue, lycopene and other carotenoids are stored in adipose tissue (Kun et al., 2006; Sahin et al., 2018).

Carotenoids have high melting points, so they remain bioavailable during different processes. Tomato tissue plays an important role in the availability of lycopene. Food processing often plays a positive role in the availability of carotenoids and their release from the tissue structure (Sahin et al., 2018). Lycopene should not be used in the presence of calcium compounds as it reduces calcium bioavailability by 84%. Autoxidation reduces the total lycopene content, the trans isomer content, and the color, and develops a bad taste in the product (Table 10) (Colle et al., 2012; Borel et al., 2016; Singh et al., 2017).

The dietary lycopene bioavailability depends on various factors such as the network to which the lycopene is attached, the physical state of the lycopene, the particle size before and after chewing, the digestion process and the presence of dietary fiber (Sahin et al., 2015).

9. Prostate cancer

The prostate cancer is one of the five leading causes of death in men. Risk factors for prostate cancer include diet, lifestyle, environment and genetics. The consumption of fruits and vegetables helps reduce the risk of the disease. In relation to prostate cancer, special attention has been given to the consumption of lycopene, green tea, epigallocatechin gallate and soy phytoestrogens. Research has shown that by consuming 2 mg lycopene, prostate cancer is reduced by 1%.

Prostate-specific antigen is a glycoprotein enzyme that is present in small amounts in the serum of healthy men and increases by prostate cancer. Some plasma carotenoids, such as lycopene and tocopherol, bind to it and reduce its levels. Research has shown that a daily intake of 30 mg lycopene reduces antigen levels in patients.

One study compared the anticancer effects of lycopene-rich foods and pure lycopene on prostate cancer. The results showed that lycopene-rich foods had a greater anti-cancer effect than pure lycopene, which is due to the synergistic effect of other preservatives on lycopene performance (Chen et al., 2015; Paur et al., 2017).

10. Male infertility

Male sperm contains large amounts of fat, and oxidative degradation reduces its function and results in male infertility. Oxidative stress in sperm can affect male infertility. In infertile men, DNA fragmentation is higher and serum levels of lycopene, beta-carotene, and vitamin A are lower. Lycopene increases spermatozoa motility and mitochondrial activity. The consumption of different antioxidants can prevent the damaging effect of free radicals on sperm and restore sperm activity and increase its fertility. Studies have confirmed that antioxidants and anti-inflammatories affect male mice. Infertility in men is also associated with an imbalance between unsaturated fatty acid of arachidonic acid and docosahexaenoic acid (Filipcikova et al., 2015; Gavabowska et al., 2019).

11. Brain diseases

Due to the absorption of large amounts of oxygen and their consumption, the human brain is one of the most sensitive organs in the body to react against oxidative. Because of the high levels of oxygen and fat and low levels of antioxidants in the brain, the central nervous system is at the risk of oxidative reactions. Lycopene as an antioxidant can flow in blood arteries of the brain and prevent oxidative reactions (Chen et al., 2019).

Oxidative stress plays an important role in neurological diseases at old ages. Most carotenoids, including lycopene, reduce the risk of Alzheimer's and Parkinson's diseases. Lycopene prevents the inflammatory response and acute stroke and can reduce the size of damaged brain areas. Lycopene protects against peripheral neurotoxins and reduces excessive levels of certain elements such as manganese. Lycopene prevents Alzheimer's by inhibiting Abeta protein oxidant production. Lycopene has been shown to decrease the risk of Alzheimer's by reducing the deaths of hippocampus neurons of the brain that are involved in memory processing (Chen et al., 2019; Ranjbar et al., 2018; Sen et al., 2019).

Administration of lycopene improved early brain injury, including brain edema, blood-brain barrier impairment, cortical apoptosis, and neurological injury (Wu et al., 2015).

12. Lung cancer

Cigarette smoke has a high level of nitric oxide (NO) that reacts with oxygen to form free radicals (NO_2). These radicals are retained in the smoke and reach the lungs and in the long-term, they may cause lung cancer. The main carotenoid in the lung is lycopene, which helps to protect the lymphocytes against free radicals (NO_2) and has the ability to inhibit singlet oxygen up to twice that of beta-carotene (Grabowska et al., 2019).

Table 10. Storage practices and their effects on lycopene content.

Variable	Range	Result	Reference
Temperature	35, 45, 55, 65	Highest extraction of 65°Cgave maximum lycopene yield	Baysal et al.(2000)
	40, 50, 60	Observed a large increase of lycopene solubility when the temperature was increased from 40 to 60°C at a constant pressure of 30 MPa.	Dela et al. (2006)
	40, 60, 80	Highest yield of lycopene achieved at the highest extraction temperature of 80°C	Egydio et al. (2010)
	40-100	Maximum total lycopene was extracted from tomato skins at the highest extraction temperature of 100 °C	Egydio et al. (2010)
Atmosphere	Oxygen; 3%	Reduced lycopene content	Yi et al .(2008)
	Co$_2$; 20%	Reduced lycopene content	
	Co$_2$; 5 to 10%	Delayed color development	

13. Cardiovascular diseases

Serum cholesterol levels are known to be a major cause of cardiovascular diseases (CVDs). ROS induces oxidative stress, which is a major cause of CVDs. Oxidation of low-density lipoproteins plays an important role in CVDs. Lycopene increases LDL receptors, thereby reducing cholesterol formation (Muller et al., 2015). Lycopene reduces cholesterol formation by 73% and increases LDL degradation by 34%. It also removes 110% of LDL from the bloodstream, and lowering the cholesterol levels reduces the risk of heart diseases. A 1:3 ratio has been observed between a decrease in cholesterol levels and a decrease in infarction. A 30 to 40 percent reduction in the risk of heart diseases is seen in people who regularly take lycopene in their diet. Lycopene consumption increases the oxidation delay of lipoproteins, in which the effect of thiobarbituric acid on blood plasma has been shown to determine the effect of lycopene consumption on reducing lipid oxidation and subsequent heart attacks (Ranjbar et al., 2018; Muller et al., 2015).

People with lower blood lycopene levels are more likely to have atherosclerosis with the vascular occlusion. They show lower levels of lycopene in the brain arteries. People with higher lycopene levels have a 45% lower risk of developing atherosclerosis and a lower risk of having a heart attack than people with lower lycopene levels. Lycopene also inhibits the powerful oxidants of hypochlorous acid associated with atherosclerosis (Bub et al., 2002).

14. Bone diseases

Destructive oxidation reactions are one of the most important causes of common bone diseases such as osteoporosis. Natural antioxidants such as lycopene can play an important role in preventing such bone diseases. Lycopene stimulates the formation of bone cells and prevents deformities of the skeleton and bones. The level of lycopene in women's blood plasma is inversely correlated with osteoporosis, and women who consume a good amount of lycopene have fewer bone deformities and osteoporosis (Ranjbar et al., 2018).

In the Chinese population, women with higher levels of beta-carotene, lycopene, and alpha-carotene showed higher bone density, indicating the effect of lycopene on the bone system. Lycopene stimulates bone formation and prevents osteoclastogenesis and osteoblastogenesis (Wang et al., 2016; Costa-Rodrigues et al., 2018).

15. Chromosomal damage caused by radiation

Ionizing rays are widely used in industry and medicine, which cause microscopic damage to the tissues, which, at high doses, can cause skin burns, genetic damage, and cancer. These rays operate mainly through the formation of oxygen free radicals, which interact with biological molecules and produce toxic compounds that cause lipid peroxidation and DNA damage. The active compounds produced by ionizing radiation cause genetic mutation and cell death by damaging the DNA (Huang et al., 2007). Research shows that lycopene neutralizes oxidant-activating factors (Ranjbar et al., 2018; Lopez-Jornet et al., 2016; Edge et al., 2016).

16. Future perspective

The growing demand for healthy foods has provided an opportunity to develop lycopene-rich processed products. Further studies are needed on serum lycopene levels, its bioavailability, the effects of factors such as dietary, metabolism and isomerization of lycopene and its biological properties.

The synergistic effect of lycopene carotenoids has shown that food sources are more effective than carotenoids alone. Tomato powder, for example, has a greater effect on preventing prostate cancer than lycopene alone. Future research will continue to reveal the role of lycopene and other carotenoids and their metabolism as well as their synergistic effect.

17. Conclusion

Replacing natural dyes with synthetic dyes is economically and healthily important to minimize negative effects including pathogenicity, allergenicity, mutation and DNA damage and to prevent bacterial and oxidative corruption in food products. Lycopene has been shown to have beneficial effects on human health and is used as a natural pigment in the food industry. Its bioavailability plays an important role in human health. Much research has been done on the effect of different food processes on the lycopene and its isomers and its health effects on humans. Food processing and formulation conditions can influence the structure and bioavailability of lycopene. Further research is needed to evaluate the performance of lycopene along with other food additives.

Researchers are trying to produce lycopene from a wide range of microbial sources in order to produce this natural and useful antioxidant through biotechnology and to use it in various nutritional and pharmaceutical cases.

Acknowledgment

This review article contains information gathered from numerous published resources, and thus, we would like to acknowledge all authors of the references used in this review.

Conflict of interest

The authors declare no conflict of interest.

References

Abdul-Hamid, M., & Salah, M. (2013). Lycopene reduces deltamethrin effects induced thyroid toxicity and DNA damage in albino rats. *The Journal of Basic & Applied Zoology*, *66*, 155-163.

Agarwal, S., & Rao, A. V. (2000). Tomato lycopene and its role in human health and chronic diseases. Cmaj, *163*, 739-744.

Agarwal, S., & Rao, A. V. (2000). Carotenoids and chronic diseases. *Drug metabolism and drug interactions*, *17*, 189-210.

Aizawa, K., Liu, C., Tang, S., Veeramachaneni, S., Hu, K. Q., Smith, D. E., & Wang, X. D. (2016). Tobacco carcinogen induces both lung cancer and non-alcoholic steatohepatitis and hepatocellular carcinomas in ferrets which can be attenuated by lycopene supplementation. *International journal of cancer*, *139*, 1171-1181.

Aktepe, O. H., Şahin, T. K., Güner, G., Arik, Z., & Yalçin, Ş. (2021). Lycopene sensitizes the cervical cancer cells to cisplatin via targeting nuclear factorkappa B (NF-**κ**B) pathway. *Turkish journal of medical sciences*, *51*, 368-374.

Ardawi, M. S. M., Badawoud, M. H., Hassan, S. M., Rouzi, A. A., Ardawi, J. M., AlNosani, N. M., & Mousa, S. A. (2016). Lycopene treatment against loss of bone mass, microarchitecture and strength in relation to regulatory mechanisms in a postmenopausal osteoporosis model. *Bone*, *83*, 127-140.

Baer-Dubowska, W., Bartoszek, A., & Malejka-Giganti, D. (Eds.). (2005). Carcinogenic and anticarcinogenic food components. CRC Press.

Bhuvaneswari, V., & Nagini, S. (2005). Lycopene: a review of its potential as an anticancer agent. *Current Medicinal Chemistry-Anti-Cancer Agents*, *5*, 627-635.

Borguini, R. G., & Ferraz da Silva Torres, E. A. (2009). Tomatoes and tomato products as dietary sources of antioxidants. *Food Reviews International*, *25*, 313-325.

Borel, P., Desmarchelier, C., Dumont, U., Halimi, C., Lairon, D., Page, D., & Remond, D.(2016). Dietary calcium impairs tomato lycopene bioavailability in healthy humans. *British Journal of Nutrition*, *116*, 2091-2096.

Boileau, T. W. M., Boileau, A. C., & Erdman Jr, J. W. (2002). Bioavailability of all-trans and cis–Isomers of Lycopene. *Experimental Biology and Medicine*, *227*, 914-919.

Boileau, T. W. M., Liao, Z., Kim, S., Lemeshow, S., Erdman, Jr, J. W., & Clinton, S. K. (2003). Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets. *Journal of the National Cancer Institute*, *95*, 1578-1586.

Bramley, P. M. (2000). Is lycopene beneficial to human health. *Phytochemistry*, *54*, 233-236.

Bucak, M. N., Ataman, M. B., Başpınar, N., Uysal, O., Taşpınar, M., Bilgili, A., & Akal, E. (2015). Lycopene and resveratrol improve post-thaw bull sperm parameters: sperm motility, mitochondrial activity and DNA integrity. *Andrologia*, *47*, 545-552.

Camara, M., de Cortes Sánchez-Mata, M., Fernández-Ruiz, V., Cámara, R. M., Manzoor, S., & Caceres, J. O. (2013). Lycopene: A review of chemical and biological activity related to beneficial health effects. *In Studies in natural products chemistry*, *40*, 383-426.

Chen, P., Zhang, W., Wang, X., Zhao, K., Negi, D. S., Zhuo, L., & Zhang, X. (2015). Lycopene and risk of prostate cancer: a systematic review and meta-analysis. *Medicine*, *94*(33), e1260.

Chen, D., Huang, C., & Chen, Z. (2019). A review for the pharmacological effect of lycopene in central nervous system disorders. *Biomedicine & Pharmacotherapy*, *111*, 791-801.

Cheng, J., Miller, B., Balbuena, E., & Eroglu, A. (2020). Lycopene protects against smoking-induced lung cancer by inducing base excision repair. *Antioxidants*, 9, 643.

Choksi, P. M., & Joshi, V. Y. (2007). A review on lycopene extraction, purification, stability and applications. *International Journal of Food Properties*, *10*, 289-298.

Choudhari, S. M., & Ananthanarayan, L. (2007). Enzyme aided extraction of lycopene from tomato tissues. Food chemistry, *102*, 77-81.

Ciriminna, R., Fidalgo, A., Meneguzzo, F., Ilharco, L. M., & Pagliaro, M. (2016). Lycopene: emerging production methods and applications of a valued carotenoid. *ACS Sustainable Chemistry & Engineering*, *4*, 643-650.

Colle, I. J., Van Buggenhout, S., Lemmens, L., Van Loey, A. M., & Hendrickx, M. E. (2012). The type and quantity of lipids present during digestion influence the in vitro bioaccessibility of lycopene from raw tomato pulp. *Food Research International*, *45*, 250-255.

Costa-Rodrigues, J., Fernandes, M. H., Pinho, O., & Monteiro, P. R. R. (2018). Modulation of human osteoclastogenesis and osteoblastogenesis by lycopene. *The Journal of nutritional biochemistry*, *57*, 26-34.

Crowe-White, K. M., Phillips, T. A., & Ellis, A. C. (2019). Lycopene and cognitive function. *Journal of nutritional science*, *8*, e20.

Edge, R., Boehm, F., & Truscott, T. G. (2016). Oxygen effect on protection of human lymphoid cells against free radicals by the carotenoid lycopene. *Free Radical Biology and Medicine*, *100*, S96.

Egydio, J. A., Moraes, Â. M., & Rosa, P. T. (2010). Supercritical fluid extraction of lycopene from tomato juice and characterization of its antioxidation activity. *The Journal of Supercritical Fluids*, *54*, 159-164.

El-Raey, M. A., Ibrahim, G. E., & Eldahshan, O. A. (2013). Lycopene and lutein; A review for their chemistry and medicinal uses. *Journal of Pharmacognosy and Phytochemistry*, *2*(1), 245-254.

Faisal, W., O'Driscoll, C. M., & Griffin, B. T. (2010). Bioavailability of lycopene in the rat: the role of intestinal lymphatic transport. *Journal of Pharmacy and Pharmacology*, *62*, 323-331.

Filipcikova, R., Oborna, I., Brezinova, J., Novotny, J., Wojewodka, G., De Sanctis, J. B., & Radzioch, D. (2015). Lycopene improves the distorted ratio between AA/DHA in the seminal plasma of infertile males and increases the likelihood of successful pregnancy. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*, *159*, 77-82.

Fraser, G. E., Jacobsen, B. K., Knutsen, S. F., Mashchak, A., & Lloren, J. I. (2020). Tomato consumption and intake of lycopene as predictors of the incidence of prostate cancer: the Adventist Health Study-2. *Cancer Causes & Control*, *31*, 341-351.

Fritsch, C., Staebler, A., Happel, A., Cubero Márquez, M. A., Aguiló-Aguayo, I., Abadias, M., & Suárez-Estrella, F. (2017). Processing, valorization and application of bio-waste derived compounds from potato, tomato, olive and cereals: A review. *Sustainability*, *9*, 1492.

Goula, A. M., Adamopoulos, K. G., Chatzitakis, P. C., & Nikas, V. A. (2006). Prediction of lycopene degradation during a drying process of tomato pulp. *Journal of Food Engineering*, *74*, 37-46.

Goel, S., & Ahmed, J. (2015). A comparative study on efficacy of different treatment modalities of oral submucous fibrosis evaluated by clinical staging in population of Southern Rajasthan. *Journal of Cancer Research and Therapeutics*, *11*, 113-118.

Grabowska, M., Wawrzyniak, D., Rolle, K., Chomczyński, P., Oziewicz, S., Jurga, S., & Barciszewski, J. (2019). Let food be your medicine: Nutraceutical properties of lycopene. *Food & function*, *10*, 3090-3102.

Han, H., & Qun, W. A. N. G. (2007). Study on the effect of ultrasonic on lycopene extraction. *Journal of Science and Emerging Technologies*, *8*(11).

Hedayati, N., Naeini, M. B., Nezami, A., Hosseinzadeh, H., Wallace Hayes, A., Hosseini, S., & Karimi, G. (2019). Protective effect of lycopene against chemical and natural toxins: A review. *BioFactors*, *45*, 5-23.

Hernández-Almanza, A., Montañez, J., Martínez, G., Aguilar-Jiménez, A., Contreras-Esquivel, J. C., & Aguilar, C. N. (2016). Lycopene: progress in microbial production. *Trends in Food Science & Technology*, *56*, 142-148.

Huang, C. S., Liao, J. W., & Hu, M. L. (2008). Lycopene inhibits experimental metastasis of human hepatoma SK-Hep-1 cells in athymic nude mice. *The Journal of nutrition*, *138*, 538-543.

Huang, X., Gao, Y., Zhi, X., Ta, N., Jiang, H., & Zheng, J. (2016). Association between vitamin A, retinol and carotenoid intake and pancreatic cancer risk: Evidence from epidemiologic studies. *Scientific reports*, *6*, 38936.

Huang, R. F. S., Wei, Y. J., Inbaraj, B. S., & Chen, B. H. (2015). Inhibition of colon cancer cell growth by nanoemulsion carrying gold nanoparticles and lycopene. *International Journal of Nanomedicine*, *10*, 2823-2846.

Ip, B. C., Liu, C., Lichtenstein, A. H., von Lintig, J., & Wang, X. D. (2015). Lycopene and apo-10′-lycopenoic acid have differential mechanisms of protection against hepatic steatosis in β-carotene-9′, 10′-oxygenase knockout male mice. *The Journal of nutrition*, *145*, 268-276.

Javanmardi, J., & Kubota, C. (2006). Variation of lycopene, antioxidant activity, total soluble solids and weight loss of tomato during postharvest storage. *Postharvest biology and technology*, *41*, 151-155.

Jhou, B. Y., Song, T. Y., Lee, I., Hu, M. L., & Yang, N. C. (2017). Lycopene inhibits metastasis of human liver adenocarcinoma SK-Hep-1 cells by downregulation of NADPH oxidase 4 protein expression. *Journal of Agricultural and Food Chemistry*, *65*, 6893-6903.

Juan, C., Oyarzún, B., Quezada, N., & del Valle, J. M. (2006). Solubility of carotenoid pigments (lycopene and astaxanthin) in supercritical carbon dioxide. *Fluid Phase Equilibria*, *247*, 90-95.

Khodaiyan, F., Razavi, S. H., & Mousavi, S. M. (2008). Optimization of canthaxanthin production by Dietzia natronolimnaea HS-1 from cheese whey using statistical experimental methods. *Biochemical Engineering Journal*, *40*, 415-422.

Kim, D. J., Takasuka, N., Kim, J. M., Sekine, K., Ota, T., Asamoto, M., & Tsuda, H. (1997). Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH. *Cancer letters*, *120*, 15-22.

Kohlmeier, L., Kark, J. D., Gomez-Gracia, E., Martin, B. C., Steck, S. E., Kardinaal, A. F.,& Martin-Moreno, J. M. (1997). Lycopene and myocardial infarction risk in the EURAMIC Study. *American Journal of Epidemiology*, *146*, 618-626.

Kong, K. W., Khoo, H. E., Prasad, K. N., Ismail, A., Tan, C. P., & Rajab, N. F. (2010). Revealing the power of the natural red pigment lycopene. *Molecules*, *15*, 959-987.

Koul, A., Bansal, M. P., Aniqa, A., Chaudhary, H., & Chugh, N. A. (2019). Lycopene enriched tomato extract suppresses chemically induced skin tumorigenesis in mice. *International Journal for Vitamin and Nutrition Research*, 90(5-6).

Krebbers, B., Matser, A. M., Hoogerwerf, S. W., Moezelaar, R., Tomassen, M. M., & van den Berg, R. W. (2003). Combined high-pressure and thermal treatments for processing of tomato puree: evaluation of microbial inactivation and quality parameters. *Innovative Food Science & Emerging Technologies*, *4*, 377-385.

Kun, Y., Ssonko Lule, U., & Xiao-Lin, D. (2006). Lycopene: Its properties and relationship to human health. *Food Reviews International*, *22*, 309-333.

Lianfu, Z., & Zelong, L. (2008). Optimization and comparison of ultrasound/microwave assisted extraction (UMAE) and ultrasonic assisted extraction (UAE) of lycopene from tomatoes. *Ultrasonics Sonochemistry*, *15*, 731-737.

Lim, S., Hwang, S., Yu, J. H., Lim, J. W., & Kim, H. (2017). Lycopene inhibits regulator of calcineurin 1-mediated apoptosis by reducing oxidative stress and down-regulating Nucling in neuronal cells. *Molecular Nutrition & Food Research*, *61*, 1600530.

Li, X., & Xu, J. (2014). Meta-analysis of the association between dietary lycopene intake and ovarian cancer risk in postmenopausal women. *Scientific reports*, *4*, 4885.

Li, H., Deng, Z., Zhu, H., Hu, C., Liu, R., Young, J. C., & Tsao, R. (2012). Highly pigmented vegetables: Anthocyanin compositions and their role in antioxidant activities. *Food research international*, *46*, 250-259.

Lopez-Jornet, P., Gómez-García, F., Carrillo, N. G., Valle-Rodríguez, E., Xerafin, A., & Vicente-Ortega, V. (2016). Radioprotective effects of lycopene and curcumin during local irradiation of parotid glands in Sprague Dawley rats. *British Journal of Oral and Maxillofacial Surgery*, *54*, 275-279.

Mantzouridou, F., & Tsimidou, M. Z. (2008). Lycopene formation in Blakeslea trispora. Chemical aspects of a bioprocess. *Trends in food science & technology*, *19*, 363-371.

Matthäus, F., Ketelhot, M., Gatter, M., & Barth, G. (2014). Production of lycopene in the non-carotenoid-producing yeast Yarrowia lipolytica. *Applied and Environmental Microbiology*, *80*, 1660-1669.

Miziorko, H. M. (2011). Enzymes of the mevalonate pathway of isoprenoid biosynthesis. *Archives of biochemistry and biophysics*, *505*, 131-143.

Mohanty, N. K., Kumar, S., Jha, A. K., & Arora, R. P. (2001). Management of idiopathic oligoasthenospermia with lycopene. *Indian journal of urology*, *18*, 57-61.

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

Motamedzadegan, A., & Tabarestani, H. S. (2018). Tomato Production, Processing, and Nutrition. *Handbook of Vegetables and Vegetable Processing*, 839-861.

Müller, L., Caris-Veyrat, C., Lowe, G., & Böhm, V. (2016). Lycopene and its antioxidant role in the prevention of cardiovascular diseases a critical review. *Critical Reviews in Food Science and Nutrition*, *56*, 1868-1879.

Otles, S, & Cagindi., O. (2008). Carotenoids as natural colorants. In: food colorants: chemicaland functional properties edited by Socaciu, C.CRC Press, Boca Raton, FL.

Özkan, E., Akyüz, C., Dulundu, E., Topaloğlu, Ü., Şehirli, A. Ö., Ercan, F., & Şener, G. (2012). Protective effects of lycopene on cerulein-induced experimental acute pancreatitis in rats. *Journal of Surgical Research*, *176*, 232-238.

Paredes-Lopez, O, & Osuna-Castro., J. A. (2007). Molecular biotechnology for nutraceuticalenrichment of food crops in: functional foods and biotechnology edited by Shetty, K., et al. CRC Press.Boca Raton, FL.

Paur, I., Lilleby, W., Bohn, S. K., Hulander, E., Klein, W., Vlatkovic, L., & Taskén, K. A. (2017). Tomato-based randomized controlled trial in prostate cancer patients: Effect on PSA. *Clinical Nutrition*, *36*, 672-679.

Perveen, R., Suleria, H. A. R., Anjum, F. M., Butt, M. S., Pasha, I., & Ahmad, S. (2015). Tomato (Solanum lycopersicum) carotenoids and lycopenes chemistry; metabolism, absorption, nutrition, and allied health claims—A comprehensive review. *Critical reviews in food science and nutrition*, *55*, 919-929.

Porrini, M., & Riso, P. (2000). Lymphocyte lycopene concentration and DNA protection from oxidative damage is increased in women after a short period of tomato consumption. The *Journal of nutrition*, *130*, 189-192.

Preedy, V. R, & Watson., R. R. (2008). Lycopene nutritional, medicinal and therapeutic properties.Science Publishers, Enfield, NH, USA.

Prema, A., Janakiraman, U., Manivasagam, T., & Thenmozhi, A. J. (2015). Neuroprotective effect of lycopene against MPTP induced experimental Parkinson's disease in mice. *Neuroscience letters*, *599*, 12-19.

Qiu, W., Jiang, H., Wang, H., & Gao, Y. (2006). Effect of high hydrostatic pressure on lycopene stability. *Food Chemistry*, *97*, 516-523.

Ranjbar, A., Ranjbar, E., Salimi, A. (2019). The role of lycopene in human health as a natural colorant. *Nutrition & Food Science*, *49*, 284-298.

Reboul, E., Richelle, M., Perrot, E., Desmoulins-Malezet, C., Pirisi, V., & Borel, P. (2006). Bioaccessibility of carotenoids and vitamin E from their main dietary sources. *Journal of Agricultural and Food Chemistry*, *54*, 8749-8755.

Saini, R. K., Rengasamy, K. R., Mahomoodally, F. M., & Keum, Y. S. (2020). Protective effects of lycopene in cancer, cardiovascular, and neurodegenerative diseases: An update on epidemiological and mechanistic perspectives. *Pharmacological research*, *155*, 104730.

Sahlin, E., Savage, G. P., & Lister, C. E. (2004). Investigation of the antioxidant properties of tomatoes after processing. *Journal of Food composition and Analysis*, *17*, 635-647.

Sahin, K., Cross, B., Sahin, N., Ciccone, K., Suleiman, S., Osunkoya, A. O., & Bilir, B. (2015). Lycopene in the prevention of renal cell cancer in the TSC2 mutant Eker rat model. *Archives of biochemistry and biophysics*, *572*, 36-39.

Sahin, E. D., Yalcın, S., Ozercan, I. H., Kaygusuz, I., Karlıdag, T., Keles, E., & Akyigit, A. (2015). The effect of lycopene on experimental myringosclerosis. *International journal of pediatric otorhinolaryngology*, *79*, 342-348.

Sahin, K., Gencoglu, H., Bilir, B., & Kucuk, O. (2018). Protective role of lycopene against oxidative stress in liver. In *The Liver* (pp. 155-167). Academic Press.

Sánchez-Moreno, C., Plaza, L., de Ancos, B., & Cano, M. P. (2003). Vitamin C, provitamin A carotenoids, and other carotenoids in high-pressurized orange juice during refrigerated storage. *Journal of Agricultural and Food Chemistry*, *51*, 647-653.

Schneider, T., Graeff-Hönninger, S., French, W. T., Hernandez, R., Merkt, N., Claupein, W., & Pham, P. (2013). Lipid and carotenoid production by oleaginous red yeast Rhodotorula glutinis cultivated on brewery effluents. *Energy*, *61*, 34-43.

Sen, S. (2019). The chemistry and biology of lycopene: antioxidant for human health. *International Journal of Advancement in Life Sciences Research*, *2*, 08-14.

Shi, J., & Maguer, M. L. (2000). Lycopene in tomatoes: chemical and physical properties affected by food processing. *Critical reviews in food science and nutrition*, *40*, 1-42.

Shi, J., Dai, Y., Kakuda, Y., Mittal, G., & Xue, S. J. (2008). Effect of heating and exposure to light on the stability of lycopene in tomato purée. *Food control*, *19*, 514-520.

Silva, Y. P., Ferreira, T. A., Jiao, G., & Brooks, M. S. (2019). Sustainable approach for lycopene extraction from tomato processing by-product using hydrophobic eutectic solvents. *Journal of food science and technology*, *56*, 1649-1654.

Singh, A., Neupane, Y. R., Panda, B. P., & Kohli, K. (2017). Lipid Based nanoformulation of lycopene improves oral delivery: formulation optimization, ex vivo assessment and its efficacy against breast cancer. *Journal of microencapsulation*, *34*, 416-429

Singh, P., & Goyal, G. K. (2008). Dietary lycopene: Its properties and anticarcinogenic effects. *Comprehensive Reviews in Food Science and Food Safety*, *7*, 255-270.

Siva, R., Palackan, M. G., Maimoon, L., Geetha, T., Bhakta, D., Balamurugan, P., & Rajanarayanan, S. (2011). Evaluation of antibacterial, antifungal, and antioxidant properties of some food dyes. *Food Science and Biotechnology*, *20*, 7-13.

Srivastava, S., & Srivastava, A. K. (2015). Lycopene; chemistry, biosynthesis, metabolism and degradation under various abiotic parameters. *Journal of Food Science and Technology*, *52*, 41-53.

Strazzullo, G., De Giulio, A., Tommonaro, G., La Pastina, C., Poli, A., Nicolaus, B., & Saturnino, C. (2007). Antioxidative activity and lycopene and β-carotene contents in different cultivars of tomato (*Lycopersicon esculentum*). *International Journal of Food Properties*, *10*, 321-329.

Stahl, W. (2006).Tomato lycopene in photoprotection and skin care. In: Rao AV, editor, Tomatoes, lycopene and human health. Scotland: *Caledonian Science Press*. 199-211.

Svelander, C. A., Lopez-Sanchez, P., Pudney, P. D., Schumm, S., & Alminger, M. A. (2007). High pressure homogenization increases the in vitro bioaccessibility of α-and β-carotene in carrot emulsions but not of lycopene in tomato emulsions. *Journal of Food Science*, *76*, 215-225.

Tibäck, E. A., Svelander, C. A., Colle, I. J., Altskär, A. I., Alminger, M. A., Hendrickx, M. E., & Langton, M. I. (2009). Mechanical and thermal pretreatments of crushed tomatoes: effects on consistency and in vitro accessibility of lycopene. *Journal of food science*, 74, 386-395.

Toor, R. K., & Savage, G. P. (2005). Antioxidant activity in different fractions of tomatoes. *Food research international*, *38*, 487494.

Vasconcelos, A. G., Valim, M. O., Amorim, A. G., do Amaral, C. P., de Almeida, M. P., Borges, T. K.,& Leite, J. R. S. (2020). Cytotoxic activity of poly-ε-caprolactone lipid-core nanocapsules loaded with lycopene-rich extract from red guava (*Psidium guajava* L.) on breast cancer cells. *Food Research International*, *136*, 109548.

Verma, S., Sharma, A., Kumar, R., Kaur, C., Arora, A., Shah, R., & Nain, L. (2015). Improvement of antioxidant and defense properties of tomato (var. Pusa Rohini) by application of bioaugmented compost. *Saudi journal of biological sciences*, *22*, 256-264.

Viuda-Martos, M., Sanchez-Zapata, E., Sayas-Barberá, E., Sendra, E., Pérez-Álvarez, J. A., & Fernández-López, J. (2014). Tomato and tomato byproducts. Human health benefits of lycopene and its application to meat products: a review. *Critical reviews in food science and nutrition*, *54*(8), 1032-1049.

Wang, X. D. (2012). Lycopene metabolism and its biological significance. *The American journal of clinical nutrition*, *96*, 1214-1222.

Wang, Q., Feng, L. R., Luo, W., Li, H. G., Zhou, Y., & Yu, X. B. (2015). Effect of inoculation process on lycopene production by Blakeslea trispora in a stirred-tank reactor. *Applied biochemistry and biotechnology*, *175*, 770-779.

Wang, Z., Fan, J., Wang, J., Li, Y., Xiao, L., Duan, D., & Wang, Q. (2016). Protective effect of lycopene on high-fat diet-induced cognitive impairment in rats. *Neuroscience Letters*, *627*, 185-191.

Wang, Y., Smith, S., Teichtahl, A. J., Hodge, A. M., Wluka, A. E., Giles, G. G., & Cicuttini, F. M. (2016). Association between dietary intake of antioxidants and prevalence of femoral head cartilage defects and bone marrow lesions in community-based adults. *The Journal of rheumatology*, *43*, 1885-1890.

Wu, A., Liu, R., Dai, W., Jie, Y., Yu, G., Fan, X., & Huang, Q. (2015). Lycopene attenuates early brain injury and inflammation following subarachnoid hemorrhage in rats. *International journal of clinical and experimental medicine*, *8*, 14316-14322.

Xi, J. (2006). Effect of high pressure processing on the extraction of lycopene in tomato paste waste. Chemical Engineering & Technology: *Industrial Chemistry-Plant Equipment-Process Engineering-Biotechnology*, *29*, 736-739.

Xu, X., Xie, B., Li, S., Wang, S., Xia, D., & Meng, H. (2021). Association of dietary tomato intake with bladder cancer risk in a prospective cohort of 101,683 individuals with 12.5 years of follow-up. *Aging (Albany NY)*, *13*(13), 17629- 17637.

Yi, C., Shi, J., Xue, S. J., Jiang, Y., & Li, D. (2009). Effects of supercritical fluid extraction parameters on lycopene yield and antioxidant activity. *Food chemistry*, *113*, 1088-1094.

Zhang, Z. Q., Cao, W. T., Liu, J., Cao, Y., Su, Y. X., & Chen, Y. M. (2016). Greater serum carotenoid concentration associated with higher bone mineral density in Chinese adults. *Osteoporosis International*, *27*, 1593-1601.

Zhao, W., Sun, Y., Cheng, Y., Ma, Y., & Zhao, X. (2019). Effect of high-pressure carbon dioxide on the quality of cold-and hot-break tomato pulps. *Journal of Food Processing and Preservation*, *43*, 13959.

Zuknik, M. H., Norulaini, N. N., & Omar, A. M. (2012). Supercritical carbon dioxide extraction of lycopene: A review. *Journal of food engineering*, *112*, 253-262.