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Preparation of Phytopharmaceuticals for the Management of Disorders

The Development of Nutraceuticals and Traditional Medicine

CHAPTER

18

Biochemical and pharmacotherapeutic potentials of lycopene in drug discovery

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18.1 Introduction

Lycopene is an extensively studied phytochemical that belongs to the hydrocarbon class of the carotenoid family. In 1876, a red-colored pigment in tomato was discovered by Millardet.

Later on, this red-colored pigment became known as "lycopene," a name that was given by Schunck. Lycopene is also known as carotene present in fruits and vegetables of red color (grapefruit, papaya, tomato, grapefruit, and watermelon) [1]. It is one of the most potent naturally and abundantly occurring antioxidants of the dietary carotenoids. Its peculiar structural and chemical features are responsible for its various pharmacological and biological activities. The antioxidant activity of lycopene is attributed to be responsible for its associated health benefits in the management of chronic diseases such as cancer, diabetes, and cardiovascular disorders. Specifically, it is an acyclic isomer of β-carotene with 11 conjugated and two unconjugated double bonds that makes it susceptible to *cis-trans* isomerization and thermal or photodegradation. The biological activity is due to the presence of double bonds in its structure. It differs from other carotenoids because it lacks pro Vitamin A activity due to the absence of a terminal beta-ionone ring [2]. The chemical formula for lycopene is $C_{40}H_{56}$. Lycopene is a potent lipophilic pigmented antioxidant that is naturally synthesized by various plants, microorganisms, and certain algae and fungi but not by animals and humans [3]. Over 80% of dietary sources of lycopene in the United States are obtained from cooked or processed tomato products such as ketchup, tomato juice, spaghetti sauce, and pizza sauce [4].

Just like lycopene, many naturally occurring coloring pigments are extracted from plant sources having excessive consideration globally. These coloring substances are obtained from different phytochemicals, and common examples of these pigments are anthocyanin (blue-purple), β-carotene (orange), chlorophyll (green), and yellowish-green (lutein) [5]. Moreover, α-carotene, β-carotene, β-cryptoxanthin, lutein, lycopene, and zeaxanthin are most abundantly found carotenoids in human plasma and tissues. Carotenoids are further classified as oxygenated carotenoids (β-cryptoxanthin, lutein, and zeaxanthin) and as a hydrocarbon carotenoid (α-carotene, β-carotene, and lycopene) [6].

Color attraction in carotenoids is attributed to the presence of long conjugated double bond system as it forms the light absorbing chromophore in these compounds [7]. Moreover, seven such conjugated double bonds are required to form a visible color in these compounds. A higher wavelength value for maximum absorption has been observed due to increase in conjugated double bond [8]. Lycopene demand increases due to their red color and antioxidant properties. It is also widely used as a food additive in food industries due to having beneficial impact on health. Lycopene also decreased the risks of certain chronic diseases like atherosclerosis, cancer, cardiovascular disease, and neurodegenerative disorders [9–13]. Moreover, significant work has been done to recognize its organic and physiochemical properties [9]. The physical and chemical properties of lycopene [14–16] are depicted in Fig. 18.1 and Table 18.1.

18.2 Biosynthesis of lycopene

The biosynthesis of lycopene just like other carotenoids is synthesized from isopentenyl pyrophosphate [17], which is made from acetyl-coenzyme-A through mevalonic acid pathway. Isopentenyl pyrophosphate isomerizes to dimethylallyl pyrophosphates, which then condenses with a molecule of isopentenyl pyrophosphate to form geranyl pyrophosphate (C10), which further condenses with a molecule of IPP to produce farnesyl pyrophosphate (C15) and finally produce geranylgeranyl pyrophosphate (C20). Carotenoids biosynthesis

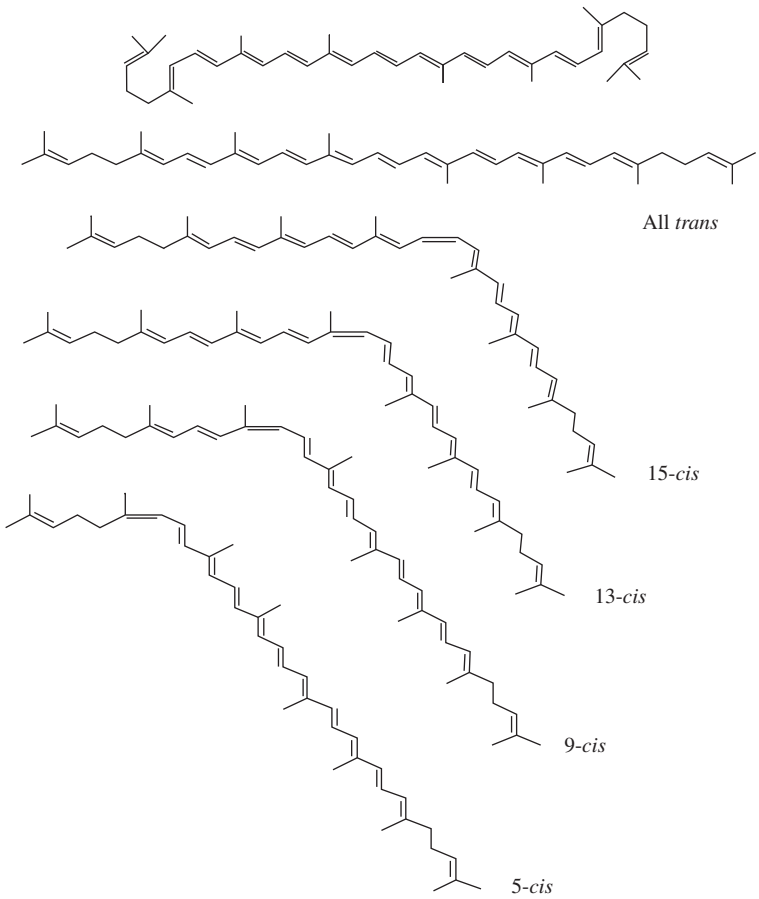

FIG. 18.1 Molecular structures of lycopene and its *trans*- and *cis*-isomers of lycopene.

then starts from a tail-to-tail configuration of two molecules of geranylgeranyl pyrophosphate, which are further condensed to give the 40-carbon phytoene, which forms the first step of carotenoid biosynthesis [17].

18.3 Sources of lycopene

Lycopene is found at high concentration in fruits and vegetables (Table 18.2). The level of lycopene in these fruits is affected by a number of factors [18–22]. These factors include environmental factors and methods of storage and processing. Being a component of many colored fruits with less toxicity, the US Food and Drug Administration (USFDA) granted lycopene the status as generally recognized as safe (GRAS) [23–25].

TABLE 18.1 Physicochemical properties of lycopene.

Physicochemical property	Remarks
Molecular formula	$C_{40}H_{56}$
Molecular weight	536.85 Da
Density	0.889 g/cm^3
Melting point	172–175°C
Crystal form	Long red needles separate from 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; insoluble in water, ethanol, and nearly insoluble in methanol
Stability	Sensitive to light, oxygen, high temperature, acids, catalysts, and metal ions
Type of hydrocarbon	Unsaturated (13 double bonds)
Nature of isomerism	*Cis-trans*
Stable isomer	All-*trans* isomer is thermodynamically stable and most predominant in tomatoes

Source: *N.S. Ganesh, K.B. Lakshmi, V. Chandy, Lycopene properties, and its benefits in human health: a brief review, WJPPS 5 (2016) 424–436; M.L. Nguyen, S.J. Schwartz, Lycopene: chemical and biological properties, Food Technol. 53 (1999) 38–45.*

TABLE 18.2 Concentration of lycopene in different food products.

S. no.	Sources	Concentration of lycopene (mg/100 g)	S. no.	Sources	Concentration of lycopene (mg/g)
1.	Apricots	0.005	9.	Tomato juice	0.05–0.12
2.	Chili	2.62	10.	Tomato paste	0.054–0.5
3.	Grapefruit (brown)	3.36	11.	Tomato powder	1.17–1.26
4.	Guava	5.40	12.	Tomato sauces	0.062
5.	Papaya	5.30	13.	Tomato soup	0.079
6.	Tomato (fresh)	3.1–7.74	14.	Ketchup	0.01–0.134
7.	Vegetable juice	7.28	15.	Cooked tomato	0.037
8.	Watermelon	4.10			

Adapted and modified from P. Singh, G.K. Goyal, Dietary lycopene: its properties and anticarcinogenic effects, Compr. Rev. Food Sci. Food Saf. 7 (2008) 255–270.

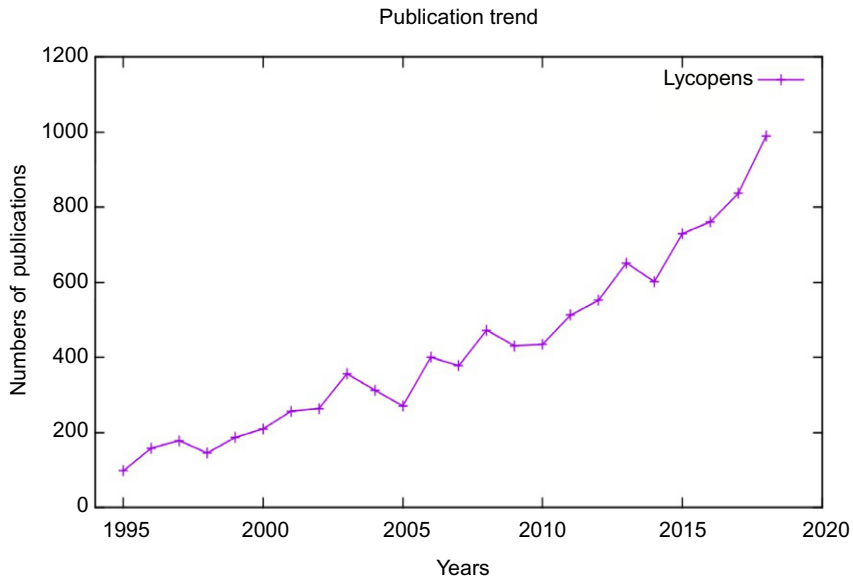

FIG. 18.2 Citation trends for lycopene between 1995 and 2018.

18.3.1 Systematic study on plant sources of lycopene

Literature search using keywords in ScienceDirect and PubMed databases such as "lycopene," "plant lycopene," or "lycopene sources" indicated that results for "lycopene" have the highest listing of 11,942 between 1995 and 2018 (Fig. 18.2). Query for plant sources of lycopene has 166 and 32 results in ScienceDirect and PubMed, respectively. Articles were sorted, and plants with scientific evidence of the presence of lycopene in their leaves, stems, seeds, or roots where applicable were considered and included in this list (Table 18.3). No restriction was made to either the period of publications or class of plants (fruits, vegetable, or seeds). Thirty-two plants were listed to contain lycopene and were distributed in 16 plant families (Fig. 18.3).

18.4 Metabolism of lycopene

This section describes the metabolism of lycopene following its ingestion, namely, absorption, transportation, and distribution. Many studies have been done to elucidate the metabolic processes that lycopene undergoes [48–53].

18.4.1 Lycopene fate in human body

18.4.1.1 Absorption

In the alimentary canal, lycopene gets separated from other food components and get absorbed in the lipid phase, which takes the form of droplet due to its interaction with bile salts and pancreatic lipases [54]. These components enter the duodenum in the form of

TABLE 18.3 Plant sources of lycopene, its family, and common name.

S. no.	Plant sources	Family	Common names	References
	Spinacia oleracea L.	*Amaranthaceae*	Spinach	[26]
	Daucus carota L.	*Apiaceae*	Red carrot	[27, 28]
	Asparagus officinalis L.	*Asparagaceae*	Asparagus Parsley	[28]
	Brassica oleracea L.	*Brassicaceae*	Red cabbage	[28]
	Brassica rapa L.	*Brassicaceae*	Swede	[29]
	Carica papaya L.	*Caricaceae*	Papaya	[30, 31]
	Momordica cochinchinensis (Lour.) Spreng.	*Cucurbitaceae*	Gac fruit-aril	[32, 33]
	Citrullus lanatus var. *lanatus*	*Cucurbitaceae*	Watermelon	[30, 34, 35]
	Cucumis melo L.	*Cucurbitaceae*	Muskmelon	[36]
	Cucurbita moschata Duchesne	*Cucurbitaceae*	Pumpkin	[36, 37]
	Cucurbita pepo L.	*Cucurbitaceae*	Zucchini	[37]
	Momordica charantia L.	*Cucurbitaceae*	Bitter melon aril	[38, 39]
	Diospyros kaki L.f.	*Ebenaceae*	Persimmon	[40]
	Elaeagnus umbellata	*Elaeagnaceae*	Autumn olive	[41]
	Artocarpus heterophyllus Lam.	*Moraceae*	Jackfruit	[30]
	Musa acuminata	*Musaceae*	Banana	[30]
	Eugenia uniflora L.	*Myrtaceae*	Pitanga	[42]
	Psidium guajava L.	*Myrtaceae*	Pink guava	[28, 34]
	Rheum rhabarbarum L.	*Polygonaceae*	Rhubarb	[36]
	Prunus armeniaca L.	*Rosaceae*	Apricots	[43]
	Prunus persica (L.) Batsch	*Rosaceae*	Peach Peaches	[36, 43]
	Rosa canina L.	*Rosaceae*	Rose hips	[44]
	Rosa rubiginosa L.	*Rosaceae*	Sweet-Brier	[45]
	Citrus paradisi Macfad.	*Rutaceae*	Red grapefruit	[28, 34]
	Citrus reticulata Blanco	*Rutaceae*	Orange	[30]
	Citrus sinensis (L.) Osbeck	*Rutaceae*	Red navel orange	[46] [35]
	Capsicum annuum L.	*Solanaceae*	Red bell	[47]

Continued

TABLE 18.3 Plant sources of lycopene, its family, and common name—cont'd

S. no.	Plant sources	Family	Common names	References
	Capsicum annuum L.	*Solanaceae*	Sweet red peppers	[28]
	Capsicum frutescens L.	*Solanaceae*	Chili pepper	[26]
	Solanum lycopersicum L.	*Solanaceae*	Tomatoes	[30, 34]
	Solanum melongena L.	*Solanaceae*	Eggplant	[37]
	Vitis vinifera L.	*Vitaceae*	Grape	[30]

vesicles multilamellar lipids. Afterward, these vesicles get absorbed in the villi of small intestine through diffusion [54]. Beside this mechanism, it was reported that the absorption of lycopene is facilitated by the involvement of particular epithelial transporters. Based on in vitro investigation conducted by the use of Caco-2 cell line, it was found that the absorption of lycopene was less compared with other carotenoids [55]. Numerous other factors influence the absorption of lycopene. For instance, the increase in the intake of indigestible dietary components causes the reduction in release of lycopene from food matrix in the alimentary tract [56]. Again the intake of diet rich in fiber also causes the reduction in the absorption of lycopene. A study conducted on supplementation of lycopene with dietary fiber showed up to 40% reduction in release of lycopene in the plasma [57]. Other studies supported this claim [58–60].

On the other hand, food processing also greatly affects the bioaccessibility of lycopene. Thermal treatment of tomato sauce increases the *trans* to *cis* isomerization and thus enhances the lycopene bioavailability [61]. Similarly, it was observed that dried tomato showed higher availability of lycopene as compared with fresh and canned tomatoes [62]. Supplementation of lycopene with oil also increases the bioavailability [63]. A research conducted on humans showed that supplementation of salad dressings with canola oil significantly increases the content of lycopene in human plasma chylomicrons [51]. Similar findings by Fielding et al. [64] show that the cooking of tomatoes with olive oil significantly enhanced the level of lycopene in plasma. Furthermore, it is estimated that the metabolism of lycopene is also affected by age [65].

18.4.1.2 Transportation

After packaging, lycopene is transported to liver for further metabolism [66]. As earlier discussed, lycopene is a hydrophobic entity and found in the lipophilic part of the lipoprotein, which act as a core of lipoprotein structure [4]. Low density lipoprotein is used for the transportation of lycopene unlike other carotenoids that require high-density lipoproteins [4]. Among *cis* and *trans* forms of lycopene, *cis* has high ability of being incorporated in lipoprotein [67].

18.4.1.3 Distribution

It was reported by Erdman [68] that in adrenal and reproductive tissues, liver has 10 times high concentration of lycopene. The concentration of lycopene was reported

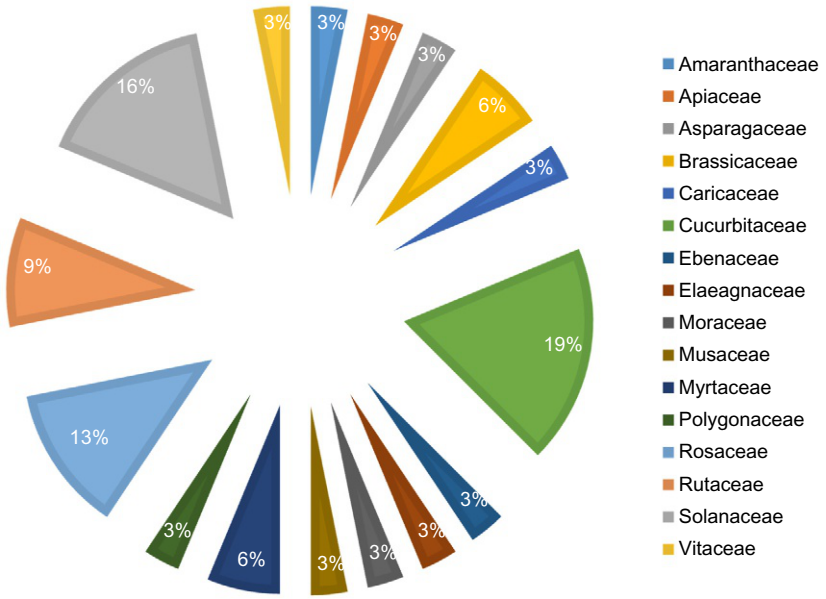

FIG. 18.3 Distributions of plant families containing lycopene.

to be between 0.2 and 21.4 nmol lycopene/g tissue [69]. The following order of lycopene concentration was reported by Goralczyk and Siler [69]: human testes > adrenal gland > liver > prostate > breast > pancreas > skin > colon > ovary > lung > stomach > kidney -> fat tissue > cervix. It was reported that in the tissues, lycopene concentration ranged between 0.15 and 21.36 nmol lycopene/g tissue. Also, other variations in the concentration of lycopene at different parts were reported [70–73]. Lycopene also has some forms of oxidative metabolites such as 2-apo-5,8-lycopenal-furanoxide, lycopene-5,6,5′,6′-diepoxide, lycopene-5,8-furanoxide isomer (I) (II), and 3-keto-lycopene-5,8-furanoxide [74–76].

18.5 General benefits of lycopene

18.5.1 Nutraceutical importance

Nutraceuticals are food or food products that have health-promoting potential and medical benefits. There is a growing interest by most food, pharmaceutical, and cosmetic industries in the use of edible foods, fruits, and vegetables as nutraceuticals. The carotenoid family including lycopene exerts important physiological and health-promoting benefits and is contained in many fruits and vegetables like tomatoes, red grapes, and watermelon.

Lycopene and other members of the carotenoid family have proven to be of high medicinal, scientific, pharmaceutical, and commercial value [77]. They have found various wide applications in the food and nutraceutical industries [78, 79]. These nutraceutical purposes have

led many companies in performing the extraction of lycopene from tomato peels and seeds, to meet the requirements of the food, pharmaceutical, and cosmetic markets.

Lycopene is employed commercially as a dietary supplement, animal feed supplements, and nutraceutical for cosmetic and pharmaceutical purposes [80, 81]. In the food industries, lycopene serves as a food colorant because of its rich red pigments [5]. Its high solubility in fats and oils makes it essential in cosmetics formulations. Therefore, lycopene is a versatile hydrocarbon member of the carotenoids with various medicinal, therapeutic, and industrial applications. The physicochemical properties and biological and chemical structure are responsible for its wide pharmacological activities. Tomatoes are not the only source of lycopene. Though it lacks pro vitamin A activity, its potent antioxidant activity is higher compared with other members of the carotenoids. Cancer, cardiovascular diseases, and neurodegenerative diseases comprise the major disease targets for lycopene.

18.5.2 Health benefits

Lycopene has been found to be beneficial to the body by preventing or ameliorating the development of different kinds of diseases (Fig. 18.4). Fig. 18.4 and Table 18.4 present studies in support of this claim.

18.6 Biological activities of lycopene and its metabolites

Lycopene is associated with multifaceted biological activities in human beings. This theory was strongly supported by several epidemiologic reports, cell culture, and animal studies. A major function of enzyme β-carotene-9′,10′-oxygenase (BCO2) regarding metabolism was indicated by excentric cleavage of provitamin and nonprovitamin A carotenoids into apo-10′-carotenoids; this cleavage was effectively demonstrated through various in vitro and in vivo studies. It was further elaborated that the lycopene and nonprovitamin A carotenoids are preferably catalyzed as compared with provitamin A carotenoids. Biological activities of lycopene can be facilitated through lycopene metabolites, which were proved through numerous in vivo and in vitro studies. Moreover, further research is compulsory to elaborate the beneficial roles of lycopene and its metabolites particularly in prevention of chronic and coronary heart melodies.

18.6.1 Antioxidant effect of lycopene

Living systems have a sensitive balance between endogenous and exogenous antioxidants responsible for the detoxification of free radicals that produced because of various reasons like UV, chemical oxidants, air pollution, or endogenous agents. The deterioration of this balance in the direction of oxidants is defined as oxidative stress, and this stress plays an important role in the development of certain diseases like cancer and many other chronic diseases. In this context, in cases where endogenous antioxidants (antioxidant enzymes such as SOD, CAT, and 6Px; melatonin; bilirubin; and uric acid) are insufficient, supplementation of the organism with exogenous antioxidants may prevent the formation of oxidative stress [90].

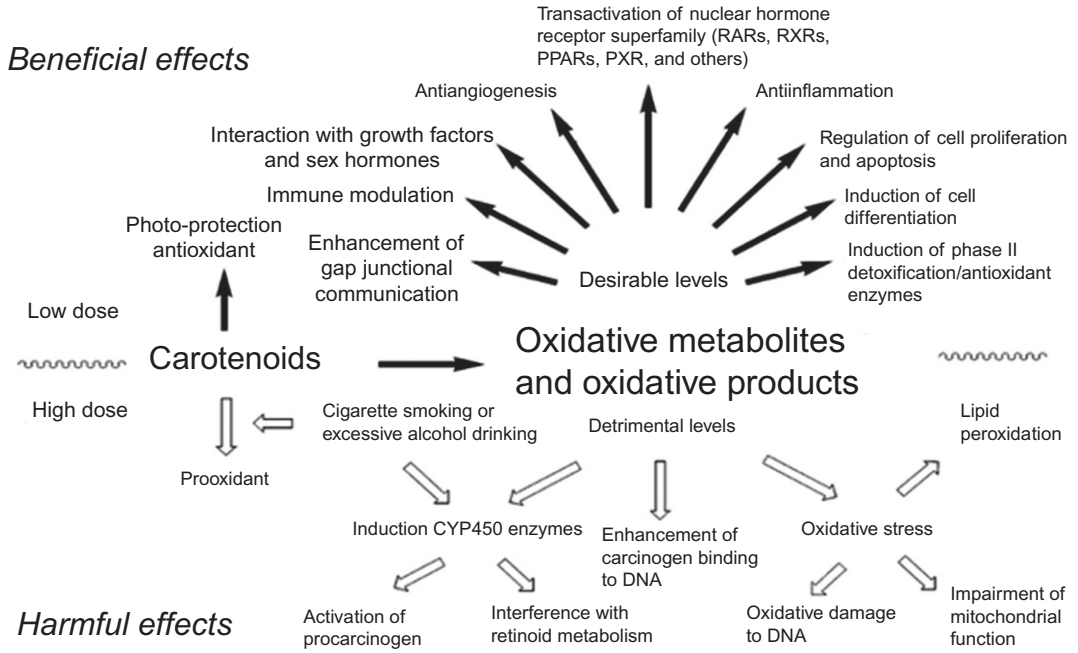

FIG. 18.4 Schematic illustration of potential biological effects attributed to lycopene and its metabolites. *From X.-D. Wang, Lycopene metabolism and its biological significance, Am. J. Clin. Nutr. 96 (5) (2012) 1214S–1222S.*

Exogenous antioxidants are mostly molecules that can be taken with foods and with some preparations and generally support the antioxidant system directly or indirectly.

Reactive oxygen species (ROS) are small molecules that originating from oxygen short-lived superoxide ($O_2^{-\bullet}$) and hydroxyl ($OH^{\bullet}$) and peroxide ($RO_2^{\bullet}$) and alkoxyl ($RO^{\bullet}$) radicals. Nonradical species such as singlet oxygen ($^1O_2$), ozone (O_3), hypochloric acid (HOCl), and hydrogen peroxide (H_2O_2) play a role as oxidizing agents and are easily converted to radicals [10, 91, 92]. ROS formation usually occurs as a result of a sequence of phenomena starting from the production of superoxide from oxygen by single electron transfer during mitochondrial respiration and is the major source of hydroxyl radicals [92]. Antioxidants are present in foods or body at lower concentrations than oxidable substrates, and they substantially delay or inhibit the oxidation of the substrate causing oxidative damage [10, 91, 92].

The human body cannot produce lycopene. Watermelon, apricot, and red grapefruit contain lycopene, but 85% of lycopene is found in tomato and tomato products [93]. Lycopene lacks of vitamin A activity because it does not contain a noncyclic and beta-ionic ring. Lycopene bioavailability increases with oil because of its highly lipophilic nature. Nutrient lycopene passes into lipid micelles in the small intestine and nutrient lipids (triacylglycerol, cholesterol, and fatty acids) in the intestine help dissolve hydrophobic lycopene and pass it through passive transport into intestinal mucosal cells. Lycopene passes to the chylomicrons through the lymphatic system into the systemic circulation from the intestinal mucosa.

TABLE 18.4 Health benefits and modes of action of Lycopene.

Disease condition	MOA/biological action	References
Cancer (prostate, breast, ovarian, cervical, liver, and organ cancers)	Gap junction communication, regulation of cell transcription, and antioxidant property	[82, 83]
Cardiovascular diseases (hypertension, atherosclerosis, and hyperlipidemia)	Antioxidant activity, inhibition of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG Co A)	[82]
Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and vascular dementia)	Protection against amyotrophic lateral sclerosis, reduction in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and environmental toxins that triggers Parkinson's disease	
Osteoporosis	Inhibition of osteoclasts formation and resorption; reduce the levels of carbonyl compounds and proliferation and the differentiation of osteoblasts	[84–86]
Eye defects (cataracts)	Antioxidant property; prevents diabetes-induced morphological changes and modulates epithelial cells in vitro	[87, 88]
Male infertility	Protects sperm from oxidative damage and improves sperm motility, sperm motility index, morphology, and functional sperm concentration	[89]
Chronic obstructive pulmonary disease (asthma)	Regulates oxidative stress and proinflammatory stress and improve lung function in asthmatics	[13]
Skin reactions (erythema)	Scavenges peroxyl radicals and protects against photooxidative process	

MOA, *mechanism of action.*

Lycopene, therefore, is most commonly found in the human body in low-density (LDL) and very low-density (VLDL) lipoprotein fractions of the serum and in adrenal glands, testes, liver, and prostate gland. Lycopene's chemical structure is responsible for its antioxidant properties [94]. Conjugated polyene chains are responsible for unstable and electrophilic attacks against free radicals because this double π electron system reduces the energy requirement for the oxidation of electrons in each double bond [92]. This reactivity contributes to the efficacy of lycopene as the basis of its antioxidant activity in biological systems and its efficacy as a chemopreventive agent [92].
As a result,

- Lycopene can capture singlet oxygen and free radicals through the long double bond system [95].
- Lycopene can protect cells against oxidative stress by acting as an antioxidant with various mechanisms such as singlet oxygen scavenger.
- One molecule of lycopene can bind thousands of singlets of oxygen molecule before reduction [96].
- Singlet oxygen capture activity mainly depends on the number of conjugated double bonds involved [97].

- In another mechanism of the reaction of lycopene with free radicals, carbon-centered carotenoid radicals occur and are stabilized with long polyene chains. Electron density is denser at the ends of the polyene chain where the reaction takes place [98].

18.6.2 Anticancer potential of lycopene

Cancer is a public health problem that causes high mortality worldwide [99, 100]. According to World Health Organization, the incidencies of cancer increased to 18.1 million new cases and caused 9.6 million deaths in 2018. Several factors are responsible for the initiation of cancers. The outgrowth of cells along with genetic and epigenetic variations in the normal cells is the main causes of cancer. The growth of cancer cells can be inhibited by controlling growth factor signaling pathways followed by cell cycle arrest [101]. There are three stages of cancer: initiation, promotion, and progression [102]. The exposure of carcinogenic agents to the cells leads to the initiation of cancer and causes DNA damage followed by inactivation of tumor suppressor genes. Furthermore the promotion and progression of tumor are characterized by the transformation of initiated cell to the epigenetic alteration that leads to tumor growth. Molnar et al. demonstrated that the treatment of cancer by radiation and chemotherapy did not significantly stop cancer cell proliferation. However, studies have found that lycopene can help reduce the incidencies of cancer by inducing apoptosis, angiogenesis, and tumor invasion [103]. In a definite concentration, lycopene can reduce the growth of cancer cell mutagenesis through binding with the signaling receptor and cell cycle progression [104,105].

A study by Jian and coworkers proposed that regularly consuming vegetables and fruits high in lycopene might reduce the onset and development of prostate cancer in Chinese men [106]. The intake of watermelon has also been associated with a reduced risk of prostate. There is also scientific evidence that lycopene has successful in preventing cervical intraepithelial neoplasia and as an inhibitor to cancer cells of the breast, endometrium, and lung [107].

18.6.2.1 Lycopene as antiproliferation and apoptosis

Extracellular signal-regulated kinase (ERK) is a major regulatory pathway to control the process of cell proliferation, apoptosis, and differentiation [108]. Lycopene can inhibit the phosphorylation of extracellular signal-regulated kinase (ERK) pathways in gastric and hepatocarcinoma cancer cells [109,110]. ERK signaling pathways can regulate the cell cycle checkpoints and cell division. Lycopene can enhance the G0-G1 phase and reduce S phase in human gastric cancer HGC-27 cells. This study demonstrated that lycopene may participate in the antiproliferation of gastric cancer cells by inducing cell cycle arrest [109]. Apoptosis is the naturally programmed cell death; Bcl-2 protein is responsible for the survival of the cells or known as antiapoptotic protein through reducing caspase 3 and 8 activation [111,112]. The natural compound lycopene is responsible for the decreasing level of Bcl-2 protein and increasing the level of Bax, caspase 3 and caspase 8 in gastric cancer cells, which cause leading to the apoptosis [104].

Nowadays, lycopene has been traditionally used as chemo preventive for the treatments of cancer in human tumor cells, rats, and rabbits. In case of leukemia (type of cancer), it is very

tough to treat, but lycopene is the option to prevent cancer in early stage [113]. The concentration of lycopene in human plasma has been found naturally greater as compared with β-carotene that possesses highly preventive potential against various types of human cancer such as prostate, gastric cancers, breast cancer, and colon and lung tumor [114–119]. Sahin et al. [120] demonstrated the effects of lycopene on the migration and tube formation inhibition in human umbilical vascular endothelial cell [120]. In another study, the dose-dependent lycopene, inhibits the growth of tumor in xenotransplanted nude mice with the PC-3 prostate carcinoma and Sk-Hep-1 hepatocellular carcinoma cell lines; study provokes antiangiogenic effects [121]. The lycopene can be including into the human lycopene deficient diet and also used in industries where oxygen quenching is required. The contribution and significant role of plant lycopene in the prevention of various cancers are evident and can more need to pharmacological aspects.

18.6.2.2 Lycopene and metastasis

Metastasis is the initialization of cancer cells that consists of stage (metastasis cascade: invasion, intravasation, and extravasation) leading to cancer spread to other organs of the body, with it 90% of death due to cancer worldwide. The penetration of tumor cells to the other surrounding cells termed invasion, which cause movement of motile cells to the other lymphatic tissues through extracellular matrix is called intravasation, a second stage of tumor. Then these infected cells leave the blood vessels and generate secondary tumor. Lycopene has been used to prevent metastasis in vitro and in vivo. Huang et al. [122] demonstrated the effect of lycopene to reduce metastasis. In their study, lycopene was orally supplemented for 12 week of different dose whereas the other group were injected with human hepatoma SK-Hep-1 cells. After some time, the level of matrix metalloproteinase (MMP)-2 and vascular endothelial growth factor (VEGF) increased in plasma and decreased significantly in proliferating cellular nuclear antigen (PCNA), MMP-9, and VEGF in mice lungs supplemented with dose-dependent lycopene. This strong study suggested that the supplementation of lycopene can inhibit the tumor metastasis in vivo.

18.6.2.3 Lycopene and angiogenesis

The growth and progression of tumor are only possible by the process of angiogenesis. Angiogenesis is a fundamental process in growth and development of tissue from preexisting blood vessels induced by hypoxia [105]. The proliferation and differentiation of vascular endothelial cells initiated by the angiogenic growth factors bind to their receptor present in endothelial cells and activate the cells, which leads to release matrix metalloproteinases. The growth factor and endothelial cells incorporated to synthesized new capillaries [123]. The growth of the cancer tissue can be inhibited by the inhibition of angiogenesis, which is considered as target point. Lycopene has been used as anticancer agent that works against cancer cells validated by experimental approaches [124, 125]. In a study demonstrated by Elgass et al. [126], lycopene can inhibit in vitro angiogenesis in human umbilical vein endothelial cells (HUVEC) and rat aortic rings in a dose-dependent manner significantly. In their experiment, the concentration of TNF-α (10 mg/L) and lycopene (1.15 mmol/L) were used and find significantly reduction in network branching (junction numbers, number of tubules, and tubule length).

18.6.3 Antihyperlipidemic activity of lycopene

Atherosclerosis develops slowly by plaque formation inside vessels from deposition of lipid that become hard later level of cholesterol; blood pressure and lack of daily activities are risk factors for diseases. Good nutrition helps prevent chronic diseases [127–129]. Tomato intake decreases risk of heart disease and cancer [130–132]. Lycopene is an antihyperlipidemic that provides protection against cellular damage caused by reactive species. It also maintains the cholesterol metabolism. Lycopene is marker that has health benefits and is antihyperlipidemic and antioxidant. It also maintains the intercellular junctions and hormonal and immune responses [133].

Cholesterol is very important organic molecule that is constituent of cell membrane, and its homeostasis is much necessary for healthy life, and it is gain by its proper intake, absorption, metabolism, and excretion [134]. If cholesterol level rises, it results in hypercholesterolemia, and it is risk factor for cardiovascular diseases. Cholesterol level should be less than 200 mg/dL: HDL and LDL 50 and 90 mg/dL, respectively. Cholesterol is up taken by mediated endocytosis and in cellular biosynthesis mostly LDL [135, 136]. An enzyme HMG-CoA reductase activity inhibition results in reduction of cholesterol by diacylation of HMG-CoA reductase into mevalonate. Cholesterol-lowering drugs are also used for inhibition of cholesterol synthesis and treating hypercholesterolemia. It also has the adverse effect such as liver damage, and drug interactions are also found [137, 138]. The need is to reduce the side effects of drugs by finding a new therapeutic agent that is more potent and much beneficial. Lycopene, which is one of natural organic pigments that belongs to carotenes found in tomatoes, is much important in lowering the risk of cardiovascular diseases due to antihyperlipidemic and antioxidant activity [2, 82, 139, 140]. It is transported to circulation by lymphatic pathway. Transport is by receptors. Liver, seminal vesicles, and prostate are sites of lycopene accumulation [141]. Lycopene is much important because it cause inhibition of LDL oxidation [142]. Carotenoids can control cholesterol metabolism [143]. Lycopene is much important because it cause inhibition of LDL oxidation [137, 144]. Evidence and experiments show that it is antihyperlipidemic. Lycopene is much important in regulation of cholesterol metabolism and treats the hypercholesterolemia.

Lycopene is recommended by dieticians due to its high level of biological activity in fruits because of its hypolipidemic and antioxidant activities [132]. These phytonutrients are much important in lowering the level of cholesterol that has health benefits [136, 145, 146]. It is found that it lowers the level of total cholesterol if dose of lycopene consumes 25 mg/day by human [136, 147]. Lycopene has protective effect for blood cells, and it reduces aortic lesions and reduces lipid in rats by improving oxidation [131]. Lycopene is much hypotensive [133] and has cholesterol lowering effects [148]. It was also found that in transgenic mice that the mixture of lycopene, fish oil, catechin, ol group, and vitamin C reduce the risks in c-reactive protein male [149]. Again, lycopene supplemented diet of 100 mg/kg and vitamin E (250 mg/dL) caused the reduction of serum and cholesterol level [150]. Lycopene-rich diet in our food increases the level of good cholesterol, which is beneficial for the body [151, 152]. In one study, Lycopene was also reported to cause the decrease in VLDL level [153]. A separate study confirmed that the consumption of lycopene causes the level of bad cholesterol to decrease [126]. In a study, different groups of men and women were administered with different concentrations of lycopene. The results of the study established that middle-aged men

with low concentrations of lycopene in blood plasma were at a higher risk of atherosclerosis as compared with individuals with high concentration of plasma lycopene. It was also established that individuals with low lycopene concentration in the adipose tissues were at higher risk of myocardial infarction as compared with the ones with high concentration of lycopene. The main underlying mechanism was found to be the antioxidant property of lycopene. Lycopene is the strongest antioxidant among all the carotenoids present in the tomatoes and is involved in preventing the oxygenation of the LDL [154]. Smoking is considered to be a well-known risk factor for developing heart diseases. Studies suggest that when a person smokes, a number of free radicals enter the body and they cause oxygenation of the bad cholesterol, leading to the formation of the foam cells, and ultimately, atherosclerosis occurs. Studies have proven that lycopene is a powerful antioxidant and therefore prevents the oxygenation of bad cholesterol LDL and thus prevents plaque formation characteristic of atherosclerosis. Several studies have suggested that smokers have a lower plasma concentration of carotenoids as compared with nonsmokers, but this did not apply to lycopene in all studies. While some studies showed an inverse relationship between lycopene and cigarette smoke, others suggested no such relationship. Therefore, the exact relationship is not properly understood, and results are not quite clear [155].

In summary, lycopene decreased the level of bad cholesterol such as LDL, VLDL, and triglycerides and elevate the level of good cholesterol. This property can be due to the prevention of lipid oxidation due to the use of lycopene-containing diet. From observations and experiments, lycopene is one of the best hypocholesterolemia constituents that regulates cholesterol metabolism. Its role is much better in protecting against heart diseases.

18.6.4 Antihypertensive effects of lycopene

In recent years, the prevalence of cardiovascular diseases and hypertension has become a major challenge all over the world and especially in developing countries. Generally, hypertension, smoking, and diabetes can be considered as the most important risk factors for heart disease [156]. In the last decade, pharmacists have synthesized a large number of antihypertensive drugs from various classes such as beta-blockers (BBs), calcium channel blockers (CCBs), diuretics, angiotensin-II receptor blockers (ARBs), and angiotensin converting enzyme inhibitors (ACEIs) [157, 158]. The increasing use of these drugs in recent years has led to different adverse reactions and side effects, which has result in drug inefficiency, nonadherence to therapy, economic loss, and increased mortality [159]. Kronish et al. [160] reported side effects and lower adherence associated with using beta-blockers and diuretics drugs. Hence, finding safe alternatives such as natural remedies could be considered to reduce these side effects and effective treatment of hypertension.

Tomato intake due to the presence of lycopene has reduced the risk of cancer and cardiovascular disease [82]. Recent studies have shown that fruit and vegetable consumption has a positive effect on the balance of blood pressure, which is often due to the presence of natural antioxidants such as lycopene, and can improve cardiovascular function [161] and antioxidative stress activity [162]. Antihypertensive properties of lycopene are due to its antioxidant effects and the inhibition of the angiotensin converting enzyme. Paran et al. [163] evaluated the possible treatment of hypertension by using the natural antioxidants in tomato extract and found that the

consumption of tomato extract for 6 weeks resulted in a significant decrease in systolic blood pressure. Their report indicated a significant correlation between lycopene levels and systolic blood pressure ($r = -0.49, P < 0.001$). Engelhard et al. [135] reported that the use of lycopene-rich tomato extract has led to decrease in systolic and diastolic blood pressure in patients with grade-1 hypertention. Petyaev et al. [164] concluded that 28-day oral intake of lycopene-containing dark chocolate had a significant effect on the reduction of blood pressure.

18.6.5 Cardioprotective effects of lycopene

Various studies have shown that lycopene intake can reduce various incidences of heart diseases such as coronary heart disease [165–173]. Epidemiological research conducted revealed that regular intake of antioxidant vitamins such as vitamin E and β-carotene may abate the risk of coronary heart disease [12, 82, 174]. Similarly, in vitro and in vivo studies have been carried out with lycopene, and many of the in vitro analysis showed that lycopene could protect natural low-density lipoprotein oxidation and impede the synthesis cholesterol [12, 175, 176]. Clinical study by physicians found an interplay between higher plasma lycopene concentration and low risk of cardiovascular disease [12, 177].

The low death rate from cardiovascular disease among the people of the Mediterranean countries compared to other Western regions was deduced to be partly due to the large consumption of fruit and vegetables especially those very rich in lycopene by the Mediterranean populace [178, 179]. Significant deficiencies in cellular concentrations of many essential nutrients such as lycopene and other carotenoids have been linked to medical conditions like aging, cardiovascular disease, and type 2 diabetes mellitus in which oxidative stress has been implicated [179–181].

18.6.6 Neuroprotective effects of lycopene

In a broad survey concerning food sources encompassing lycopene, it was observed that lycopene has both antidiabetic and antioxidant activities [182]. Lycopene is an aliphatic hydrocarbon carotenoid haul out from plants like watermelons, papayas, and tomatoes. Preceding research has revealed that lycopene can employ prophylactic and/or therapeutic properties in diverse ailments, like heart failure and neoplasm through antiinflammatory, antiproliferative, and antioxidative accomplishments. Some other benefits of lycopene in various pathological conditions (colchicine exposure, aging high-fat diet, and diabetes) are cognition and memory improvement of rodents. Neurotoxicities induced by cadmium (Cd), methylmercury (MeHg), monosodium glutamate (MSG), *tert*-butyl hydroperoxide (*t*-BHP), and trimethyltin (TMT) could also be prevented by lycopene. A distinct therapeutic effect of lycopene is exhibited against haloperidol-induced orofacial dyskinesia and ethanol addiction. A neuroprotective effect of lycopene is denoted by reversal of mitochondrial dysfunction, reticence of oxidative stress, and neuroinflammation and reticence of neuronal apoptosis. There are other inhibition mechanisms by lycopene as well, such as intracellular Ca^{2+} homeostasis restoration, nuclear factor erythroid 2-related factor (Nrf2) activation, brain-derived neurotrophic factor (BDNF) activation, and c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) inhibition [183].

A number of studies identified the biological activities of carotenoids comprising lycopene. It reduces cholesterol; regular uptake of lycopene is also involved in reducing myocardial infarction. It was examined that β-carotene and lycopene carotenoids are elated principally in LDL, which sets them in leading position to protect oxidation of LDL. An experiment was conducted on smokers; their food was supplemented with lycopene, and it was observed that lycopene inhibit LDL oxidation. It was concluded because there was a decrease in conjugated diene (CD) propagation rate; pentene excretion was decreased along with a significant increase CD lag time of observed persons [155]. In vitro experiments were performed in humans by adding lycopene and β-carotene to macrophage cell lines; it resulted in an increase in LDL receptors and decrease in cholesterol synthesis (73%) as compared to β-carotene. Lycopene was involved in 110% removal of LDL from the circulation, and there was 34% increase in LDL degradation. It is necessary to evaluate the percentage bioavailability of lycopene while investigating the significant pharmacological role of lycopene. Two crucial factors are involved in determining the bioavailability of lycopene: firstly, absorption rate of lycopene in intestine and, secondly, breakdown process of lycopene [184]. Bioavailability of lycopene is also dependent on some pathological conditions such as cardiovascular diseases and aging presence of lycopene isomers in tissues and blood. Among different isomers, tetra-*cis*-lycopene bioavailability is higher than all *trans*-lycopene [185, 186]. Besides, lycopene is present in lower concentration, and after absorption, it is distributed in adrenals, prostate, and liver. To explore the neuroprotective mechanism of lycopene in the CNS, more methods to raise the lycopene contents in brain tissues are precarious.

18.6.7 Lycopene effects against neurodegenerative disease

Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and epilepsy often are consequences of oxidative stress. Being a good antioxidant, lycopene helps stabilize this effect by reducing the risk of neurodegenerative diseases [186–190].

18.6.8 Antibacterial activities of lycopene

Lycopene possesses potent antibacterial properties. Chandra et al. [191] examined the effect of lycopene on gingivitis caused by bacterial plaque adherence to tooth surfaces leading to inflammation of the gums around the teeth. The authors tested the effect of lycopene among a randomized group of 10 patients with clinical manifestations of gingivitis. They discovered that lycopene treatment induced a significant decrease in gum inflammation. In addition, Umar et al. [192] attributed the effective antibacterial effect of *Solanum lycopersicum* Linn. on *Bacillus subtilis* to its lycopene content. The aqueous and methanolic tomato fruit extract had minimum inhibitory concentration (MIC) values of 100 and 50 mg/mL, respectively, on *B. subtilis.* This observation was reinforced by the findings of Omodamiro and Amechi [193]. The authors also reported MIC values of 31.25 mg/mL for *Proteus mirabilis* and *Pseudomonas aeruginosa* also attributed the effectiveness of ethanol extracts of tomato against *Staphylococcus aureus, Proteus*, and *Bacillus* to its lycopene content. Maitra and Sangeeta [194] reported that lycopene extracted from *Lycopersicon esculentum* inhibited the growth of *P. aeruginosa.* In another study in 2012, Dhanawade and Sakhare [195] isolated lycopene from

tomatoes using TLC, UV spectroscopy, and IR. The authors observed a significant zone of inhibition of *B. subtilis* (25 mm). Lee and Lee [196] observed that lycopene exerts its antibacterial effect on *Escherichia coli* by inducing hydroxyl radicals mediated DNA damage that cannot be remediated by the SOS response. Sung et al. [197] assessed the bactericidal activity of lycopene against *S. aureus* by conducting a killing-curve assay against the gram-positive bacteria; the result reaffirmed lycopene's antimicrobial nature.

18.6.9 Antifungal activities of lycopene

Numerous studies have established the antifungal potentials of lycopene. Sung et al. [197] reported that lycopene possesses antifungal activity against *Candida albicans*. They observed that lycopene exerts its potent antifungal activity by causing significant damage to the cell membranes of *C. albicans*. This observation was further confirmed by Desai et al. [198] as the examination of the action of lycopene against fungal cell membranes by fluorescence-activated cell sorter (FACS) scan analysis and glucose and trehalose—release test. Choi and Lee [199] observed that lycopene has a potent antifungal activity on *C. albicans* by inducing apoptosis via the production of reactive oxygen species and mitochondrial dysfunction.

18.6.10 Antiplasmodial/antimalarial properties of lycopene

The report of World Health Organization [200] indicated that malaria is a significant public health problem in over 100 countries with estimated 200 million infections and over 500 thousand deaths annually. Majority (over 90%) of these deaths occur in sub-Saharan Africa, where one child dies of the disease every half an hour [201]. Malaria is transmitted by the bites of female *Anopheles* mosquitoes infected with the parasites, *Plasmodium falciparum P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. The disease primarily affects poor populations in tropical and subtropical areas especially in Africa where the weather conditions encourage the development of vectors and parasites [202]. Malaria caused by *P. falciparum* is a leading cause of death worldwide from a single infectious agent [203].

The major challenge in the treatment of malaria infection is the development of antimalarial drug resistance by *P. falciparum*, which makes it necessary to search for more effective antimalarial compound from plants and plant products. Moreover, report indicates that the derivatives of artemisinin and quinine that are main groups of antimalarial drug are sourced from plant materials [204, 205]. As earlier discussed, lycopene exhibits antioxidant activities which is valuable for good health [9, 82, 206–211].

18.6.11 Ophthalmological effects of lycopene

The onset of eye diseases may at times go undetected till it gets to an advanced stage when serious damage could have been done to the eye. Although regular eye examination by a professional who is usually an ophthalmologist can aid early detection, however, to guaranty a healthy eye sight, nature has evolved some mechanisms via some novel bioactive compounds readily available in foods or foodstuffs consumed by humans such as vegetables, fruits, seeds, and fish oils. A notable compound of interest present in these foods is lycopene found readily

in red fruits such as tomatoes, pink guava, and watermelon. Lycopene, without provitamin-A activity, is implicated for the prevention of some eye diseases because of its powerful antioxidant properties that is a marked characteristics of the carotenoids. Common eye diseases or disorders such as cataracts, color blindness, eyelid twitching, diabetic macular edema, glaucoma, ocular hypertension, retinitis pigmentosa, and age-related macular degeneration are preventable when adequate level of antioxidant bioactive substances is present in the body. As an example, lycopene is found present in the human eye around the retinal pigment epithelium (RPE) choroid, ciliary body, and iris [212]. In the eye, it plays a very pivotal role in preventing free radicals from damaging vital biocomponents of the human eye. This is supported by Fernandez and Afshari [213], who suggested that nutritional antioxidants slow down the progression of cataracts and age-related macular degeneration. Many other scientific evidences are available that support this notion. For instance, a publication in the journal *Ophthalmology* by Gale et al. [214] found that a cross-sectional studies of 362 men and women born, living in Shefield, England, at the time of the experiment, whose age vary between 66 and 75 years, shows that those with high blood plasma concentration of lycopene have lowest cataract. This supports the idea that nutritional antioxidants might play a role in maintaining eye function. It is recommended that at least 10 mg of lycopene should be consumed daily for enhanced health benefits. To arrive at this concentration, each cup of sliced tomatoes offers 4.6 mg, in which two and half cup should be sufficient to give 11.5 mg, which is slightly above 10 mg. Other foods consumed by man should be assessed for their lycopene composition through high-throughput techniques described in this work.

18.6.12 Dental and oral diseases

Interestingly, lycopene has been widely studied against a variety of oral disease conditions such as gingivitis, periodontitis, submucous fibrosis, oral leukoplakia, and oral cancer. Lycopene treatment (8 mg) in gingivitis patients showed potential in reducing gingivitis, bleeding index, and noninvasive measures of plaque [215]. Lycopene has been investigated for clinical management of periodontitis owing to its inherent antioxidant activity. In a randomized, double-blind study, short-term exposure to lycopene at 4 mg/day for 2 weeks has significantly improved mild periodontitis due to its free radical quenching properties [216]. In periodontitis patients, systemic lycopene (8 mg daily) supplementation for 2 months significantly reduced lipid peroxidation in serum, and prominent improvement was observed in periodontitis parameters such as modified gingival index, probing depth, and clinical attachment loss, and the follow-up of these patients revealed significant improvement with routine scaling and root planning (SRP) for 4 months even after discontinuation of lycopene treatment [217].

Different methods of drug delivery systems with lycopene have been developed and targeted against different periodontal conditions. For instance, in a clinical trial, local delivery of lycopene antioxidant gel (2%) was found effective in increasing clinical attachment, and it ameliorates the oxidative stress in periodontal pockets and thereby reduces the gingival inflammation and probing depth [206]. Solid lipid microparticles encapsulated lycopene (LP-SLMs) was developed with the particle size of 77.28 μM with entrapment efficiency of 98.03%, and it was tested against the clinical management of periodontitis. LP-SLMS drug

delivery system was reported to possess effective local drug delivery and antioxidant effect, along with routine SRP protects the periodontal tissue due to antioxidative effect [218].

Oral submucous fibrosis (OSMF) is a malignancy of oral cavity that primarily occurs due to chewing tobacco and betel nut. In clinical studies, lycopene treatment (8 mg/day for 3 months) in OSMF patients showed better improvement [219]. In a randomized controlled trial, comparative efficacy of curcumin (300 mg) and lycopene (4 mg) have been studied, in which lycopene was found equally effective when compared with curcumin in decreasing burning sensation in patients with OSMF. After 3 months of treatment, thrice daily, lycopene showed better result in improving mouth opening than curcumin [220]. In a similar study, curcumin (300 mg) and lycopene (8 mg) treatment in OSMF patients for 9 months also showed an equal efficacy in cheek flexibility mouth opening burning sensation and tongue protrusion. Lycopene treatment in OSMF patients particularly exhibited overall improvement when compared with placebo control [221]. Lycopene was very effective in patients with oxidative stress induced oral lichen planus, and the inherent antioxidative effect was attributed for this activity [222].

Oral leukoplakia (OL) is a potential malignant disorder of the oral mucosa. This precancerous lesion has 0.2%–5.2% of prevalence among Indian population and may progress into oral squamous cells carcinoma (OSCC). There are 16%–62% of OSCC cases that are associated with OL [223]. In clinical studies, 4 and 8 mg/day of lycopene regimen for 3 months reported to have dose-dependent reversal in dysplastic changes and hyperkeratosis in OL patients [224]. Another study reported that even 4 mg/day regimen was effective in OL patients. Further, they reported that there was no significance between the OL patients who treated with 4 and 8 mg of lycopene [225]. In experimental studies, intragastric administration of lycopene (2.5, 5, and 10 mg/kg b.w.) in the form of tomato paste reduces oxidative stress and tumor progression and enhances antioxidant enzymes in 7,12-dimethylbenz[*a*]anthracene-induced buccal pouch carcinogenesis in a hamster model [226]. Interestingly a low plasma level of lycopene concentration was associated with increase in the mortality rate of patients who had different types of oral cancer [227]. These studies clearly show that lycopene have the potential to develop as a therapeutic drug candidate for a variety of oral diseases. However, the exact mechanism behind the lycopene action in reducing the oral diseases is not reported. Further, the need of the hour is to perform more RCTs to confirm the tolerance and potential effect of lycopene in oral cancer patients.

18.6.13 Antiosteoporosis activity of lycopene

Osteoporosis is a condition where the rate of bone formation by osteoblast is outpaced by the bone destruction of the osteoclast [228, 229]. Thus, a good candidate antiosteoporosis compound should help in facilitating and activating the activities of the osteoblast. Lycopene has been studied for the past decade as an antiosteoporotic agent. This natural product, sourced from a common tomato, has shown to possess significant effects on the proliferation and differentiation of osteoblasts [230]. This antiosteoporotic activity of lycopene was believed to be due to the stimulation of human SaOS-2 cell growth and differentiation owing to its unique antioxidant properties. Moreover, the differentiation marker alkaline phosphatase (ALP) activity, with or without dexamethasone, has been found to be affected by lycopene and is dependent on osteoblasts from human origin. It was also found out that the lycopene stimulates the

activity and proliferation of this marker is found in the osteoblasts [231]. In postmenopausal women, the antioxidant lycopene was found to inhibit or reduce oxidative stress, formation of osteoclast, and resorption of bones using *N*-telopeptide as the marker for bone resorption [232]. Also, the level of estrogen also decreases in postmenopausal women that is known to be associated with the brittleness of bones and the production of ROS, thus affecting bone homeostasis [233]. Again, the reduction of oxidative stress also helps regulate bone metabolism by inhibiting production of ROS and increasing antioxidative capacity [234]. This is important since high levels of ROS were found to prevent normal growth and development of osteoblasts hence damage it [235]. Additionally, ROS is suggested to be a required signaling intermediate for the differentiation of osteoclast and that antioxidants like lycopene limits bone resorption in vivo [236]. This further suggests that oxidants increase bone destruction activity of osteoclast and inhibit bone formation activity of the osteoblast. H_2O_2, a strong oxidant, was also found to affect osteoblasts by reducing its cell growth, calcification, and mineralization; ALP activity; and its gene expression [237, 238]. Thus this suggests that antioxidants like lycopene can help address oxidative stress that promotes osteoporosis [239, 240].

18.6.14 Antiaging effect of lycopene

Ultraviolet radiations emitted from the sun induce many pathological changes in the body; on prolonged exposure, these result in photoaging and also may lead to skin cancer. Photoaging is caused due to generation of reactive oxygen species by the action of UV on skin, in addition to nitrosative stress and production of inflammatory mediators that lead to activation of p38, matrix metalloproteinases (MMPs) [241]. Consequently, antioxidant substances are expected to slow down photoaging so that high levels of antioxidant substances may be correlated to lower levels of skin roughness [242].

Shah and Mahajan [241] studied the effect of lycopene gel, dexamethasone gel, and combination of dexamethasone and lycopene gel on UV radiation-induced photoaging in mice. The animals that had received lycopene and standard treatment showed less wrinkles in comparison with UV irradiated and dexamethasone treated group. Lycopene treatment inhibited the lipid peroxidation through the reduction of the levels of thiobarbituric acid reactive substance (TBARS) level from $51.2 \pm 2.417\%$ to $23.593 \pm 3.945\%$ that was elevated due to chronic exposure to UV radiation. Additionally, lycopene gel has reduced the degradation of collagen from $56.12 \pm 2.626\%$ to $20.56 \pm 2.029\%$, also decreased the damage in catalase from $64.59 \pm 1.743\%$ to $19.507 \pm 4.997\%$. Lycopene gel also restored the percentage reduction in glutathione (GSH) from $48.780 \pm 1.682\%$ reduction to $21.927 \pm 7.248\%$. Lycopene protection against UV radiation was also confirmed from the epidermal thickness of the treated skin. Dexamethasone alone or in combination with lycopene has no significant protection ($P < 0.001$). It is noteworthy to report that lycopene provide protection against photoaging by virtue of antioxidant property.

Darvin et al. [242] utilized a modern optical noninvasive in vivo method to study the structures of the furrows and wrinkles in correlation to the concentration of lycopene on the forehead skin of 20 volunteers aged between 40 and 50 years. No significant correlation was found between the age of the volunteers and their skin roughness, while a significant correlation was found between the skin roughness and the lycopene concentration.

Lycopene can provide significant protection to the cellular DNA. Hence, the topical application of lycopene protects skin against UVB-induced damage, through inhibiting ornithine decarboxylase enzyme, thus helping in stabilizing DNA structure in the skin cells and maintaining the DNA double-strand break repair pathway [243, 244]. Also, lycopene on topical application reverses the reduction of proliferating cell nuclear antigen (PCNA) caused by UVB exposure to a significant degree; PCNA is vital for DNA synthesis and cell repair.

In the research performed by Shahtalebi et al. [245], freeze-dried tomatoes (*S. lycopersicum* L.) were rubbed out to a fine powder and formulated into an oil-in-water lotion (5% w/w tomato powder) that could easily be dispersed over the skin. Each 100 g lotion contains 25 mg lycopene. In vivo trial was conducted to measure the antiwrinkle activity of the lotion using Visioface devices on 10 healthy women as case group compared with 10 volunteers using the placebo lotion (lotion base without tomato powder) as control group. The prepared formulation did not show any erythema or edema; this means that it is nonirritant to skin. The wrinkle measurements via charts showed that the efficient time duration for the lotion to cause significant reduction of wrinkles was 42 days. This study proved that lycopene has antiaging effect and is a strong candidate for treating skin wrinkles.

Lycopene is known to have a limited natural bioavailability, but its bioavailability is enhanced in lycopene-rich functional foods. Chernyshova et al. [246] assessed a new lycopene-enriched ice cream for systemic antioxidant effects and facial skin surface in healthy volunteers.

Chernyshova et al. [246] conducted a randomized crossover study, for 4 weeks to compare the effect of lycopene-enriched ice cream to a control. Consumption of lycopene-enriched ice cream increased the lycopene concentrations in the serum and skin steadily that caused significant reduction in both inflammatory oxidative damage and low-density lipoprotein peroxidase protein values when compared with the control ice cream consumption. Control ice cream significantly increased corneocyte desquamation and bacterial presence in the residual skin surface components (RSSC), but these adverse effects, which may be a predisposing factor for acne development, were absent in volunteers consuming lycopene-enriched ice cream. This study proved that lycopene-enriched ice cream is a new functional food with clear antioxidant properties that can alleviate proinflammatory action of ice cream at the level of facial skin and decreases diet-associated acne development risk in the consumers.

18.6.15 Antidiabetic activity of lycopene

Lycopene, a functional phytochemical in the group of carotenoids, has been demonstrated to exhibit antidiabetic activity by reducing hypoglycemic condition in the blood [247–249]. In addition, 0.5 mmol/L of lycopene is reported to be present in human blood plasma, adrenals, adipose tissues, and testes [250].

18.6.15.1 Fruit extracts

Tomato-extracted lycopene is widely reported to possess antidiabetic properties. It was found that lycopene exhibits dose-dependent antidiabetic effects by decreasing the glucose level, elevate insulin concentration and activities of antioxidant enzymes and enhances the serum lipid profile [251]. In recent times, it is evident from various other reports that

lycopene, especially which are extracted from tomatoes, possesses enhanced antidiabetic activity along with antioxidant effects [252, 253]. Moreover, lycopene extracted from *Artocarpus heterophyllus* (Jack fruit) was also demonstrated to possess antidiabetic activity. The results of the hemoglobin glycation inhibition method revealed that the combined effort of lycopene with ascorbic acid and β-carotene leads to hydroxyl and hydrogen peroxide radical scavenging and ferrous iron chelation activities. These activities of lycopene eventually help in reducing the levels of glycated hemoglobin and hence are proposed to be a potential antidiabetic agent [254]. Likewise, *Citrullus vulgaris* Schrad (watermelon) contains 40% higher concentration of lycopene than the mean data of raw tomato. The combined effect of citrulline and lycopene in flesh powder of watermelon was proved to reduce blood glucose and serum insulin level in streptozotocin-induced diabetic mice [255]. Moreover, lycopene has also been reported to be beneficial in the antiinflammatory and oxidative stress-mediated treatment of antidiabetic nephropathy to avoid kidney damage in diabetic patients. Further, lycopene was proved to reduce blood sugar and low-density lipoprotein cholesterol concentration in blood serum and lead to decrement in urine protein content and elevates high-density lipoprotein cholesterol level [256]. In addition, the antioxidant property of lycopene helps in the treatment of thyroid profile in diabetic rats [257] by reducing plasma glucose, insulin levels, and oxidative stress [258]. Recently, lycopene extracted from fruits such as watermelon [259], *Ficus carica* [260], *Solanum incanum* [261], citrus fruit extracts [262], *Momordica charantia* [263], and *Ficus sycomorus* [264] were also proved to contain lycopene that can reduce glucose levels and other diabetic complications.

18.6.15.2 Leaf extracts

Similar to fruits, certain leaves also contain lycopene that can be beneficial in reducing blood glucose and other diabetic complications. It has been reported that the phenolic extract of *Origanum vulgare* subsp. *glandulosum* Desf. from Tunisia contains essential oils, β-carotene, lycopene, and chlorophyll A and B. The presence of lycopene and their combinatorial effect with other phytochemicals leads to inhibition of α-amylase activity, which helps in reducing glucose absorption in diabetic conditions [265]. Further the leaf extracts of oil palm such as *Elaeis guineensis* [266] and *Ficus deltoidea* [267] possess lycopene in their phytochemical content that can reduce hyperglycemia and lipid oxidation in diabetes-induced rats [268]. Furthermore, phytochemical extracts of leaves from *Psidium guajava* (Guava) [269] and *Carica papaya* [270] were demonstrated to contain lycopene and exhibited antidiabetic properties in in vivo studies [268, 271]. Recently, methanolic and flavonoid-rich extracts of *Synsepalum dulcificum* leaves with lycopene content are proved to possess enhanced antidiabetic activity among type 2 diabetic rates via daily oral administration for 21 days [272]. In addition, tomato plant leaves [273] and *Amaranthus tricolor* (red spinach) also contains lycopene in their phytochemical content [274], which further elevates their antidiabetic property along with flavonoids [275]. Moreover, aqueous phytochemical extracts of Iranian *Mentha piperita* and *Mentha spicata* were reported to possess potential hypoglycemic, hypocholesterolemic, and antioxidant activities in diabetic rats [276]. It is noteworthy that both these leaves contain lycopene along with other phytochemicals that may contribute to their antidiabetic activity [277, 278]. However, there is no study that reports antidiabetic activity of these leaf extracts are due to the presence of lycopene. Thus it is evident from these studies that lycopene exhibited synergistic antidiabetic activity in diabetic rats with other phytochemicals.

18.6.15.3 Root extract

The root extracts of plants such as *Arctium lappa* [279], sweet potato (*Ipomoea batats*) [280], *Harpagophytum procumbens* (Devil's claw) [281], and *Decalepis hamiltonii* [282] are demonstrated to contain lycopene in their phytochemical mixture. It is noteworthy that the roots of carrot produce higher concentrations of lycopene that includes lycopene ε-cyclase and β-cyclase [283]. Further, it is also reported that the polyacetylenes from carrots (*Daucus carota*) helps in enhancing glucose uptake in myotubes and adipocytes, which confirms that lycopene can also add on to their antidiabetic property [284]. Recently, several studies showed that the lycopene phytocompound is widely present in root extracts of plants such as *Citrus sinensis* [285], *Manihot esculenta* Crantz [286], *Withania somnifera* [287], *Bunchosia glandulifera* [288], and *Beta vulgaris* (beetroot) [289]. The lycopene extracted from these plants can possibly possess antidiabetic activity, similar to the fruit and leaf extracted lycopene that has to be evaluated and confirmed through experimental investigations in future.

18.6.15.4 Other extracts

Seeds are the unique plant parts were lycopene is present and can be extracted for pharmaceutical benefits. The seeds of tomato present in the fruit contain a wide variety of carotenoids including lycopene that has therapeutic potential against diabetes [290, 291]. Moreover, lycopene in the seed extracts of *Trigonella foenum-graecum* and bark extract of *Pterocarpus marsupium* were investigated in alloxan-induced diabetic rats. The results showed that the extracted lycopene possess enhanced anticataract activity in diabetic rats [292]. Further, *n*-hexane fraction of hydromethanolic seed extract of *Tamarindus indica* that contains lycopene exhibits enhanced antidiabetic property in streptozotocin-induced diabetic rat [293]. Likewise, lycopene present in the seed extracts of *M. charantia* [263], *P. guajava* [294], and grape seed extracts [295] are also useful in formulating antidiabetic drugs. Other than seeds, lycopene present in the flowers of *Calendula officinalis* [296], papaya [297], marigold [298], and *Bixa orellana* [299], barks of Magnolia [300], stems of *Ailanthus altissima* [301], and Portuguese wild edible mushrooms [302] also possess antidiabetic activity. However, it is recommended to carry out extensive research in lycopene present in other parts of the plants than fruit, to expand the potential of lycopene toward targeted diabetic medications with better yield and formulation capability.

18.6.15.5 Nanoformulated lycopene for targeted antidiabetic activity

The structure of lycopene contains unsaturated bonds, which make them susceptible to light and heat and are easily oxidizable. Thus, it is necessary to formulate lycopene to protect them from chemical damages in body fluids. Niosomes are vehicles that can microencapsulate lycopene for their effective targeted delivery. Recently, lycopene extracted from *Lycopersicum esculentum* was formulated in niosomes and is orally administered among alloxan-induced diabetes to evaluate their targeted antidiabetic activity. The results showed that the niosome encapsulated lycopene were delivered in a sustained and prolonged profile for the efficient diabetes treatment [303]. In addition, lipid-based nanoformulations were demonstrated to improve the oral delivery of lycopene for diabetes and cancer treatments [304]. Moreover, self-assembled green tea catechin derivatives were used to load lycopene that was coated with chitosan as a shell to form core–shell nanoparticle delivery system.

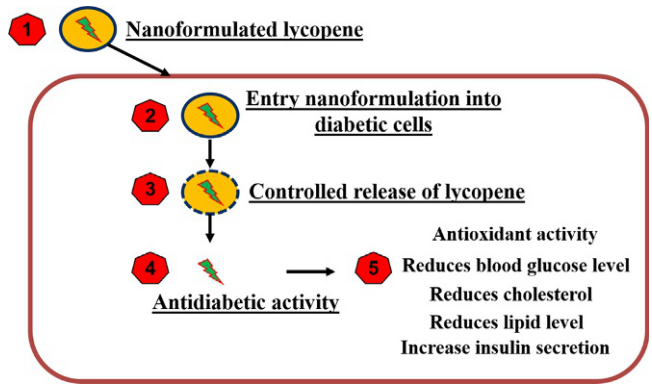

FIG. 18.5 Antidiabetic activity of nanoformulated lycopene.

The result further adds as an evidence that nanoformulation can enhance oral delivery of lycopene in patients [305]. In future, these nanoformulated lycopenes will replace the conventional lycopene delivery systems and enhances its antidiabetic activity via controlled delivery in the target site. Fig. 18.5 is a schematic representation of nanoformulated lycopene-based targeted delivery systems in the treatment of diabetes.

18.7 Hair loss and male pattern balding

Hair loss is a chronic condition that involves the shrinking of hair follicles right in the epidermal region leading to thinning of hair, reduction in hair growth rate, and subsequent stoppage of hair growth cycle. It affects both men and women, but male pattern hair loss is the most common one. Internal factors and external factors are responsible for causing hair loss. Currently, natural products are presenting promising leads in lycopene to manage and treat hair loss. To recap, lycopene (UIPAC: [6*E*,8*E*,10*E*,12*E*,14*E*,16*E*,18*E*,20*E*,22*E*,24*E*,26*E*]-2,6,10,14,19,23,27,31-octamethyldotriaconta-2,6,8,10,12,14,16,18,20,22,24,26,30-tridecaene), a carotenoid [86], is a symmetrically arranged tetraterpene built from eight units of isoprenes. It is responsible for most fruit and vegetable red-orange pigmentation although it is also available in green vegetables [306]. Despite being a carotene, it has no vitamin properties and nor is it a provitamin A carotenoid because its conversion to retinol in the body is not possible [307]. Apart from being found in plants, it is also highly present as the most predominant carotenoid in blood plasma but lowly present in serum of humans and are found concentrated in the prostate gland, liver, adrenal gland, and testes [4, 308].

18.7.1 Hair loss and current treatment options

Hair grows from skin follicles, hair growing tissues, embedded in the dermis, and protecting the body from external harm. The follicles grow in the papilla layer in a phase known as the anagen phase after which comes the second phase, the catagen phase, where

the dermal thickness decreases pushing the growing follicles toward the epidermis, popping out some papilla cells from where begins a new cycle of hair growth [309].

Hair loss (alopecia) is a progressive and chronic condition affecting at least 50% of all men and 40 of women with 80% of Caucasian men affected [310, 311]. Androgenetic alopecia is the most common type of hair loss [311]. Generally, hair loss in females has been studied considerably more than male pattern hair loss, which is yet to be explored [312]. Hair loss has a negative psychological effect on bearers due to the fact that it deforms one's preference of looks and the thinking that is has narrow to almost no available treatment [311]. In developed countries, available treatment options for hair loss include platelet-rich plasma injections that is time consuming as it must be done repetitively and cumulatively too [311].

Successful permanent treatment for hair loss remains a challenge worldwide with only two drugs, Minoxidil ($C_9H_{15}N_5O$) and Finasteride ($C_{23}H_{36}N_2O_2$), having been approved by the FDA by the end of the year 2017 for the treatment of androgenetic alopecia [313]. Minoxidil and Finasteride offer unsatisfactory results characterized by lack of a permanency and other potential complications. Another treatment option, which happens to be the most commonly known one, is a surgical procedure and hair transplantation [311], which appears to probably be the only successful permanent option available amidst other medical options such as oral contraceptives, antiandrogens (e.g., flutamide, spironolactone, dutasteride, and cyproterone), ketoconazole, and analogs of prostaglandin (e.g., latanoprost and bimatoprost), which are reported to some extent to be beneficial [314]. With no profound benefits, laser light therapies are also getting popular on the market. In developing countries, people cannot afford such options due to high costs and/or lack of technology, appropriate facilities, and specialized personnel. People with hair loss are currently getting more and more inclined toward natural products for hair recovery and/or inhibition of hair loss [311]. These include supplements and herbal medicines. Supplements used in hair loss treatment are usually found to be disappointingly ineffective that is said to partly be due to lack of standardization [311]. In this regard, scientists are still exploring hair loss treatment options to either reduce hair loss processes or to permanently stop them. One of the potential treatment options that are gaining attention is lycopene.

18.7.2 Male pattern hair loss

Male pattern hair loss (MPHL) is usually a natural aging phenomenon with no links to serious medical conditions. However, it is seldom correlated to some medical conditions such as enlarged prostate, diabetes, obesity, high blood pressure, and heart diseases [315]. MPHL can develop as early as teenage years and increases with age. Genetic dispositions play a significant role for those who have MPHL in their ancestral line.

Male pattern baldness can begin in your teenage years, but it more commonly occurs in adult men, with the likelihood increasing with age. MPHL may begin at the crown or the temples of the head manifesting as a recession of the hair line of the front forming an "M" shape or as a singular bald spot on the head. MPHL may be caused by medical conditions if it is accompanied by peeling off the scalp, rashes on the scalp, pain, patchy hair loss, redness, and unusual loss pattern [316,317]. If medical conditions are suspected, a biopsy of the scalp or blood samples may be taken to diagnose specific causes [317].

18.7.3 Lycopene in the treatment of hair loss

Hair growth is genetically stimulated by keratinocyte growth factor (KGF) and vascular endothelial growth factor (VEGF). Any drug or drug compounds that are introduced to counter hair loss need to mimic or be associated with VEGF and KGF or similar resultant mechanisms. Research on lycopene in the treatment of hair loss remains limited. The cosmetic industry, both conventional and traditional, is advancing in using herbal products in the development of hair care products. Besides topical products, oral products in the form of food supplements are also gaining popularity. Lycopene in foods has been reported to be associated with reduced risks of chronic conditions of which hair loss is one. Taken daily for 6 months and in combination with other ingredients (460 mg of fish oil, 5 mg of vitamin E, and 30 mg of ascorbic acid), lycopene (1 mg) contributed to reduction in hair loss in 90% and increased hair density in 62% of 120 participants with mild hair loss at the beginning of the study [318]. Its activity on prostate-specific antigen (PSA) was reported to present evidence of its efficacy in reducing hair loss [319]. Lycopene is also reported to play a significant role in the amelioration of blood circulation and cell restoration, which is critically beneficial for the health of the scalp in addition to the reduction of inflammations and collagen production facilitation.

Due to the little literature on its efficacy against hair loss and community experiences with it, lycopene is increasingly getting the attention of hair care manufacturers and reviewers as they get confident enough to claim its efficacy in their write-ups and talks. Some confirm that even raw and processed lycopene in fruits such as tomatoes can demonstrate some positive effect on hair loss [18].

18.8 Hepatoprotective role of lycopene against various cellular abnormalities

18.8.1 Cholestasis-induced hepatotoxicity

Clinical conditions such as gallstone complications of pancreatitis, stricture of the bile duct, or biliary surgery are well established among aetiologies that lead to the reduction in biliary flow and causing cholestasis [320]. The excessive production of reactive oxygen species (ROS) causes lipid peroxidation, which further altered the functioning of cellular membranes and develops hepatic injury [321]. In cholestasis, glutathione peroxidase (GSH-Px) activity was suppressed with a decline in reduced glutathione (GSH), which may alter the antioxidant defense system [322]. Pretreatment of lycopene (25 mg/kg/day) for 14 days significantly diminished the hepatic injury markers (transaminases and lactate dehydrogenase), which were developed by ischemia reperfusion in an animal model [323]. Oxidative stress in cholestasis could also harm the hepatic antioxidant system [324]. It was found that lycopene had curative property against oxidative damage-mediated cell membranes and DNA injury in case of cholestasis. Pool-Zobel et al. [325] suggested that administration of tomato juice (40 mg/day lycopene) for 16 days resulted in considerably reduced DNA strand breaks in the lymphocytes.

18.8.2 Bisphenol-A-induced hepatotoxicity

Bisphenol-A (BPA) is an endocrine disruptor xenoestrogen and is enormously present in the atmosphere. It is a monomer used in polycarbonate plastic industry and epoxy resins that shape like cans that are used to preserved food and beverages. It can be easily mixed with food or water on heating [326,327]. BPA predominantly metabolized in the liver and disrupted liver integrity and their functions. Moreover, it leads to lipid peroxidation by diminishing endogenous antioxidants system in the liver [328]. BPA-associated lipid metabolism exerts a negative impact on serum profile while activating lipid accumulation through differentiation of 3T3-L1 fibroblast cells into adipocytes [329]. Furthermore, BPA triggered oxidative stress in the liver as it suppressed the activities of glutathione peroxidase (GPx), superoxide dismutase (SOD), and CYP450, while upturn MDA level which is an end product for lipid peroxidation. The depletion in SOD action could be due to massive increment in the autoxidation process mediated by BPA. Besides, lycopene exerted a reciprocal impression on the markers of hepatic tissue in the animal model when treated with a combination of BPA and lycopene. The antioxidant activity of lycopene could be indorsed to being a β-carotene, where lycopene had been demonstrated to protect against DNA, protein, and lipid oxidation [330] through scavenging singlet oxygen [331] and peroxyl radicals [332], hence regulating MDA production as lipid peroxidation end product [333].

18.8.3 Carbon tetrachloride (CCl_4)-induced hepatotoxicity

Intracellular enzymes (like ALP and transaminases) are the most profound biomarkers of hepatic abnormalities. The higher values of these enzymes are indicators of primary symptom of loss of functional integrity of cell membrane and causing cellular leakage. CCl_4 is frequently used to develop model of free radical-mediated hepatic injury. The liver not only is the target organ of CCl_4 but also exerts adverse effects on different body organs such as brain hearts, kidneys, testes, and lungs. In the initial phase of CCl_4-mediated hepatotoxicity, cytochrome P450 (CYP450) breaks CCl_4 to two trichloromethyl radicals that are supposed to stimulate lipid peroxidation process facilitated by free radicals, whereas in the second phase, kupffer cells are activated and start secreting proinflammatory mediators. Besides the formations of other products including lipid hydroperoxides, conjugated dienes, and peroxyl radicals that are released by kupffer cells lead to develop oxidative stress that further inactivates the antioxidant enzymes (CAT, SOD, GPx, and GST) and reduces GSH activity and upturn lipoxygenase action [334]. The enhanced lipid peroxidation and inactivation of glutathione reductase by free radical products derived from CCl_4 metabolism lead to a declined activities of GST and GPx. GST and GPx were nearly reinstated to the normal level in a lycopene pretreated groups with a dose of 0.65 mg/kg.

18.8.4 Acetaminophen drug-induced hepatotoxicity

Free radicals are formed by protein kinase-C (PKC) signaling pathway, whereas PKC-dependent nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation is moderately accountable for the elevation in oxidative stress that is responsible for many diseases, including hepatic abnormalities [335]. In vitro and in vivo analysis revealed that lycopene

decreases ROS generation in SK-Hep-1 cells by preventing NADPH oxidase. In a study, lycopene has been observed to exert an antiinflammatory effect in acetaminophen-mediated hepatic injury by enhancing the redox state in C57BL/6 mice [336]. Yefsah-Idres and coworkers [337] suggested that rats with high methionine diet showed abnormal histological features supplemented by amplified serum AST, ALT, and homocysteine and hepatic MDA levels and reduced hepatic cystathionine-β-synthase and *S*-adenosyl-homocysteine hydrolase activities. Moreover, they stated that the intake of lycopene reversed hyperhomocysteinemia condition, which provides further confirmation for the hepatoprotective potential of lycopene.

18.8.5 Nonalcoholic fatty liver disease (NAFLD)-induced hepatotoxicity

Nonalcoholic fatty liver disease (NAFLD) is a condition where without excessive alcohol intake fat is deposited in the liver, which is also related to insulin resistance and metabolic syndrome [338,339]. NAFLD entails wide range of hepatic infirmities, such as liver fibrosis, simple steatosis, cirrhosis, nonalcoholic steatohepatitis, and hepatocellular carcinoma [340,341]. Recent studies revealed that lycopene is nearly two times more potent then β-carotene in curing lymphocytes from NO_2 radical-mediated membrane damage [342,343], which supported that lycopene is the potent ROS scavenger apart from other major dietary carotenoids. In high-fat diet (HFD)-mediated NAFLD, the levels of serum transaminases, triglycerides (TG), and total cholesterol (TC) were expressively high, the levels of low-density lipoprotein-cholesterol (LDL-C) and free fatty acid (FFA) were augmented significantly, and high-density lipoprotein-cholesterol (HDL-C) was remarkably suppressed. Moreover, animal pretreated with lycopene exhibited potential to prevent the rise in serum transaminase, to reduction of LDL-C, TG, TC, and FFA levels and to upsurge the HDL-C level. TNF-α is a major proinflammatory cytokine, which is related with a various pathological and physiological disorders. Increased TNF-α generation by kupffer cells may also be accountable for NAFLD. Prevention of TNF-α could decline the content of fatty storage in the HFD-induced NAFLD model [344,345]. Rats treated with HFD show upregulated TNF-α expression, while pretreatment with lycopene directed to downregulated TNF-α expression compared with the HFD-model group.

18.8.6 D-Galactosamine/lipopolysaccharide-induced hepatotoxicity

D-Galactosamine/lipopolysaccharide (D-GalN/LPS) causes hepatocellular damage. It is a well-stablished model of developing fulminant hepatitis within a few hours of intoxication [346]. A high dose of D-GalN develops necrosis in hepatic tissue by reduction of UTP and prevents protein synthesis, eventhough D-GalN is frequently used with lipopolysaccharide or tumor necrosis factor. Augmentation of UDP-sugar nucleotides may facilitate the modification in the rough endoplasmic reticulum and to imbalance in protein metabolism [347,348]. Additionally, high galactosamination in the membrane is supposed to be accountable for loss in the functioning of ionic pumps. The dysfunction of calcium pump, with a subsequent rise in the intracellular calcium, is considered to be responsible for cell death [349]. Recently, besides the well-stablished prevention of protein synthesis, it has also been recommended that ROS generated by stimulated macrophages might be the primary cause in D-GalN-mediated hepatic injury [350]. γ-Glutamyl transferase (GGT) is the most sensitive indicator of hepatic

abnormalities. This may be due to the fact that the depletion of GSH may induce hepatic GGT activity through an increased synthesis of its mRNA [351]. Pretreatment with lycopene in hepatic injury showed lessening in GGT activity, thus indicating the membrane stabilizing property of lycopene. While enhanced LDH activity in serum confirms the augmented permeability of the hepatic membrane and cellular leakage. Lycopene pretreatment reversed back its levels to near normal in animal model indicating the therapeutic value of lycopene [352].

18.8.7 Nonalcoholic steatohepatitis (NASH)-induced hepatotoxicity

NASH has been reported to promote diethylnitrosamine (DEN)-mediated hepatocarcinogenesis in rats [353]. It was also suggested that DEN-mediated hepatocarcinogenesis in rats had a poor number of hepatic placental GST-positive preneoplastic lesions and the smaller size of lesions in the liver [354,355]. In a study, administration of lycopene (100 mg/kg) for 24 weeks provides comparable accumulation of hepatic lycopene and exerts similar effects on diminishing HFD-associated hepatocellular carcinoma and multiplicity in wild-type and BCO2-knockout mice. It is of interest that the cancer curing effects of lycopene in wild-type mice were due to suppressed hepatic inflammation through downregulating the expression of NF-kB, p65, and IL-6, STAT3 activation, and inflammatory foci, whereas the curative effects of lycopene in BCO2-knockout mice were associated with reduced hepatic endoplasmic reticulum (ER) stress-mediated unfolded protein response (UPR), through inhibiting activation of protein kinase RNA (PKR)-like ER kinase (PERK)-eukaryotic initiation factor 2α and inositol-requiring (IRE) 1α-X-box-binding protein 1 (XBP1) signaling pathways. In BCO2-knockout mice lycopene administration prevented tumorigenic signals, including Met mRNA, β-catenin protein, and mTOR complex 1 activation, resulting in increased levels of tumor suppressive microRNA (miR)-199a/b and miR214 levels in the liver.

18.9 Lycopene in human detoxification

In the mammalian system, the CYP450 enzyme establishes one of the crucial defense systems against broad-spectrum toxic chemicals. The stimulation of CYP450 enzyme not only inhibits acute toxic properties from external chemicals but also results in oxidant by-products that impair DNA. CYP450 enzyme promotes detoxification by two separate mechanisms known as phase-I and phase-II detoxification mechanism. A study revealed that lycopene expressively triggered phase-I enzymes in a dose-related manner and enhanced phase-II enzyme, quinone reductase (QR). It has also been found that lycopene increases removal of xenobiotics through urine or stool. Xenobiotics are digested by CYP450 enzyme associated phase I and phase II mechanism. Oxidation of the lipid molecule is a normal biological process through which we generate energy from fatty substance. Injurious lipid oxidation that arises in the body is commonly described as peroxidation of polyunsaturated fatty acids (PUFAs) and produces hydroperoxides. In biological membranes, excessive oxidation of lipids leads to several abnormalities like cardiac disease, cancer, and neurodegeneration. Initiation and progression of lipid peroxidation were examined in extracted liver microsomes. The reaction was catalyzed by iron and microsomal NADPH-CYP450 reductase enzyme. This enzyme generates superoxide anion

by the adding an extra electron on diatomic oxygen molecule. Aust and Swingen [356] stated that lipid peroxidation occurs in two stages. In early-stage CYP450 reductase catalyzes the reduction of ADP-Fe^{3+}, which is further reacting with an oxygen molecule to form ADP-perferyl radical. The perferyl radical in turn initiates the process of lipid peroxidation. DNA damage mediated by oxidation could be a major risk factor that develops tumors. Therefore, dietary antioxidants are capable of reducing such damage that would be likely to have cancer inhibition properties. Thus, antioxidant substances when present in foods at low amount compared with those of oxidizable substrate markedly reduce, delay, or avoid the oxidation of the substrate. Because of the safety concerns over manmade compounds, research has been concentrated toward the search of the novel antioxidant constituents present in foods.

18.10 Antiinfertility properties

About 10%–15% of couples worldwide are facing infertility problem, and 50% of the cases are caused by the male part. The prime causes of male factor infertility are varicocele (35%) and idiopathic infertility (25%). [357]. Disorders of endocrine, infections of urogenital system, congenital and genetic abnormalities, and immunological factors are also contributing toward infertility [357,358]. Lycopene is well-known for the free radical scavenging properties and high antioxidant capacities [359]. Under oxidative stress, lycopene protects nonenzymatic antioxidant defense system of semen in male mammals. In testes and seminal plasma of infertile men, lycopene concentration was also found to be reduced significantly [89,360–362]. Although several studies have provided few evidences that lycopene can help toward alleviating male infertility, the precise mechanism of lycopene induced improvement of semen quality is hitherto unexplored [363,364]. Zini et al. [364] showed relatively higher lycopene concentrations in the testes as compared with other body parts, and lycopene may play a pivotal role as an antioxidant in the process of spermatogenesis. Goyal et al. [363] reported augmented concentration of lycopene in seminal plasma following oral lycopene supplementation. Lycopene plays protective function against cisplatin and adriamycin-induced intratesticular toxicity in rats [365]. Türk et al. [366] also found preventive effect of lycopene against cyclosporine A induced damage of testicular tissues in male rats. The therapeutic antioxidant properties of lycopene on motility and abnormal sperm rates in situational infertility problems like testicular torsion were also reported [366].

Therefore it may be assumed that lycopene acts as natural antioxidant and lycopene intake will provide protection from ROS in seminal plasma and reduce oxidative stress and thereby decrease the probability of idiopathic male factor infertility [363,364]. In recent time, researchers have found evidences to establish the nonoxidative mechanisms of lycopene in the testis such as cell cycle regulation, enhancement of immune system, gene expression modulation, and gap junction communication by which of it exerts the beneficial effects of semen quality [367]. Research investigations with human volunteers and animal models have confirmed that lycopene alleviate male infertility by decreasing lipid peroxidation and DNA damage. It also improves sperm count, viability, and general immunity that in turn increase the probability of fertilization. The possible mechanism of action of lycopene in improving semen quality and restoring male fertility includes ROS scavenging, protection of spermatozoa from lipid peroxidation, activation of the antioxidant system, improvement of

mitochondrial function, DNA integrity, and decreasing the transcription of proinflammatory factors [10,362,367–375]. The effect of lycopene supplementation on semen quality parameters in human and animal trails is presented in Table 18.5.

The beneficial effect of lycopene includes improvement of semen quality and antioxidant status that results in reduced risk of idiopathic male factor infertility induced by oxidative stress. Lycopene supplementation reduces ROS, DNA damage, and lipid peroxidaton and increases antioxidants and thereby general immunity and improved sperm count and viability. Lycopene was implicated in Chapter 15 of this book as an imporant nutraceutical for the management of male infertility. However, more detailed and extensive research investigations and large-scale placebo-controlled clinical trial need to be conducted to prove the efficacy of lycopene on improvement of semen quality and pregnancy rates.

18.11 Lycopene: Updates on clinical trials

Since the chemical isolation of lycopene more than a century ago, thousands of studies have been carried out regarding its nature and uses such as we have discussed above. Being a member of the carotenoid family as earlier stated, its antioxidant activities and potential role in the prevention and management of chronic diseases and cancer have been most popular. A number of systematic reviews have been published regarding the clinical effects of lycopene in the body. This section summarizes the findings of the different systematic reviews done on lycopene (Table 18.6). In the series of systematic reviews presented in Table 18.6, it is apparent that an increase in lycopene intake can significantly decrease the risk of prostate cancer [382–384]. As low as 9 mg of oral lycopene per day equivalent to about 53 g of tomato ketchup and 75 g of fresh tomatoes [385] is enough to achieve significant protection. Although the effect is more on the prevention of prostate cancer rather than its cure, lycopene intake also showed protective effect against the occurrence of metabolic syndrome regardless of dose and duration of intake [386]. For cardiovascular protection, higher dosage of lycopene at $\geq$25 mg/day was found to be effective [136,387]. On the other hand, more studies are still needed to prove its clinical effect as an antioxidant [388]. Overall the benefit of increasing lycopene intake far outweighs its harm if any; thus its consumption should be promoted.

18.12 Techniques for structural elucidation of lycopene

Advances in the techniques for separation and recognition of biocompounds from natural sources have resulted in increase in carotenoids number. Compared to chemical methods of identification, spectral methods have the advantage that it provides data sooner and perfectly that require small amounts of material and enable incessant examination at diverse stages of dispensation of the compound extracted without altering the masterpiece of the biosubstance investigated, which enables its revival.

Carotenoids containing oxygen (xanthophylls) are yellow [391]. *Cis-trans* isomerism, fact that determines the presence of many geometric isomers, is attributed to the incidence of double bonds in the molecules of carotenoids. The most common of carotenoids contain a *trans*

TABLE 18.5 Summary of research investigations demonstrating the effect of lycopene supplementation on oxidative stress and sperm quality associated factors.

Volunteers/ animals	Source of lycopene	Dosage of lycopene	Duration	Oxidative stress-associated factors	Sperm quality associated factors	References
50 Infertile human males	Unknown	8 mg daily	Until achievement of outcome	–	Concentration (%) ↑, Count (%) ↑, Motility (%) ↑, Morphology (%) ↑	[376]
30 Infertile human males	Unknown	2000 μg twice daily	3 months	–	Concentration (%) ↑, Motility (%) ↑, Morphology (%) ↑	[89]
42 Wistar albino rat males	Purchased	4 mg/kg daily	30 days	–	Motility (%) ↑, Morphology (%) ↑	[366]
12 Healthy human males	Purchased	0, 2 or 5 mmol L^{-1}	30 min	DNA damage ↓	–	[364]
25 Brolier breeder males	Supplementation in drinking water	0.5 g L^{-1} or none	Over 17 weeks	Immunity ↑	Count (%) ↑, Viability ↑	[377]
25 Hybrid Martini rabbit males	Supplementation in drinking water	0, 0.1, or 0.5 g L^{-1}	8 weeks	–	Count (%) ↑, Motility (%) ↑	[378]
24 Healthy Wistar rat males	Purchased	4 mg/kg	7 days	Lipid peroxidation ↓, Antioxidant ↑	Count (%) ↑, Motility (%)↑	[379]
6 Healthy human male	Heated cream of tomato soup	≈22.8 mg daily	2 weeks	No measurable increase in total ROS scavenging capacity of semen	–	[363]
82 Healthy human male	Synthetic crystalline lycopene (all-*trans*)	Placebo, 6.5, 15, or 30 mg daily	8 weeks	DNA damage ↓, Urinary 8OHdG ↓	–	[380]
28 Healthy hybrid large white turkey male	Purchased (preheated Sigma L9879)	0, 0.05, or 0.1 mg mL^{-1}	48 h for chilled, 2 weeks for cryopreserved	DNA damage ↓	–	[372]
82 Human males with oxidative stress, 30 healthy controls	Lycopene capsule or tomato products (soup, paste, ketchup)	Placebo or 15 mg daily	10 weeks	Lipid peroxidation ↓	–	[381]
40 Healthy Mongolian gerbil males	5% Lycopene extracted from tomatoes (purchased)	Four different experimental diets, one of which is a 0.5 g kg^{-1} lycopene diet	6 weeks	Antioxidant ↑	–	[373]

–, not investigated; ↑, increase; ↓, decrease.

pattern. Carotenoids occur mostly in free form in natural products [392]. They can be grouped into two major classes: carotenoid hydrocarbons and oxygenated derivatives of hydrocarbon carotenoids. Hydrocarbon carotenoids are made up of 40 carbon atoms. The molecular formula is $C_{40}H_{56}$. Common examples are lycopene known as (red carotenoid dye) α-carotene (α-carotene is a forerunner to retinoic acid, or a provitamin A), β-carotene, and γ-carotene [392]. Like all carotenoids, lycopene is atetraterpene [392] and insoluble in water. Eleven conjugated double bonds give lycopene its deep red color. Owing to the strong color, lycopene is useful as a food coloring [393,394].

Lycopene is one of the significant and functional carotenoids and a prevailing antioxidant that play critical role in cancer prevention [392]. Twenty six types of tomato samples were studied, by means of various analytical methods. UV-VIS spectrophotometry resolves the absorption peaks of carotenoids from tomato samples in sequence. UV spectrum analysis shows that the maximum wavelengths of lycopene are 447.2, 473.2, and 504.2 nm, which are the maximum wavelengths of pure lycopene. The FTIR method is a good analytical technique for quantification of lycopene in tomatoes [392].

The IR spectra show typical bands arising from amide (1650 and 1540 cm^{-1}) and lipid (1730–1765 and 3000–2800 cm^{-1} groups. Additional bands occur at 1477–1400 (C—H bending), 1100–1400 (C—C and C—C—H stretching), and 1170–1115 cm^{-1} (C—O stretching). Burly and wide absorption bands of water are revealed in the 3700–3000 and 1600–1700 cm^{-1} range. The spectral signal obtained at a frequency of 957 cm^{-1} can be attributed to the presence of *trans* CH out-of-plane deformation vibration [395–398] of lycopene found in tomatoes. The lycopene content of the tomato ranged around 8–9 μg/mg of dried matter based on the HPLC analysis, values within those reported in the literature [397]. For high-performance liquid chromatography (HPLC) analysis of lycopene, the dried lipid segment aliquots have been redissolved in methanol solvent. Ten microliter sample has been injected in the HPLC for carotenoid analysis. In all separation, 1351 A C30 YMC column (5 μg particle size, 250 × 4.6 mm) (Waters Corp., Milford, MA) was used. Solvents used for elution in the experiments are (A) water; (B) methanol; (C) 86% acetonitrile, 10% water, 4% formic acid; and (D) 96% ethyl acetate, 4% water. Separations were approved out with a 35 min linear gradient (10% C + 90% D) at area temperature, linear gradient (100% C) 55 min at room temperature. Flow rate was 1.5 mL/min, with detection at 470 for lycopene, and the retention time was 69 min. The qualified standard divergence of replicates (accuracy) was 5% [397,399].

Mass spectrum shows a mol. wt. 536 m/z; 536 (37%), 1459 (38%), 119 (25%), 105 (27%), 93 (930%), 91 (30%), 81 (40%), 69 (77%), 41 (60%) [400]. ^{1}H NMR Spectrum was recorded for lycopene as singlet at δ 5.12 ppm (2H,C-2), 2.13 (4H,C-3), 2.23 (4H,C-4), 5.96 (2H,C-6), 6.63 (2H,C-7), 6.26 (2H,C-8), 6.11 (2H,C-6), 6.86 (2H,C-11), 6.33 (2H,C-12), 6.11 (2H,C-14), 6.20–6.21 (2H,C-15), 1.63 (12H,C-16,C-17), 1.83 (6H,C-18), and 1.98 (12H,C-19,C-20) [400]. Lycopene in CDCl3 was analyzed by ^{1}H NMR and ^{13}C NMR. Chemical shifts (ppm) corresponding to 56 protons in the ^{1}HNMR spectrum and to 40 carbons in the ^{13}C NMR spectrum were assigned [400].

Nearly five isomers of lycopene were remote from a photoisomerized combination using a semipreparative C_{30} column and identified through UV-vis spectroscopy, mass spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy [401]. ^{1}H NMR and 2D NMR measurements were used to unambiguously assign the double bond configuration of five isomers: (5*Z*, 9′*Z*)-, (9*Z*)-, (5*Z*, 9*Z*)-, (all-*E*)-, and (5*Z*)-lycopene.

TABLE 18.6 Summary of systematic reviews on lycopene.

Study title (year published)	Type of study	Number of included studies/ participants	Results	References
A. Lycopene and prostate cancer				
1. Increased dietary and circulating lycopene are associated with reduced prostate cancer (PCa) risk (2017)	Systematic review of observational studies and dose response metaanalysis	42 Studies/692,012 participants	PCa decreased by 1% for every 2 mg of lycopene consumed PCa risk decreased by 3.5%–3.6% for each additional 10 μg/dL of circulating lycopene	[382]
2. Effect of carotene and lycopene on the risk of prostate cancer (2015)	Systematic review with metaanalysis of observational studies	34 Studies/592,479 participants	Risk for PCa decreased by 2% per 0.2 mg/day increased in dietary α-carotene or 3% per 1 mg/day increased in dietary lycopene intake No risk reduction noted for advanced PCa	[383]
3. Lycopene and risk for prostate cancer (2015)	Systematic review with metaanalysis of observational studies	26 Studies/563,299 participants	Higher lycopene intake resulted to reduced incidence of PCa Risk reduction was noted at doses between 9 and 21 mg/day	[384]
4. Lycopene for the prevention and treatment of benign prostatic hypertrophy (BPH) and prostate cancer (2012)	Systematic review of randomized controlled trials	8 Studies, 4 studies had metaanalysis	No significant decrease in the incidence of BPH or PCa diagnosis; two studies showed significant decrease in prostate-specific antigen (PSA) levels among men with PCa who received lycopene	[389]
5. Lycopene for the prevention of prostate cancer (2011)	Systematic review of randomized controlled trials	3 Studies/154 participants	No statistical difference in PSA levels between men who received lycopene and the comparison group; data were insufficient	[390]
B. Lycopene and metabolic syndrome				
Lycopene and metabolic syndrome: a systematic review of the literature (2018)	Systematic review of cross-sectional and intervention studies	11 Studies 8 Cross sectional 3 Intervention	All studies reported protective association; Intake of lycopene-rich beverage resulted to protective effects regardless of dose and duration of intake	[386]

C. Lycopene and cardiovascular diseases (CVDs)				
1. Lycopene and tomato and the risk of cardiovascular diseases (2017)	Systematic review with metaanalysis of longitudinal and cross-sectional studies	28 Studies 25 Studies included in the metaanalysis	High intake or high serum concentration of lycopene was associated with significant reduction in risk of stroke (26%), mortality (37%) and CVDs (14%)	[387]
2. Protective effect of lycopene on serum cholesterol and blood pressure (2011)	Systematic review of randomized controlled trials with metaanalysis	12 Study effects of lycopene on serum lipids/ 401participants 4 Study effects on blood pressure	Lycopene had significant total cholesterol and LDL (10%) lowering effect at a dose $\geq$25 mg/day; A significant blood pressure lowering effect was also noted	[136]
D. Lycopene and oxidative stress				
Effect of lycopene supplementation on oxidative stress (2013)	Systematic review of randomized controlled trials	13 studies, 6 Studies were metaanalyzed	Lycopene significantly decreased DNA tail length but does not significantly prolong the lag time of low-density lipoproteins; Lycopene may alleviate oxidative stress	[388]

18.13 Conclusion

Lycopene is a naturally occurring red color carotenoid pigment found in various vegetables and fruits, such as tomatoes, carrot, papaya, apricots, guava, watermelon, and grapes. It has no vitamin A activity due to the absence of beta-anion ring. It is synthesized in both eukaryotes and prokaryotes by similar mechanism. Synthesis occurs when dimethylallyl pyrophosphate is formed by conversion of mevalonic acid. Condensation of isopentenyl pyrophosphate molecule occurs, and it gives geranyl pyrophosphate molecule. Two molecules combine to form phytoene. Phyotene is then converted to lycopene. Lycopene is absorbed in the body by combining with bile salts and fat to form micelles. Several studies have proved that lycopene has potentials to treat cardiovascular diseases and cancer because of its antioxidative properties. In a view of this property, it is encouraged that foods rich in lycopene should be consumed, which would help supply lycopene that will help mitigate oxidative stress-mediated disorders.

References

[1] A.C. Vogele, Effect of environmental factors upon the color of the tomato and the watermelon, Plant Physiol. 12 (4) (1937) 929.
[2] A.V. Rao, L.G. Rao, Carotenoids and human health, Pharmacol. Res. 55 (3) (2007) 207–216.
[3] S.A.R. Paiva, R.M. Russell, β-Carotene and other carotenoids as antioxidants, J. Am. Coll. Nutr. 18 (5) (1999) 426–433.
[4] S.K. Clinton, Lycopene: chemistry, biology, and implications for human health and disease, Nutr. Rev. 56 (2) (1998) 35–51.
[5] A. Mortensen, Carotenoids and other pigments as natural colorants, Pure Appl. Chem. 78 (8) (2006) 1477–1491.
[6] G. Britton, S. Liaaen-Jensen, H. Pfander, Carotenoids handbook, J. Appl. Cosmetol. 22 (2) (2004) 118–120.
[7] D.B. Rodriguez-Amaya, M. Kimura, HarvestPlus Handbook for Carotenoid Analysis, vol. 2, International Food Policy Research Institute (IFPRI), Washington, DC, 2004.
[8] D.B. Rodriguez-Amaya, A Guide to Carotenoid Analysis in Foods, ILSI Press, Washington, 2001, pp. 5–10.
[9] E.N. Story, R.E. Kopec, S.J. Schwartz, G.K. Harris, An update on the health effects of tomato lycopene, Annu. Rev. Food Sci. Technol. 1 (2010) 189–210.
[10] J.W. Erdman Jr., N.A. Ford, B.L. Lindshield, Are the health attributes of lycopene related to its antioxidant function? Arch. Biochem. Biophys. 483 (2009) 229–235.
[11] K. Dahan, M. Fennal, N.B. Kumar, Lycopene in the prevention of prostate cancer, J. Soc. Integr. Oncol. 6 (1) (2008) 29–36 (PubMed: 18302908).
[12] G. Riccioni, B. Mancini, E. di Ilio, T. Bucciarelli, N. D'Orazio, Protective effect of lycopene in cardiovascular disease, Eur. Rev. Med. Pharmacol. Sci. 12 (3) (2008) 183–190.
[13] L.G. Wood, M.L. Garg, H. Powell, P.G. Gibson, Lycopene-rich treatments modify noneosinophilic airway inflammation in asthma: proof of concept, Free Radic. Res. 42 (1) (2008) 94–102 (PubMed: 18324527).
[14] G.A. Chasse, M.L. Mak, E. Deretey, I. Farkas, L.L. Torday, et al., An ab initio computational study on selected lycopene isomers, J. Mol. Struct. 571 (2001) 27–37.
[15] L. Zechmeister, Cis-trans isomerization and stereochemistry of carotenoids and diphenyl-polyenes, Chem. Rev. 34 (2) (1944) 267–344.
[16] L. Zechmeister, A.L. LeRosen, W.A. Schroeder, A. Polgár, L. Pauling, Spectral characteristics and configuration of some stereoisomeric carotenoids including prolycopene and pro-γ-carotene, J. Am. Chem. Soc. 65 (1943) 1940–1951.
[17] M.Á. Ruiz-Sola, M. Rodríguez-Concepción, Carotenoid biosynthesis in Arabidopsis: a colorful pathway. Arabidopsis Book 10 (2012) e0158. https://doi.org/10.1199/tab.0158.

[18] J. Shi, M. Le-Maguer, Lycopene in tomatoes: chemical and physical properties affected by food processing, Crit. Rev. Biotechnol. 20 (4) (2000) 293–334.
[19] D.J. Hart, K.J. Scott, Development and evaluation of an HPLC method for the analysis of carotenoids in foods, and the measurement of the carotenoid content of vegetables and fruits commonly consumed in the UK, Food Chem. 54 (1995) 101–111.
[20] A.V. Rao, Z. Waseem, S. Agarwal, Lycopene content of tomatoes and tomato products and their contribution to dietary lycopene, Food Res. Int. 31 (10) (1998) 737–741.
[21] M.L. Nguyen, S.J. Schwartz, Lycopene stability during food processing, Proc. Soc. Exp. Biol. Med. 218 (2) (1998) 101–105 (PubMed: 9605205).
[22] P. Singh, G.K. Goyal, Dietary lycopene: its properties and anticarcinogenic effects, Compr. Rev. Food Sci. Food Saf. 7 (2008) 255–270.
[23] P.R. Trumbo, Are there adverse effects of lycopene exposure?. J. Nutr. 135 (8) (2005) 2060S–2061S, https://doi.org/10.1093/in/135.8.2060s.
[24] M. Porrini, P. Riso, What are typical lycopene intakes? J. Nutr. 135 (8) (2005) 2042S–2045S (PubMed: 16046736).
[25] W. Mellert, K. Deckardt, C. Gembardt, S. Schulte, B. Van Ravenzwaay, R. Slesinski, Thirteen-week oral toxicity study of synthetic lycopene products in rats, Food Chem. Toxicol. 40 (2002) 1581–1588.
[26] G.T. Fadupin, O.T. Osadola, T. Atinmo, Lycopene content of selected tomato based products, fruits and vegetables consumed in South Western Nigeria, Afr. J. Biomed. Res. 15 (2012) 187–191.
[27] R.L. Surles, N. Weng, P.W. Simon, S.A. Tanumihardjo, Carotenoid profiles and consumer sensory evaluation of specialty carrots (*Daucus carota*, L.) of various colors, J. Agric. Food Chem. 52 (2004) 3417–3421.
[28] U.S. Department of Agriculture, Agric, Research Service, USDA Nutrient Database for Standard Reference Release 18, (2005).
[29] J. Burns, P.D. Fraser, P.M. Bramley, Identification and quantification of carotenoids, tocopherols, and chlorophylls in commonly consumed fruits and vegetables, Phytochemistry 62 (2003) 939–947.
[30] T. Suwanaruang, Analyzing lycopene content in fruits, Agric. Agric. Sci. Procedia 11 (2016) 46–48.
[31] D.B. Rodriguez-Amaya, Latin American food sources of carotenoids, Arch. Latinoam. Nutr. 49 (1999) 74S–84S.
[32] B.K. Ishida, C. Turner, M.H. Chapman, T.A. McKeon, Fatty acid and carotenoid composition of gac (*Momordica cochinchinensis* Spreng) fruit, J. Agric. Food Chem. 52 (2004) 274–279.
[33] H. Aoki, N.T. Kieu, N. Kuze, K. Tomisaka, N. Van Chuyen, Carotenoid pigments in GAC fruit (*Momordica cochinchinensis* Spreng), Biosci. Biotechnol. Biochem. 66 (2002) 2479–2482.
[34] A.L. Holden, A.L. Eldridge, G.R. Beecher, I.M. Buzzard, S.A. Bhagwat, C.S. Davis, L.W. Douglas, S.E. Gebhardt, D.B. Haytowitz, S. Schakel, Carotenoid content of U.S. foods: an update of the database, J. Food Compos. Anal. 12 (1999) 169–196.
[35] G.R. Beecher, I.M. Buzzard, J. Holden, D. Trainer, C. Spangler, C. Davis, A.L. Eldridge, S. Schakel, D. Haytowitz, S. Gebhardt, S. Bhagwat, Carotenoid content of U.S. foods, FASEB J. 11 (1997) A447 Data generated at the USDA Food Composition Laboratory as part of NIH Grant No. 1 ROI CA59791 (Awarded 1993).
[36] A. Lugasi, L. Bíró, J. Hóvárie, V.K. Sági, S. Brandt, É. Barna, Lycopene content of foods and lycopene intake in two groups of the Hungarian population, Nutr. Res. 23 (2003) 1035–1044.
[37] A. Ben-amotz, R. Fishler, Analysis of carotenoids with emphasis on 9-cis β-carotene in vegetables and fruits commonly consumed in Israel, Food Chem. 62 (4) (1998) 515–520.
[38] T.L.H. Tran, L.C. Raymundo, Biosynthesis of carotenoids in bittermelon at high temperature, Phytochemistry 52 (1999) 275–280.
[39] G.C. Yen, L.S. Hwang, T.C. Lee, Lycopene from the seeds of ripe bitter melon (*Momordica charantia*) as a potential red food colorant, J. Chin. Agric. Chem. Soc. 19 (1981) 227–235.
[40] B. de Ancos, E. Gonzalez, M.P. Cano, Effect of high-pressure treatment on the carotenoid composition and the radical scavenging activity of persimmon fruit purees, J. Agric. Food Chem. 48 (2000) 3542–3548.
[41] I.M. Fordham, B.A. Clevidence, E.R. Wiley, R.H. Zimmerman, Fruit of autumn olive: a rich source of lycopene, HortScience 36 (2001) 1136–1137.
[42] M.L. Cavalcante, D.B. Rodriguez-Amaya, Carotenoid composition of the tropical fruits *Eugenia uniflora* and *Malpighia glabra*, in: G. Charalambous (Ed.), Food Science and Human Nutrition, Elsevier, N.Y., 1992, pp. 643–650.
[43] F. Khachik, G.R. Beecher, W.R. Lusby, Separation, identication, and quantication of the major carotenoids in extracts of apricots, peaches, cantaloupe, and pink grapefruit by liquid chromatography, J. Agric. Food Chem. 37 (1989) 1465–1473.

[44] T. Hodisan, C. Socaciu, I. Ropan, G. Neamtu, Carotenoid composition of *Rosa canina* fruits determined by thin-layer chromatography and high-performance liquid chromatography, J. Pharm. Biomed. Anal. 16 (3) (1997) 521–528.
[45] D. Hornero-Méndez, M.I. Mínguez-Mosquera, Carotenoid pigments in rosa mosqueta hips, an alternative carotenoid source for foods, J. Agric. Food Chem. 48 (2000) 825–828.
[46] S.H. Lee, Characterization of carotenoids in juice of red navel orange (Cara Cara), J. Agric. Food Chem. 49 (5) (2001) 2563–2568.
[47] A.J. Perez-Lopez, J.M. Lopez-Nicolas, E. Nunez-Delicado, F.M. del Amor, A.A. Carbonell-Barrachina, Effects of agricultural practices on color, carotenoids composition and minerals contents of sweet peppers, cv. Almuden, J. Agric. Food Chem. 55 (2007) 8158–8164.
[48] W. Stahl, H. Sies, Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans, J. Nutr. 122 (11) (1992) 2161–2166.
[49] R.S. Parker, Absorption, metabolism, and transport of carotenoids, FASEB J. 10 (1996) 542–551.
[50] Y. Kun, U.S. Lule, D. Xiao-Lin, Lycopene: its properties and relationship to human health, Food Rev Intr. 22 (4) (2006) 309–333.
[51] M.J. Brown, M.G. Ferruzzi, M.L. Nguyen, D.A. Cooper, A.L. Eldridge, et al., Carotenoid bioavailability is higher from salads ingested with full-fat than with fat-reduced salad dressing as measured with electrochemical detection, Am. J. Clin. Nutr. 80 (2) (2004) 396–403 (PubMed: 15277161).
[52] A. During, H.D. Dawson, E.H. Harrison, Carotenoid transport is decreased and expression of the lipid transporters SR-BI, NPC1L1, and ABCA1 is downregulated in caco-2 cells treated with ezetimibe, J. Nutr. 135 (10) (2005) 2305–2312 (PubMed: 16177187).
[53] M. Moussa, J. Landrier, E. Reboul, O. Ghiringhelli, C. Comera, et al., Lycopene absorption in human intestinal cells and in mice involves scavenger receptor class B type I but not Niemann-Pick C1-like 1, J. Nutr. 138 (8) (2008) 1432–1436 (PubMed: 18641187).
[54] N.I. Krinsky, E.J. Johnson, Carotenoid actions and their relation to health and disease, Mol. Asp. Med. 26 (6) (2005) 459–516.
[55] A. During, E.H. Harrison, An in vitro model to study the intestinal absorption of carotenoids, Food Res. Int. 38 (8–9) (2005) 1001–1008.
[56] I. Goñi, J. Serrano, F. Saura-Calixto, Bioaccessibility of β-carotene, lutein, and lycopene from fruits and vegetables, J. Agric. Food Chem. 54 (15) (2006) 5382–5387.
[57] J. Riedl, J. Linseisen, J. Hoffmann, G. Wolfram, Some dietary fibers reduce the absorption of carotenoids in women, J. Nutr. 129 (12) (1999) 2170–2176.
[58] M.L. Failla, C. Chitchumroonchokchai, B.K. Ishida, In vitro micellarization and intestinal cell uptake of cis isomers of lycopene exceed those of all-trans lycopene, J. Nutr. 138 (2008) 482–486.
[59] M. Richelle, K. Bortlik, S. Liardet, C. Hager, P. Lambelet, M. Baur, L.A. Applegate, E.A. Offord, A food-based formulation provides lycopene with the same bioavailability to humans as that from tomato paste, J. Nutr. 132 (2002) 404–408.
[60] R. Re, P.D. Fraser, M. Long, P.M. Bramley, C. Rice-Evans, Isomerization of lycopene in the gastric milieu, Biochem. Biophys. Res. Commun. 281 (2) (2001) 576–581.
[61] N.Z. Unlu, T. Bohn, D.M. Francis, H.N. Nagaraja, S.K. Clinton, S.J. Schwartz, Lycopene from heat-induced cis-isomer-rich tomato sauce is more bioavailable than from all-trans-rich tomato sauce in human subjects, Br. J. Nutr. 98 (1) (2007) 140–146.
[62] S. Karakaya, N. Yılmaz, Lycopene content and antioxidant activity of fresh and processed tomatoes and in vitro bioavailability of lycopene, J. Sci. Food Agric. 87 (12) (2007) 2342–2347.
[63] K.D. Ahuja, J.K. Pittaway, M.J. Ball, Effects of olive oil and tomato lycopene combination on serum lycopene, lipid profile, and lipid oxidation, Nutrition 22 (3) (2006) 259–265.
[64] J.M. Fielding, K.G. Rowley, P. Cooper, K. O'Dea, Increases in plasma lycopene concentration after consumption of tomatoes cooked with olive oil, Asia Pac. J. Clin. Nutr. 14 (2) (2005).
[65] N. Cardinault, V. Tyssandier, P. Grolier, B.M. Winklhofer-Roob, J. Ribalta, C. Bouteloup-Demange, P. Borel, Comparison of the postprandial chylomicron carotenoid responses in young and older subjects, Eur. J. Nutr. 42 (6) (2003) 315–323.
[66] J.M. Roldán-Gutiérrez, M.D.L. de Castro, Lycopene: the need for better methods for characterization and determination, TrAC Trends Anal. Chem. 26 (2) (2007) 163–170.
[67] T.W.M. Boileau, A.C. Boileau, J.W. Erdman Jr., Bioavailability of all-trans and cis-isomers of lycopene, Exp. Biol. Med. 227 (10) (2002) 914–919.

[68] J.W. Erdman Jr., How do nutritional and hormonal status modify the bioavailability, uptake, and distribution of different isomers of lycopene? J. Nutr. 135 (8) (2005) 2046S–2047S.
[69] R. Goralczyk, U. Siler, The role of lycopene in human health, in: Phytochemicals in Health and Disease, CRC Press, 2004, , pp. 273–293.
[70] S. Zaripheh, T.W.M. Boileau, M.A. Lila, J.W. Erdman Jr., [^{14}C]-Lycopene and [^{14}C]-labeled polar products are differentially distributed in tissues of F344 rats prefed lycopene, J. Nutr. 133 (12) (2003) 4189–4195.
[71] Q. Su, K.G. Rowley, N.D. Balazs, Carotenoids: separation methods applicable to biological samples, J. Chromatogr. B 781 (1–2) (2002) 393–418.
[72] M. Porrini, P. Riso, A. Brusamolino, C. Berti, S. Guarnieri, F. Visioli, Daily intake of a formulated tomato drink affects carotenoid plasma and lymphocyte concentrations and improves cellular antioxidant protection, Br. J. Nutr. 93 (1) (2005) 93–99.
[73] J.P. Stimpson, N.A. Lackan, Serum carotenoid levels vary by marital status, J. Am. Diet. Assoc. 107 (9) (2007) 1581–1585.
[74] B.L. Lindshield, K. Canene-Adams, J.W. Erdman Jr., Lycopenoids: are lycopene metabolites bioactive? Arch. Biochem. Biophys. 458 (2) (2007) 136–140.
[75] A.L. dos Anjos Ferreira, K.J. Yeum, R.M. Russell, N.I. Krinsky, G. Tang, Enzymatic and oxidative metabolites of lycopene, J. Nutr. Biochem. 15 (8) (2004) 493–502.
[76] S.J. Kim, E. Nara, H. Kobayashi, J. Terao, A. Nagao, Formation of cleavage products by autoxidation of lycopene, Lipids 36 (2) (2001) 191.
[77] M. Bacanli, N. Nurşen Başaran, A.A. Başaran, Lycopene: is it beneficial to human health as an antioxidant? Turk. J. Pharm. Sci. 14 (3) (2017) 311–318.
[78] G.N. Liu, Y.H. Zhu, J.G. Jiang, The metabolomic of carotenoids in engineered cell factory, Appl. Microbiol. Biotechnol. 83 (2009) 989–999.
[79] T.Y.P. Bonnie, Y.M. Choo, Oxidation and thermal degradation of carotenoids, J. Oil Palm Res. 2 (1) (1999) 62–78.
[80] C. Schmidt-Dannert, Engineering novel carotenoids in microorganisms, Curr. Opin. Biotechnol. 11 (2000) 255–261.
[81] P.C. Lee, C. Schmidt-Dannert, Metabolic engineering towards biotechnological production of carotenoids in microorganisms, Appl. Microbiol. Biotechnol. 60 (2002) 1–11.
[82] S. Agarwal, A.V. Rao, Tomato lycopene and its role in human health and chronic diseases, Can. Med. Assoc. J. 163 (6) (2000) 739–744.
[83] A. Rao, L. Rao, Lycopene and human health, Curr. Top. Nutr. Res. 2 (2004) 127–136.
[84] C.K. Park, Y. Ishimi, M. Ohmura, M. Yamaguchi, S. Ikegami, Vitamin A and carotenoids stimulate differentiation of mouse osteoblastic cells, J. Nutr. Sci. Vitaminol. 43 (1997) 281–296.
[85] L.G. Rao, N. Krishnadev, K. Banasikowska, A.V. Rao, Lycopene I—effect on osteoclasts: lycopene inhibits basal and parathyroid hormone-stimulated osteoclast formation and mineral resorption mediated by reactive oxygen species in rat bone marrow cultures, J. Med. Food 6 (2) (2003) 69–78.
[86] L. Kim, L.G. Rao, Lycopene consumption decreses oxidative stress and bone resorption markers in postmenopausal women, Osteoporos. Int. 18 (1) (2007) 109–115.
[87] S.K. Gupta, D. Trivedi, S. Srivastava, S. Joshi, N. Halder, S.D. Verma, Lycopene attenuates oxidative stress induced experimental cataract development: an in vitro and in vivo study, Nutrition 19 (2003) 794–799.
[88] G. Edward, Tomatoes, tomato-based products, lycopene and cancer: review of the epidemiologic literature, J. Natl. Cancer Inst. 91 (4) (1999) 317–331.
[89] N.P. Goyal, R. Kumar, Lycopene therapy in idiopathic male infertility—a preliminary report, Int. Urol. Nephrol. 34 (3) (2002) 369–372.
[90] E. Büyüktuncel, Toplam Fenolik İçerik Ve Antioksidan Kapasite Tayininde Kullanılan Başlıca Spektrofotometrik Yöntemler, Marmara Pharm. J. 17 (2013) 93–103.
[91] H. Wiseman, B. Halliwell, Damage to DNA by reactive oxygen and nitrogen species: role in İnfammatory disease and progression to cancer, Biochem. J. 313 (1996) 17–29.
[92] A. Hekimoğlu, The anticarcinogenic action mechanisms of lycopene, F. Ü. Sağ. Bil. Tıp Derg. 25 (1) (2010) 57–62.
[93] M. Kujawska, M. Ewertowska, T. Adamska, C. Sadowski, E. Ignatowicz, J. Jodynis-Liebert, Antioxidant effect of lycopene-enriched tomato paste on *N*-nitrosodiethylamine-induced oxidative stress in rats, J. Physiol. Biochem. 70 (2014) 981–990.
[94] H.D. Bıçaklı, R. Uslu, Lycopene and cancer, Türk. Onkoloji Dergisi 27 (2) (2012) 93–97.
[95] G. Britton, Carotenoids 1: structure and properties of carotenoids in relation to function, FASEB J. 9 (1995) 1551–1558.

[96] N. Krinsky, Overview of lycopene, carotenoids, and disease prevention, Proc. Soc. Exp. Biol. Med. 218 (1988) 95–97.
[97] N. Ukai, Y. Lu, H. Etoh, Photosensitized oxygenation of lycopene, Biosci. Biotechnol. Biochem. 58 (1994) 1718–1719.
[98] N. Krinsky, Mechanism of action of biological antioxidants, Proc. Soc. Exp. Biol. Med. 200 (1992) 248–254.
[99] A. Jemal, F. Bray, M.M. Center, et al., Global cancer statistics, CA Cancer J. Clin. 61 (2011) 69.
[100] T. Chinembiri, L. du Plessis, M. Gerber, J. Hamman, J. du Plessis, Review of natural compounds for potential skin cancer treatment, Molecules 19 (8) (2014) 11679–11721.
[101] M. Takeshima, M. Ono, T. Higuchi, C. Chen, T. Hara, S. Nakano, Anti-proliferative and apoptosis-inducing activity oflycopene against three subtypes of human breast cancer cell lines, Cancer Sci. 105 (3) (2014) 252–257.
[102] H.C. Pitot, The molecular biology of carcinogenesis, Cancer 72 (Suppl. 3) (1993) 962–970.
[103] J. Molnar, N. Gyemant, I. Mucsietal, Modulation of multidrug resistance and apoptosis of cancer cells by selected carotenoids, In Vivo 18 (2) (2004) 237–244.
[104] N. Khan, F. Afaq, H. Mukhtar, Apoptosis by dietary factors: the suicide solution for delaying cancer growth, Carcinogenesis 28 (2007) 233–239.
[105] P. Carmeliet, R.K. Jain, Molecular mechanisms and clinical applications of angiogenesis, Nature 473 (2011) 298–307.
[106] J. Le, H. Lee Andy, W. Binns Colin, Tea and lycopene protect against prostate cancer, Asia Pac. J. Clin. Nutr. 16 (Suppl. 1) (2007) 453–457.
[107] J. Levy, et al., Lycopene is a more potent inhibitor of human cancer cell proliferation than either α-carotene or β-carotene, Nutr. Cancer 24 (3) (1995) 257–266.
[108] M. Kohno, J. Pouyssegur, Targeting the ERK signaling pathway in cancer therapy, Ann. Med. 38 (2006) 200–211.
[109] B. Zhang, Y. Gu, Low expression of ERK signaling pathway affecting proliferation, cell cycle arrest and apoptosis of human gastric HGC-27 cells line, Mol. Biol. Rep. 41 (2014) 3659–3669.
[110] C.M. Yang, T.Y. Hu, M.L. Hu, Antimetastatic effects and mechanisms of apo-8′-lycopenal, an enzymatic metabolite of lycopene, against human hepatocarcinoma SK-Hep-1 cells, Nutr. Cancer 64 (2012) 274–285.
[111] J. Yang, X. Liu, K. Bhalla, C.N. Kim, A.M. Ibrado, J. Cai, et al., Prevention of apoptosis by Bcl-2: release of cytochrome c from mitochondria blocked, Science 275 (1997) 1129–1132.
[112] B. Velmurugan, A. Mani, S. Nagini, Combination of S-allylcysteine and lycopene induces apoptosis by modulating Bcl-2, Bax, Bim and caspases during experimental gastric carcinogenesis, Eur. J. Cancer Prev. 14 (2005) 387–393.
[113] S. Wilhelm, S. Helmut, Lycopene: a biologically important carotenoid for humans, Arch. Biochem. Biophys. 336 (1) (1996) 1–9.
[114] M.Y. Wei, E.L. Giovannucci, Lycopene, tomato products, and prostate cancerincidence: a review and reassessment in the PSA screening era, J. Oncol. 2012 (2012) 271063.
[115] C. Liu, R.M. Russell, Nutrition and gastric cancer risk: an update, Nutr. Rev. 66 (2008) 237–249.
[116] D. Aune, D.S. Chan, A.R. Vieira, et al., Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies, Breast Cancer Res. Treat. 134 (2012) 479–493.
[117] T. Tanaka, M. Shnimizu, H. Moriwaki, Cancer chemoprevention by carotenoids, Molecules 17 (2012) 3202–3242.
[118] T. Narisawa, Y. Fukaura, M. Hasebe, et al., Prevention of *N*-methylnitrosoureainduced colon carcinogenesis in F344 rats by lycopene and tomato juice rich in lycopene, Jpn. J. Cancer Res. 89 (1998) 1003–1008.
[119] D.J. Kim, N. Takasuka, J.M. Kim, et al., Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH, Cancer Lett. 120 (1997) 15–22.
[120] M. Sahin, E. Sahin, S. Gumuslu, Effects of lycopene and apigenin on human umbilical vein endothelial cells in vitro under angiogenic stimulation, Acta Histochem. 114 (2) (2012) 94–100.
[121] C.-M. Yang, Y.-T. Yen, C.-S. Huang, M.-L. Hu, Growth inhibitory efficacy of lycopene and β-carotene against androgen-independent prostate tumor cells xenografted in nude mice, Mol. Nutr. Food Res. 55 (4) (2011) 606–612.
[122] C.S. Huang, Y.E. Fan, C.Y. Lin, M.L. Hu, Lycopene inhibits matrix metalloproteinase-9 expression and down-regulates the binding activity of nuclear factor-kappa B and stimulatory protein-1, J. Nutr. Biochem. 18 (7) (2007) 449–456.
[123] P. Carmeliet, Angiogenesis in life, disease and medicine, Nature 438 (2005) 932–936.

[124] R.G. Ziegler, A review of epidemiological evidence that carotenoids reduce the risk of cancer, J. Nutr. 119 (1989) 116–122.
[125] E.S. Hwang, H.J. Lee, Inhibitory effects of lycopene on the adhesion, invasion and migration of SK-Hep1 human hepatoma cells, Exp. Biol. Med. (Maywood) 231 (2006) 322–327.
[126] S. Elgass, A. Cooper, M. Chopra, Lycopene inhibits angiogenesis in human umbilical vein endothelial cells and rat aortic rings, Br. J. Nutr. 108 (2012) 431–439.
[127] W. Willet, Coffee and coronary heart disease. A new problem with old brew? Ann. Epidemiol. 4 (6) (1994) 497–498.
[128] G. Mazza, C.D. Kay, et al., Absorption of anthocyanins from blueberries and serum antioxidant status in human subjects, J. Agric. Food Chem. 50 (26) (2002) 7731–7737.
[129] P. Iannelli, V. Zarrilli, et al., The dietary antioxidant resveratrol affects redox changes of PPARα activity, Nutr. Metab. Cardiovasc. Dis. 17 (4) (2007) 247–256.
[130] H. Gerster, The potential role of lycopene for human health, J. Am. Coll. Nutr. 16 (2013) 109–126.
[131] A.V. Rao, S. Agarwal, Role of antioxidant lycopene in cancer and heart disease, J. Am. Coll. Nutr. 19 (2000) 563–569.
[132] S.A. Mulkalwar, N.S. Munjal, et al., Effect of purified lycopene on lipid profile, antioxidant enzyme and blood glucose in hyperlipidemic rabbits, Am. J. Pharm. Tech Res. 2 (2012) 461–470.
[133] M. Shyamala, M. Venukumar, et al., Antioxidant potential of the *Syzygium aromaticum* (Gaertn.) Linn. (cloves) in rats fed with high fat diet, Indian J. Pharmacol. 35 (2) (2003) 99–103.
[134] R. Misra, S. Mangi, et al., LycoRed as an alternative to hormone replacement therapy in lowering serum lipids and oxidative stress markers: a randomized controlled clinical trial, J. Obstet. Gynaecol. Res. 32 (3) (2006) 299–304.
[135] Y.N. Engelhard, B. Gazer, et al., Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study, Am. Heart J. 151 (1) (2006) 100 e101–106.
[136] K. Ried, P. Fakler, Protective effect of lycopene on serum cholesterol and blood pressure: meta-analyses of intervention trials, Maturitas 68 (4) (2011) 299–310.
[137] J. Pincemail, Free radicals and antioxidants in human diseases, in: Analysis of Free Radicals in Biological Systems, Springer, 1995, , pp. 83–98.
[138] B.N. Ames, L.S. Gold, et al., The causes and prevention of cancer, Proc. Natl. Acad. Sci. U. S. A. 92 (12) (1995) 5258–5265.
[139] A. Agarwal, H. Shen, S. Agarwal, A.V. Rao, Lycopene content of tomato products: its stability, bioavailability and in vivo antioxidant properties, J. Med. Food 4 (1) (2001) 9–15.
[140] J.L. Witztum, D. Steinberg, The oxidative modification hypothesis of atherosclerosis: does it hold for humans? Trends Cardiovasc. Med. 11 (3–4) (2001) 93–102.
[141] S. Zaripheh, J.W. Erdman Jr., The biodistribution of a single oral dose of [^{14}C]-lycopene in rats prefed either a control or lycopene-enriched diet, J. Nutr. 135 (9) (2005) 2212–2218.
[142] A. Rao, Lycopene, tomatoes, and the prevention of coronary heart disease, Exp. Biol. Med. 227 (10) (2002) 908–913.
[143] D. Heber, Q.-Y. Lu, Overview of mechanisms of action of lycopene, Exp. Biol. Med. 227 (10) (2002) 920–923.
[144] B. Halliwell, Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet 344 (8924) (1994) 721–724.
[145] P. Palozza, M. Colangelo, et al., Lycopene induces cell growth inhibition by altering mevalonate pathway and Ras signaling in cancer cell lines, Carcinogenesis 31 (10) (2010) 1813–1821.
[146] I. Mozos, D. Stoian, et al., Lycopene and vascular health, Front. Pharmacol. 9 (2018).
[147] M. Lorenz, M. Fechner, et al., Effects of lycopene on the initial state of atherosclerosis in New Zealand White (NZW) rabbits, PLoS One 7 (1) (2012) e30808.
[148] W.T. Friedewald, R.I. Levy, et al., Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge, Clin. Chem. 18 (6) (1972) 499–502.
[149] K.K. Maung, A. Miyazaki, et al., Induction of acyl-coenzyme A: cholesterol acyltransferase-1 by 1,25-dihydroxyvitamin D3 or 9-cis-retinoic acid in undifferentiated THP-1 cells, J. Lipid Res. 42 (2) (2001) 181–187.
[150] N. Sahin, K. Sahin, et al., Effects of dietary lycopene and vitamin E on egg production, antioxidant status and cholesterol levels in Japanese quail, Asian Australas. J. Anim. Sci. 19 (2) (2005) 224–230.
[151] J.L. Witztum, The oxidation hypothesis of atherosclerosis, Lancet 344 (8925) (1994) 793–795.

[152] G. Kolovou, K. Anagnostopoulou, et al., Pathophysiology of dyslipidaemia in the metabolic syndrome, Postgrad. Med. J. 81 (956) (2005) 358–366.
[153] K.S.C. Bose, B. Agrawal, Effect of lycopene from tomatoes (cooked) on plasma antioxidant enzymes, lipid peroxidation rate and lipid profile in grade-I hypertension, Ann. Nutr. Metab. 51 (5) (2007) 477–481.
[154] T. Rissanen, S. Voutilainen, et al., Lycopene, atherosclerosis, and coronary heart disease, Exp. Biol. Med. 227 (10) (2002) 900–907.
[155] L. Arab, S. Steck, Lycopene and cardiovascular disease, Am. J. Clin. Nutr. 71 (6) (2000) 1691S–1695S.
[156] P. Greenland, M.D. Knoll, J. Stamler, J.D. Neaton, A.R. Dyer, D.B. Garside, P.W. Wilson, Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 290 (2003) 891–897, https://doi.org/10.1001/jama.290.7.891.
[157] S. Laurent, Antihypertensive drugs. Pharmacol. Res. 124 (2017) 116–125, https://doi.org/10.1016/j.phrs.2017.07.026.
[158] S.J. Mann, Redefining beta-blocker use in hypertension: selecting the right beta-blocker and the right patient. J. Am. Soc. Hypertens. 11 (2017) 54–65, https://doi.org/10.1016/j.jash.2016.11.007.
[159] S.D. Ross, K.S. Akhras, S. Zhang, M. Rozinsky, L. Nalysnyk, Discontinuation of antihypertensive drugs due to adverse events: a systematic review and meta-analysis. Pharmacotherapy 21 (2001) 940–953, https://doi.org/10.1592/phco.21.11.940.34520.
[160] I.M. Kronish, M. Woodward, Z. Sergie, G. Ogedegbe, L. Falzon, D.M. Mann, Meta-analysis: impact of drug class on adherence to antihypertensives. Circulation 123 (2011) 1611–1621, https://doi.org/10.1161/CIRCULATIONAHA.110.983874.
[161] J.H. John, S. Ziebland, P. Yudkin, L.S. Roe, H.A. Neil, Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. Lancet 359 (2002) 1969–1974, https://doi.org/10.1016/s0140-6736(02)98858-6.
[162] J.Y. Kim, J.K. Paik, O.Y. Kim, H.W. Park, J.H. Lee, Y. Jang, J.H. Lee, Effects of lycopene supplementation on oxidative stress and markers of endothelial function in healthy men. Atherosclerosis 15 (2011) 189–195, https://doi.org/10.1016/j.atherosclerosis.2010.11.036.
[163] E. Paran, V. Novack, Y.N. Engelhard, I. Hazan-Halevy, The effects of natural antioxidants from tomato extract in treated but uncontrolled hypertensive patients. Cardiovasc. Drugs Ther. 23 (2009) 145–151, https://doi.org/10.1007/s10557-008-6155-2.
[164] I.M. Petyaev, P.Y. Dovgalevsky, N.E. Chalyk, V.A. Klochkov, N. Kyle, Reduction in blood pressure and serum lipids by lycosome formulation of dark chocolate and lycopene in prehypertension. Food Sci. Nutr. 2 (2014) 744–750, https://doi.org/10.1002/fsn3.169.
[165] T. Wolak, E. Paran, Can carotenoids attenuate vascular aging? Vasc. Pharmacol. 59 (3–4) (2013) 63–66.
[166] P.A. Jacques, A. Lyass, J.M. Massaro, R.S. Vasan, R.B. D'Agostino Sr., Relation of lycopene intake and consumption of tomato products to incident cardiovascular disease, Br. J. Nutr. 110 (3) (2013) 545–551.
[167] M. Jenab, P. Ferrari, M. Mazuir, et al., Variations inlycopene blood levels and tomato consumption across European countries based on the European Prospective Investigation into Cancer and Nutrition (EPIC) study, J. Nutr. 135 (2005) 2032S–2036S.
[168] M. Friedman, Anticarcinogenic, cardioprotective, and other health benefits of tomato compoundslycopene, α-tomatine, and tomatidine in pure form andin fresh and processed tomatoes, J. Agric. Food Chem. 61 (2013) 9534–9550.
[169] B. Fuhramn, A. Elis, M. Aviram, Hypo-cholesterolemic effect of lycopene and α-carotene is related to suppression of cholesterol synthesis and augmentation of LDL receptor activity in macrophage, Biochem. Biophys. Res. Commun. 233 (1997) 658–662.
[170] A. Rao, S. Agarwal, Bioavailability and in vivo antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer, Nutr. Cancer 31 (1998) 199–203.
[171] K. Klipstein-Grobusch, L.J. Launer, J.M. Geleijnse, H. Boeing, A. Hofman, J.C. Witteman, Serum carotenoids and atherosclerosis. The Rotterdam study., Atherosclerosis 148 (2000) 49–56.
[172] T.H. Rissanen, S. Voutilainen, K. Nyyssorien, T.A. Lakka, J. Sivenius, R. Salonen, G.A. Kaplan, J.T. Salonen, Low serum lycopene concentration is associated with an excess incidence of acute coronary events and stroke: the Kuopio Ischaemic Heart Disease Risk Factor Study, Br. J. Nutr. 85 (2001) 749–754.
[173] E. Paran, Y. Engelhard, Effect of Lyc-O-Mato, standardized tomato extract on blood pressure, serum lipoproteins, plasma homocysteine and oxidative stress markers in grade 1 hypertensive patients, in: Proceedings of the 16th Annual Scientific Meeting of the Society of Hypertension, San Francisco, USA, 2001.

[174] L. Kohlmeier, J.D. Kark, E. Gomez-Garcia, B.C. Martin, S.E. Steck, A.F.M. Kardinal, Lycopene and myocardial infarction risk in the EURAMIC study, Am. J. Epidemiol. 146 (1997) 618–626.
[175] J.L. Witztum, Role of oxidized low densirty lipoprotein in atherogenesis, Br. Heart J. 69 (1993) S12–S18.
[176] B. Frei, Cardiovascular disease and nutrient antioxidants: role of low-density lipoprotein oxidation, Crit. Rev. Food Sci. Nutr. 351 (1995) 83–98.
[177] H.D. Sesso, J.E. Buring, E.P. Norkus, J.M. Gaziano, Plasma lycopene, other carotenoids, retinol and the risk of cardiovascular disease in men, Am. J. Clin. Nutr. 81 (2005) 990–997.
[178] E. García-Fernández, L. Rico-Cabanas, R. Estruch, A. Bach-Faig, A. Bach-Faig, Mediterranean diet and cardiodiabesity: a review, Nutrients 6 (9) (2014) 3474–3500.
[179] I.M. Petyaev, Lycopene deficiency in ageing and cardiovascular disease, Oxid. Med. Cell. Longev. 2016 (2016).
[180] B. Kaur, J. Henry, Micronutrient status in type 2 diabetes: a review, Adv. Food Nutr. Res. 71 (2014) 55–100.
[181] S.C. Montgomery, S.M. Streit, M.L. Beebe, P.J. Maxwell, Micronutrient needs of the elderly, Nutr. Clin. Pract. 29 (4) (2014) 435–444.
[182] A. Kuhad, R. Sethi, K. Chopra, Lycopene attenuates diabetes-associated cognitive decline in rats, Life Sci. 83 (2008) 128–134.
[183] D. Chen, C. Huang, Z. Chen, A review for the pharmacological effect of lycopene in central nervous system disorders, Biomed. Pharmacother. 111 (2019) 791–801.
[184] M. Vertzoni, G. Valsami, C. Reppas, Plasma profiles of lycopene after single oral and intravenous administrations in dogs, J. Pharm. Pharmacol. 58 (2006) 1211–1217.
[185] B.J. Burri, M.H. Chapman, T.R. Neidlinger, J.S. Seo, B.K. Ishida, Tangerine tomatoes increase total and tetra-cis-lycopene isomer concentrations more than red tomatoes in healthy adult humans, Int. J. Food Sci. Nutr. 60 (2009) 1–16.
[186] J.L. Cooperstone, R.A. Ralston, K.M. Riedl, T.C. Haufe, R.M. Schweiggert, S.A. King, C.D. Timmers, D. M. Francis, G.B. Lesinski, S.K. Clinton, Enhanced bioavailability of lycopene when consumed as cis-isomers from tangerine compared to red tomato juice, a randomized, cross-over clinical trial, Mol. Nutr. Food Res. 59 (2015) 658–669.
[187] M. Qu, L. Li, C. Chen, M. Li, L. Pei, F. Chu, J. Yang, Z. Yu, D. Wang, Z. Zhou, Protective effects of lycopene against amyloid β-induced neurotoxicity in cultured rat cortical neurons, Neurosci. Lett. 505 (2011) 286–290.
[188] M. Qu, Z. Zhou, C. Chen, M. Li, L. Pei, F. Chu, J. Yang, Y. Wang, L. Li, C. Liu, L. Zhang, G. Zhang, Z. Yu, D. Wang, Lycopene protects against trimethyltin-induced neurotoxicity in primary cultured rat hippocampal neurons by inhibiting the mitochondrial apoptotic pathway, Neurochem. Int. 59 (2011) 1095–1103.
[189] N.T. Akbaraly, H. Faure, V. Gourlet, A. Favier, C. Berr, Plasma carotenoid levels and cognitive performance in an elderly population: results of the EVA study, J. Gerontol. Ser. A 62 (2007) 308–316.
[190] S. Hwang, J.W. Lim, H. Kim, Inhibitory effect of lycopene on amyloid-β-induced apoptosis in neuronal cells, Nutrients 9 (8) (2017) 883.
[191] R.V. Chandra, M.L. Prabhuji, D.A. Roopa, S. Ravirajan, H.C. Kishore, Efficacy of lycopene in the treatment of gingivitis: a randomised, placebo-controlled clinical trial, J. Nutr. 138 (1) (2008) 49–53.
[192] M. Umar, A. Zubairu, H.S. Hamisu, I.B. Mohammed, J.O. Oko, I.M. Abdulkarim, A. Salisu, A.A. Yaya, A. A. Aliko, Evaluation of phytochemical and in vitro antimicrobial effects of *Solanum lycopersicum* Linn. (tomato) on oral thrush and human cariogenic pathogens, J. Adv. Med. Pharm. Sci. 11 (4) (2016) 1–9.
[193] O.D. Omodamiro, U. Amechi, Thephytochemical content, antioxidant, antimicrobial and anti-inflammatoryactivities of *Lycopersicon esculentum* (tomato), Asian J. Plant Sci. Res. 3 (5) (2013) 70–81.
[194] J. Maitra, Sangeeta, Antibacterial property of lycopene extracted from *Lycopersicon esculentum* against *Pseudomonas aeruginosa*, Eur. J. Biomed. Pharm. Sci. 3 (9) (2016) 353–356.
[195] S.S. Dhanawade, A.V. Sakhare, Isolation of lycopene from tomato and study of its antimicrobial activity, Int. J. Sci. Res. 3 (12) (2012) 671–673.
[196] W. Lee, D.G. Lee, Lycopene-induced hydroxyl radical causes oxidative DNA damage in *Escherichia coli*, J. Microbiol. Biotechnol. 24 (9) (2014) 1232–1237.
[197] W.S. Sung, I.S. Lee, D.G. Lee, Damage to the cytoplasmic membrane and cell death caused by lycopene in *Candida albicans*, J. Microbiol. Biotechnol. 17 (11) (2007) 1797–1804.
[198] P.R. Desai, P.D. Holihosur, V.S. Marathe, B.B. Kulkarni, U.K. Vishal, R.K. Geetanjali, R.P. Rajeev, S.V. Hiremath, Studies on isolation and quantification of lycopene from tomato and papaya and its antioxidant and antifungal properties, Int. J. Agric. Innov. Res. 6 (5) (2018) 257–260.

[199] H. Choi, D.G. Lee, Lycopene induces apoptosis in *Candida albicans* through reactive oxygen species production and mitochondrial dysfunction, Biochimie 115 (2015) 108–115.
[200] WHO, World Malaria Report 2011, World Health Organization Press, Geneva, Switzerland, 2011.
[201] S. Percário, D.R. Moreira, B.A.Q. Gomes, M.E.S. Ferreira, A.C.M. Gonçalves, P.S.O.C. Laurindo, T.C. Vilhena, M.F. Dolabela, M.D. Green, Oxidative stress in malaria, Int. J. Mol. Sci. 13 (2012) 16346–16372.
[202] J.O. Adebayo, A.U. Krettli, Potential antimalarials from Nigerian plants: a review, J. Ethnopharmacol. 133 (2011) 289–302.
[203] WHO, World Malaria Report 2008, World Health Organization, Geneva, 2008, pp. 7–15 99–101.
[204] F.M. Madaki, Antiplasmodial activity of ethanol extract of *Vernonia amygdalina* leaf in *Plasmodium berghei* infected mice: in vivo study, IOSR J. Pharm. Biol. Sci. 10 (2) (2015) 37–42.
[205] B.S. Shewo, B. Girma, Review on nutritional and medicinal values of *Vernonia amygdalina* and its uses in human and veterinary medicines, Global Vet. 19 (3) (2017) 562–568.
[206] D. Bhowmik, K.P.S. Kumar, S. Paswan, S. Srivastava, Tomato—a natural medicine and its health benefits, J. Pharmacogn. Phytother. 1 (1) (2012) 33–43.
[207] N. Holzapfel, B. Holzapfel, S. Champ, J. Feldthusen, J. Clements, D. Hutmacher, The potential role of lycopene for the prevention and therapy of prostate cancer: from molecular mechanisms to clinical evidence, Int. J. Mol. Sci. 14 (7) (2013) 14620–14646.
[208] S. Agarwal, V. Sharma, T. Kaul, M.Z. Abdin, S. Singh, Cytotoxic effect of carotenoid phytonutrient lycopene on *P. falciparum* infected erythrocytes, Mol. Biochem. Parasitol. 197 (2014) 15–20.
[209] M. Clerc, Observations sur les vitamines anti-oxydantes et/ou anti-radicalaires en medecine tropicale, Bull. Acad. Natl Med. 176 (1992) 1393–1406.
[210] A. Metzger, G. Mukasa, A.H. Shankar, G. Ndeezi, G. Melikian, R.D. Semba, Antioxidant status and acute malaria in children in Kampala, Uganda, Am. J. Trop. Med. Hyg. 65 (2001) 115–119.
[211] R.C. Ekeanyanwu, N. Achuka, B.U. Akpoilih, Serum level of antioxidant vitamins (vitamin A, C and E) in *Plasmodium falciparum* malaria infected children in Owerri, Eastern Nigeria, Biokemistri 21 (2) (2009) 53–58.
[212] C. Chan, C. Hung, Lycopene and retinal pigment epithelial cells: molecular aspects, in: V.R. Preedy (Ed.), Handbook of Nutrition, Diet and the Eye, Academic Press, US, 2014, pp. 587–598.
[213] M.M. Fernandez, N.A. Afshari, Nutrition and the prevention of cataracts, Curr. Opin. Ophthalmol. 19 (1) (2008) 66–70.
[214] C.R. Gale, N.F. Hall, D.I. Phillips, C.N. Martyn, Plasma antioxidant vitamins and carotenoids and age-related cataract, Ophthalmology 108 (11) (2001) 1992–1998.
[215] R.V. Chandra, M.L. Prabhuji, D.A. Roopa, S. Ravirajan, H.C. Kishore, Efficacy of lycopene in the treatment of gingivitis: a randomised, placebo-controlled clinical trial, Oral Health Prev. Dent. 5 (4) (2007) 327–336.
[216] S.A. Belludi, S. Verma, R. Banthia, P. Bhusari, S. Parwani, S. Kedia, S.V. Saiprasad, Effect of lycopene in the treatment of periodontal disease: a clinical study, J. Contemp. Dent. Pract. 14 (6) (2013) 1054–1059.
[217] M. Ambati, K.R. Rani, P.V. Reddy, J. Suryaprasanna, R. Dasari, H. Gireddy, Evaluation of oxidative stress in chronic periodontitis patients following systemic antioxidant supplementation: a clinical and biochemical study, J. Nat. Sci. Biol. Med. 8 (1) (2017) 99–103.
[218] M.S. Tawfik, K.A. Abdel-Ghaffar, A.Y. Gamal, F.H. El-Demerdash, H.A. Gad, Lycopene solid lipid microparticles with enhanced effect on gingival crevicular fluid protein carbonyl as a biomarker of oxidative stress in patients with chronic periodontitis, J. Liposome Res. (2019) 1–33.
[219] T.V. Karemore, M. Motwani, Evaluation of the effect of newer antioxidant lycopene in the treatment of oral submucous fibrosis, Indian J. Dent. Res. 23 (4) (2012) 524–528.
[220] G. Saran, D. Umapathy, N. Misra, S.G. Channaiah, P. Singh, S. Srivastava, S. Shivakumar, A comparative study to evaluate the efficacy of lycopene and curcumin in oral submucous fibrosis patients: a randomized clinical trial, Indian J. Dent. Res. 29 (3) (2018) 303–312.
[221] P. Piyush, A. Mahajan, K. Singh, S. Ghosh, S. Gupta, Comparison of therapeutic response of lycopene and curcumin in oral submucous fibrosis: a randomized controlled trial. Oral Dis. (2018). https://doi.org/10.1111/odi.12947.
[222] N. Saawarn, M.C. Shashikanth, S. Saawarn, V. Jirge, N.C. Chaitanya, R. Pinakapani, Lycopene in the management of oral lichen planus: a placebo-controlled study, Indian J. Dent. Res. 22 (5) (2011) 639–643.
[223] I. Parlatescu, C. Gheorghe, E. Coculescu, S. Tovaru, Oral leukoplakia—an update, Maedica (Buchar) 9 (2014) 88–93.
[224] M. Singh, R. Krishanappa, A. Bagewadi, V. Keluskar, Efficacy of oral lycopene in the treatment of oral leukoplakia, Oral Oncol. 40 (6) (2004) 591–596.
[225] J.M. Zakrzewska, Oral lycopene—an efficacious treatment for oral leukoplakia? Evid. Based Dent. 6 (1) (2005) 17–18.

[226] V. Bhuvaneswari, B. Velmurugan, S. Nagini, Dose-response effect of tomato paste on 7,12-dimethylbenz[a] anthracene-induced hamster buccal pouch carcinogenesis, J. Exp. Clin. Cancer Res. 23 (2) (2004) 241–249.
[227] S.T. Mayne, B. Cartmel, H. Lin, T. Zheng, W.J. Goodwin Jr., Low plasma lycopene concentration is associated with increased mortality in a cohort of patients with prior oral, pharynx or larynx cancers, J. Am. Coll. Nutr. 23 (1) (2004) 34–42.
[228] E. Jahanian, M. Karimifar, M. Rafieian-Kopaei, Antioxidants as a novel way to alleviate the adverse effects of oxidative stress in osteoporosis, J. Parathyroid Dis. 4 (2) (2016) 60–65.
[229] R. Maurya, G. Singh, P.P. Yadav, Antiosteoporotic agents from natural sources. Stud. Nat. Prod. Chem. 35 (2008) 517–548, https://doi.org/10.1016/S1572-5995(08)80013-0.
[230] L. Kim, A.V. Rao, L.G. Rao, Lycopene II—effect on osteoblasts: the carotenoid lycopene stimulates cell proliferation and alkaline phosphatase activity of SaOS-2 cells. J. Med. Food 6 (2003) 79–86, https://doi.org/10.1089/109662003322233468.
[231] S. Sahni, M.T. Hannan, J. Blumberg, L.A. Cupples, D.P. Kiel, K.L. Tucker, Protective effect of total carotenoid and lycopene intake on the risk of hip fracture: a 17-year follow-up from the Framingham Osteoporosis Study. J. Bone Miner. Res. 24 (6) (2009) 1086–1094, https://doi.org/10.1359/jbmr.090102.
[232] E.S. Mackinnon, A.V. Rao, R.G. Josse, L.G. Rao, Supplementation with the antioxidant lycopene significantly decreases oxidative stress parameters and the bone resorption marker N-telopeptide of type I collagen in postmenopausal women, Osteoporos. Int. 22 (4) (2011) 1091–1101.
[233] D.A. Callaway, J.X. Jiang, Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases. J. Bone Miner. Metab. 33 (4) (2015) 359–370, https://doi.org/10.1007/s00774-015-0656-4.
[234] M. Jia, Y. Nie, D.P. Cao, Y.Y. Xue, J.S. Wang, L. Zhao, … L.P. Qin, Potential antiosteoporotic agents from plants: a comprehensive review. Evid. Based Complement. Alternat. Med. (2012) 1–28, https://doi.org/10.1155/2012/364604.
[235] N. Mody, F. Parhami, T.A. Sarafian, L.L. Demer, Oxidative stress modulates osteoblastic differentiation of vascular and bone cells. Free Radic. Biol. Med. 31 (2001) 509–519, https://doi.org/10.1016/S0891-5849(01)00610-4.
[236] J.K. Zhang, L. Yang, G.L. Meng, Z. Yuan, J. Fan, D. Li, … J. Liu, Protection by salidroside against bone loss via inhibition of oxidative stress and bone-resorbing mediators. PLoS One 8 (2) (2013) e57251. https://doi.org/10.1371/journal.pone.0057251.
[237] M. Arai, Y. Shibata, K. Pugdee, Y. Abiko, Y. Ogata, Effects of reactive oxygen species (ROS) on antioxidant system and osteoblastic differentiation in MC3T3-E1 cells. IUBMB Life 59 (2007) 27–33, https://doi.org/10.1080/15216540601156188.
[238] A.L. Liu, Z.M. Zhang, B.F. Zhu, Z.H. Liao, Z. Liu, Metallothionein protects bone marrow stromal cells against hydrogen peroxide-induced inhibition of osteoblastic differentiation. Cell Biol. Int. 28 (2004) 905–911, https://doi.org/10.1016/j.cellbi.2004.09.004.
[239] Y. Ishimi, M. Ohmura, X. Wang, M. Yamaguchi, S. Ikegami, Inhibition by carotenoids and retinoic acid of osteoclast-like cell formation induced by bone-resorbing agents in vitro, J. Clin. Biochem. Nutr. 27 (1999) 113–122.
[240] M.S.M. Ardawi, M.H. Badawoud, S.M. Hassan, A.A. Rouzi, J.M.S. Ardawi, N.M. AlNosani, et al., Lycopene treatment against loss of bone mass, microarchitecture and strength in relation to regulatory mechanisms in a postmenopausal osteoporosis model, Bone 83 (2016) 127–140.
[241] H. Shah, S.R. Mahajan, Screening of topical gel containing lycopene and dexamethasone against UV radiation induced photoaging in mice, Biomed. Aging Pathol. 4 (2014) 303–308.
[242] M. Darvin, A. Patzelt, S. Gehse, S. Schanzer, C. Benderoth, W. Sterry, J. Lademann, Cutaneous concentration of lycopene correlates significantly with the roughness of the skin, Eur. J. Pharm. Biopharm. 69 (2008) 943–947.
[243] L. Raluca, B. Lionel, L. Christel, Administration of Lycopene for Combating Skin/Mucous Membrane Damage (U.S. Patent No. 6623769), (September 23, 2003).
[244] S.P. Indena, Formulations Containing Carotenoids and Procarotenoids Combined with Polyphenols in the Prevention of the Damages Due to an Abnormal Production of Free Radicals (U.S. Patent No. 5648377), (July 15, 1997).
[245] M.A. Shahtalebi, A.H. Siadat, S. Karbasizade, Preparation and evaluation of the clinical efficacy and safety of tomato lotion containing lycopene, J. Herb. Med. Pharmacol. 4 (4) (2015) 142–148.
[246] M.P. Chernyshova, D.V. Pristenskiy, M.V. Lozbiakova, N.E. Chalyk, T.Y. Bandaletova, I.M. Petyaev, Systemic and skin-targeting beneficial effects of lycopene-enriched ice cream: a pilot study, J. Dairy Sci. 102 (2018) 14–25.
[247] T. Coyne, T.I. Ibiebele, P.D. Baade, A. Dobson, C. McClintock, S. Dunn, D. Leonard, J. Shaw, Diabetes mellitus and serum carotenoids: findings of a population-based study in Queensland, Australia, Am. J. Clin. Nutr. 82 (2005) 685–693.

[248] V. Duzguner, A. Kucukgul, S. Erdogan, S. Celik, K. Sahin, Effect of lycopene administration on plasma glucose, oxidative stress and body weight in streptozotocin diabetic rats, J. Appl. Anim. Res. 33 (2008) 17–20.
[249] Z.R. Dixon, F.S. Shie, B.A. Warden, B.J. Burri, T.R. Neidlinger, The effect of a low carotenoid diet on malondialdehydethiobarbituric acid (MDA-TBA) concentrations in women: aplacebo-controlled double-blind study, J. Am. Coll. Nutr. 17 (1998) 54–58.
[250] P.M. Choksi, V.Y. Joshi, A review on lycopene—extraction, purification, stability and applications, Int. J. Food Prop. 10 (2) (2007) 289–298.
[251] M.M. Ali, F.G. Agha, Amelioration of streptozotocin-induced diabetes mellitus, oxidative stress and dyslipidemia in rats by tomato extract lycopene, Scand. J. Clin. Lab. Invest. 69 (3) (2009) 371–379.
[252] M. Sayahi, S. Shirali, The antidiabetic and antioxidant effects of carotenoids: a review, Asian J. Pharm. Res. Health Care 9 (4) (2017) 186–191.
[253] E.D. Eze, A.M. Afodun, S.O. Sulaiman, N. Ponsiano, I. Ezekiel, M.D. Adams, A.O. Okpanachi, K.M. Rabiu, Lycopene attenuates diabetes-induced oxidative stress in Wistar rats, J. Diabetes Endocrinol. 9 (2) (2018) 11–19.
[254] A. Biworo, E. Tanjung, K. Iskandar, E. Suhartono, Antidiabetic and antioxidant activity of jackfruit (*Artocarpus heterophyllus*) extract, J. Med. Bioeng. 4 (4) (2015).
[255] J. Ahn, W. Choi, S. Kim, T. Ha, Anti-diabetic effect of watermelon (*Citrullus vulgaris* Schrad) on streptozotocin-induced diabetic mice, Food Sci. Biotechnol. 20 (1) (2011) 251–254.
[256] Y. Guo, Y. Liu, Y. Wang, Beneficial effect of lycopene on anti-diabetic nephropathy through diminishing inflammatory response and oxidative stress, Food Funct. 6 (4) (2015) 1150–1156.
[257] E.E. Daniel, A. Mohammed, Y. Tanko, A. Ahmed, M.D. Adams, D. Atsukwei, Effects of lycopene on thyroid profile in streptozotocin-induced diabetic Wistar rats, Eur. J. Biotechnol. Biosci. 3 (1) (2015) 21–28.
[258] M. Aydin, S. Celik, Effects of lycopene on plasma glucose, insulin levels, oxidative stress, and body weights of streptozotocin-induced diabetic rats, Turk. J. Med. Sci. 42 (Suppl. 2) (2012) 1406–1413.
[259] M. Chopra, A. Bhaumik, A.G. Reddy, P.S. Kumar, B. Srikant, Extraction and isolation of bioactive molecule lycopene from water melon and evaluation of anti diabetic activity against STZ induced rats, Res. J. Pharm. Technol. 11 (1) (2018) 101–106.
[260] A. Wojdyło, P. Nowicka, Á.A. Carbonell-Barrachina, F. Hernández, Phenolic compounds, antioxidant and antidiabetic activity of different cultivars of *Ficus carica* L. fruits, J. Funct. Foods 25 (2016) 421–432.
[261] S. Sabiu, E.O. Ajani, R.A. Aladodo, T. Garuba, M.O. Agunbiade, A.A. Alimi, N. Lekena, M. Abdulrazaq, Membrane stabilization and probable mechanisms of hypoglycemic activity of fruit extract of *Solanum incanum* L. (Solanaceae), Comp. Clin. Pathol. 27 (6) (2018) 1611–1619.
[262] R.A. Wahyuono, J. Hesse, U.-C. Hipler, P. Elsner, V. Böhm, In vitro lipophilic antioxidant capacity, antidiabetic and antibacterial activity of citrus fruits extracts from Aceh, Indonesia, Antioxidants 6 (1) (2017) 11.
[263] N.P.S. Dhillon, C.-C. Lin, Z. Sun, P.M. Hanson, D.R. Ledesma, S.D. Habicht, R.-Y. Yang, Varietal and harvesting stage variation in the content of carotenoids, ascorbic acid and tocopherols in the fruit of bitter gourd (*Momordica charantia* L.), Plant Genet. Res. 15 (3) (2017) 248–259.
[264] H.S. El-Beltagi, H.I. Mohamed, A.S. Abdelazeem, R. Youssef, G. Safwat, GC-MS analysis, antioxidant, antimicrobial and anticancer activities of extracts from *Ficus sycomorus* fruits and leaves, Not. Bot. Horti Agrobot. 47 (2) (2018) 493–505.
[265] A. Béjaoui, A. Boulila, M. Boussaid, Chemical composition and biological activities of essential oils and solvent extracts of *Origanum vulgare subsp. glandulosum* Desf. from Tunisia, J. Med. Plants Res. 7 (32) (2013) 2429–2435.
[266] C. Ofori-Boateng, K.T. Lee, Sustainable utilization of oil palm wastes for bioactive phytochemicals for the benefit of the oil palm and nutraceutical industries, Phytochem. Rev. 12 (1) (2013) 173–190.
[267] M. Hakiman, M.A. Syed, A. Syahida, M. Maziah, Total antioxidant, polyphenol, phenolic acid, and flavonoid content in *Ficus deltoidea* varieties, J. Med. Plants Res. 6 (33) (2012) 4776–4784.
[268] R.T. Rosalina Tan, S. Mohamed, G.F. Samaneh, M.M. Noordin, Y.M. Goh, M.Y.A. Manap, Polyphenol rich oil palm leaves extract reduce hyperglycaemia and lipid oxidation in STZ-rats, Int. Food Res. J. 18 (1) (2011).
[269] R. Sato, K.M. Dang, B.G. McPherson, A.C. Brown, Anticancer activity of guava (*Psidium guajava*) extracts, J. Complement. Integr. Med. 7 (1) (2010).
[270] P. Ranasinghe, P. Ranasinghe, W.P.K.M. Abeysekera, G.A.S. Premakumara, Y.S. Perera, P. Gurugama, S. B. Gunatilake, In vitro erythrocyte membrane stabilization properties of *Carica papaya* L. leaf extracts, Pharmacogn. Res. 4 (4) (2012) 196.

[271] I.E. Juárez-Rojop, J.C. Díaz-Zagoya, J.L. Ble-Castillo, P.H. Miranda-Osorio, A.E. Castell-Rodríguez, C. A. Tovilla-Zárate, A. Rodríguez-Hernández, H. Aguilar-Mariscal, T. Ramón-Frías, D.Y. Bermúdez-Ocaña, Hypoglycemic effect of *Carica papaya* leaves in streptozotocin-induced diabetic rats, BMC Complement. Altern. Med. 12 (1) (2012) 236.
[272] T.O. Obafemi, A.C. Akinmoladun, M.T. Olaleye, S.O. Agboade, A.A. Onasanya, Antidiabetic potential of methanolic and flavonoid-rich leaf extracts of *Synsepalum dulcificum* in type 2 diabetic rats, J. Ayurveda Integr. Med. 8 (4) (2017) 238–246.
[273] M. Figueiredo-Gonzalez, P. Valentao, P.B. Andrade, Tomato plant leaves: from by-products to the management of enzymes in chronic diseases, Ind. Crop. Prod. 94 (2016) 621–629.
[274] G. Fuxing, Extraction of red pigment from amaranth and its stability, J. Xingyang Agric. Coll. 3 (2000).
[275] M. Rahmatullah, M. Hosain, S. Rahman, M. Akter, F. Rahman, F. Rehana, M. Munmun, M.A. Kalpana, Antihyperglycemic and antinociceptive activity evaluation of methanolic extract of whole plant of *Amaranthus tricolor* L. (Amaranthaceae), Afr. J. Tradit. Complement. Alternat. Med. 10 (5) (2013) 408–411.
[276] M. Bayani, M. Ahmadi-Hamedani, A. Jebelli Javan, Study of hypoglycemic, hypocholesterolemic and antioxidant activities of Iranian *Mentha spicata* leaves aqueous extract in diabetic rats, Iran. J. Pharm. Res. 16 (Suppl.) (2017) 75–82.
[277] M.A. Khan, M. Singh, M.S. Khan, W. Ahmad, A.K. Najmi, S. Ahmad, Alternative approach for mitigation of doxorubicin-induced cardiotoxicity using herbal agents, Curr. Clin. Pharmacol. 9 (3) (2014) 288–297.
[278] G.N. Rao, K. Balaswamy, K. Srinivasulu, G. Sulochanamma, G. Venkateswaran, P.G.P. Rao, Development of an instant spice mix from gongura (*Hibiscus cannabinus* L.) for deep fat fried snacks and evaluation of its antioxidant activity, Indian J. Tradit. Knowl. 16 (3) (2017) 490–497.
[279] F.S. Predes, A.L.T.G. Ruiz, J.E. Carvalho, M.A. Foglio, H. Dolder, Antioxidative and in vitro antiproliferative activity of *Arctium lappa* root extracts, BMC Complement. Altern. Med. 11 (1) (2011) 25.
[280] L.M. K'Osambo, E.E. Carey, A.K. Misra, J. Wilkes, V. Hagenlmana, Influence of age, farming site, and boiling on pro-vitamin A content in sweet potato (*Ipomoea batats* (L.) Lam.) storage roots, J. Food Technol. Africa 4 (3) (1999).
[281] A. Betancor-Fernández, A. Pérez-Gálvez, H. Sies, W. Stahl, Screening pharmaceutical preparations containing extracts of turmeric rhizome, artichoke leaf, devil's claw root and garlic or salmon oil for antioxidant capacity, J. Pharm. Pharmacol. 55 (7) (2003) 981–986.
[282] R. Harish, S. Divakar, A. Srivastava, T. Shivanandappa, Isolation of antioxidant compounds from the methanolic extract of the roots of *Decalepis hamiltonii* (Wight and Arn.), J. Agric. Food Chem. 53 (20) (2005) 7709–7714.
[283] D. Maass, J. Arango, F. Wüst, P. Beyer, R. Welsch, Carotenoid crystal formation in Arabidopsis and carrot roots caused by increased phytoene synthase protein levels, PLoS One 4 (7) (2009) e6373.
[284] R.B. El-Houri, D. Kotowska, K.B. Christensen, S. Bhattacharya, N. Oksbjerg, G. Wolber, K. Kristiansen, L. P. Christensen, Polyacetylenes from carrots (*Daucus carota*) improve glucose uptake in vitro in adipocytes and myotubes, Food Funct. 6 (7) (2015) 2135–2144.
[285] M. Zahoor, A.B. Shah, S. Gul, S. Amin, HPLC-UV analysis of antioxidants in *Citrus sinensis* stem and root extracts, J. Chem. Soc. Pak. 40 (3) (2018).
[286] R. Moresco, V.G. Uarrota, A. Pereira, M. Tomazzoli, E.D.C. Nunes, L.A.M. Peruch, C. Costa, M. Rocha, M. Maraschin, Carotenoid Analysis of Cassava Genotypes Roots (*Manihot esculenta* Crantz) Cultivated in Southern Brazil Using Chemometric Tools, Springer, 2015.
[287] S. Takshak, S.B. Agrawal, Alterations in metabolite profile and free radical scavenging activities of *Withania somnifera* leaf and root extracts under supplemental ultraviolet-B radiation, Acta Physiol. Plant. 37 (12) (2015) 260.
[288] C.R. de Menezes Peixoto, S. Fraga, J. da Rosa Justim, M.S. Gomes, D.G. Carvalho, J.A. Jarenkow, N.F. de Moura, Voltammetric determination of total antioxidant capacity of *Bunchosia glandulifera* tree extracts, J. Electroanal. Chem. 799 (2017) 519–524.
[289] V.J.H. Sumathy, A study on the ant crude extract and carotenoid pigments from fruits, Vegetables 41 (2016) 1–13.
[290] S. Machmudah, S. Winardi, M. Sasaki, M. Goto, N. Kusumoto, K. Hayakawa, Lycopene extraction from tomato peel by-product containing tomato seed using supercritical carbon dioxide, J. Food Eng. 108 (2) (2012) 290–296.
[291] S. Bakir, S. Kamiloglu, M. Tomas, E. Capanoglu, Tomato polyphenolics: putative applications to health and disease, in: Polyphenols: Mechanisms of Action in Human Health and Disease, Elsevier, 2018, pp. 93–102.

[292] V. Vats, S.P. Yadav, N.R. Biswas, J.K. Grover, Anti-cataract activity of *Pterocarpus marsupium* bark and *Trigonella foenum-graecum* seeds extract in alloxan diabetic rats, J. Ethnopharmacol. 93 (2–3) (2004) 289–294.
[293] R. Maiti, D. De, D. Ghosh, Antidiabetic effect of *N*-hexane fraction of hydro-methanolic extract of *Tamarindus indica* Linn. seed in streptozotocin-induced diabetic rat: a correlative approach with in vivo and in vitro anti-oxidant activities, Int. J. Pharm. Sci. Res. 9 (5) (2018) 1821–1830.
[294] P. Mittal, V. Gupta, G. Kaur, A.K. Garg, A. Singh, Phytochemistry and pharmacological activities of *Psidium guajava*: a review, Int. J. Pharm. Sci. Res. 1 (9) (2010) 9–19.
[295] J.A. Nowshehri, Z.A. Bhat, M.Y. Shah, Blessings in disguise: bio-functional benefits of grape seed extracts, Food Res. Int. 77 (2015) 333–348.
[296] A. Pintea, HPLC analysis of carotenoids in four varieties of *Calendula officinalis* L. flowers, Acta Biol. Szeged. 47 (1–4) (2003) 37–40.
[297] R.L. Skelton, Q. Yu, R. Srinivasan, R. Manshardt, P.H. Moore, R. Ming, Tissue differential expression of lycopene β-cyclase gene in papaya, Cell Res. 16 (8) (2006) 731.
[298] S. Siriamornpun, O. Kaisoon, N. Meeso, Changes in colour, antioxidant activities and carotenoids (lycopene, β-carotene, lutein) of marigold flower (*Tagetes erecta* L.) resulting from different drying processes, J. Funct. Foods 4 (4) (2012) 757–766.
[299] J.A. Trujillo-Hdz, Y. Cárdenas-Conejo, P.E. Turriza, M. Aguilar-Espinosa, V. Carballo-Uicab, L.E. Garza-Caligaris, L. Comai, R. Rivera-Madrid, Functional polymorphism in lycopene beta-cyclase gene as a molecular marker to predict bixin production in *Bixa orellana* L. (achiote), Mol. Breed. 36 (9) (2016) 135.
[300] H.J. Busscher, M.W. Dodds, A. Maitra, S. Wessel, H.C. Van der Mei, Magnolia Bark Extract as a Hydrophobic Ligand for Preferential Removal of Gram Negative Bacteria from the Oral Cavity, Google Patents, (2018).
[301] I. Zhelev, K. Georgiev, I. Dimitrova-Dyulgerova, Carotenoid profile of *Ailanthus altissima* stem bark, in-vitro antioxidant and antineoplastic activities, World J. Pharm. Res. 5 (3) (2016) 1816–1825.
[302] L. Barros, M.-J. Ferreira, B. Queirós, I.C.F.R. Ferreira, P. Baptista, Total phenols, ascorbic acid, β-carotene and lycopene in Portuguese wild edible mushrooms and their antioxidant activities, Food Chem. 103 (2) (2007) 413–419.
[303] U.K. Sharma, A.K. Sharma, A. Gupta, R. Kumar, A. Pandey, A.K. Pandey, Pharmacological activities of cinnamaldehyde and eugenol: antioxidant, cytotoxic and anti-leishmanial studies, Cell. Mol. Biol. 63 (2017) 73–78.
[304] A. Singh, Y.R. Neupane, B.P. Panda, K. Kohli, Lipid based nanoformulation of lycopene improves oral delivery: formulation optimization, ex vivo assessment and its efficacy against breast cancer, J. Microencapsul. 34 (4) (2017) 416–429.
[305] W. Li, M. Yalcin, Q. Lin, M.-S.M. Ardawi, S.A. Mousa, Self-assembly of green tea catechin derivatives in nanoparticles for oral lycopene delivery, J. Control. Release 248 (2017) 117–124.
[306] USDA, Foods Highest in Lycopene, Nutrition Data, Database UN: Conde Nast, 2014. nutritiondatacom.
[307] LPI, α-Carotene, β-Carotene, β-Cryptoxanthin, Lycopene, Lutein, and Zeaxanthin, University OS, Linus Pauling Institute: Micronutrient Information Center, Oregon, 2019.
[308] REKZE, The Amazing Benefits of Lycopene for Hair, REKZE Laboratories, 2016.
[309] P.K. Farris, N. Rogers, A. McMichael, S. Kogan, A novel multi-targeting approach to treating hair loss, using standardized nutraceuticals, J. Drugs Dermatol. 16 (11) (2017) 141–148.
[310] G. Ablon, S. Kogan, A six-month, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of a nutraceutical supplement for promoting hair growth in women with self-perceived thinning hair, J. Drugs Dermatol. 17 (5) (2018) 558–565.
[311] E.J. van Zuuren, Z. Fedorowicz, J. Schoones, Interventions for female pattern hair loss, Cochrane Database Syst Rev. 5 (2016) CD007628.
[312] A. Adil, M. Godwin, The effectiveness of treatments for androgenetic alopecia: A systematic review and meta-analysis. J Am Acad Dermatol 77 (1) (2017) 136–141, https://doi.org/10.1016/j.jaad.2017.02.054.
[313] L.L. Levy, J.J. Emer, Female pattern alopecia: current perspectives, Int. J. Women's Health 29 (5) (2013) 541–556.
[314] N. Weger, T. Schlake, Igf-I signalling controls the hair growth cycle and the differentiation of hair shafts, J. Invest. Dermatol. 125 (2005) 873–882.
[315] Healthline, Male Pattern Baldness, Healthline, 2018. https://www.healthline.com/health/male-pattern-baldness;.
[316] G. Fabbrocini, M. Cantelli, A. Masarà, M.C. Annunziata, C. Marasca, S. Cacciapuoti, Female pattern hair loss: a clinical, pathophysiologic, and therapeutic review, Int. J. Womens Dermatol. 4 (4) (2018) 203–211.

[317] V. Rathi, J.C. Rathi, S. Tamizharasi, A.K. Pathak, Plants used for hair growth promotion: a review, Phcog. Rev. 2 (2008) 185–187.
[318] MPB-Research, Lycopene—A 5 Alpha Reductase Inhibitor, https://wwwhairloss-researchorg/LinkUpdateLycopene1-08htmlResearch MPB, 2017.
[319] ECURI, Tomatoes and do they really affect a healthy hair growth? in: ECURI Cosmetics, 2016.
[320] B.L. Woolbright, H. Jaeschke, Novel insight into mechanisms of cholestatic liver injury, World J. Gastroenterol. 18 (2012) 4985–4993.
[321] S.F. Assimakopoulos, C.E. Vagianos, G. Zervoudakis, K.S. Filos, C. Georgiou, V. Nikolopoulou, C.D. Scopa, Gut regulatory peptides bombesin and neurotensin reduce hepatic oxidative stress and histological alterations in bile duct ligated rats, Regul. Pept. 120 (2004) 185–193.
[322] M. Dirlik, H. Canbaz, D. Dusmez Apa, M. Çaglikulekci, F. Yaylak, E. Balli, L. Tamer, A. Kanik, S. Aydin, The monitoring of progress in apoptosis of liver cells in bile duct-ligated rats, Turk. J. Gastroenterol. 20 (2009) 247–256.
[323] L. Bignotto, J. Rocha, B. Sepodes, M. Eduardo-Figueira, R. Pinto, M. Chaud, J. De Carvalho, H. Moreno, H. Mota-Filipe, Anti-inflammatory effect of lycopene on carrageenan-induced paw oedema and hepatic ischaemia-reperfusion in the rat, Br. J. Nutr. 102 (2009) 126–133.
[324] A. Cruz, F.J. Padillo, I. Tunez, C. Munoz, J. Granados, C. Pera-Madrazo, P. Montilla, Melatonin protects against renal oxidative stress after obstructive jaundice in rats, Eur. J. Pharmacol. 425 (2001) 135–139.
[325] B.L. Pool-Zobel, A. Bub, H. Muller, I. Wollowski, G. Rechkemmer, Consumption of vegetables reduces genetic damage in humans: first results of a human intervention trial with carotenoid-rich foods, Carcinogenesis 18 (1997) 1847–1850.
[326] A. Schecter, N. Malik, D. Haffner, S. Smith, T.R. Harris, O. Paepke, L. Birnbaum, Bisphenol A (BPA) in U.S. food, Environ. Sci. Technol. 44 (2010) 9425–9430.
[327] H.H. Le, E.M. Carlson, J.P. Chua, S.M. Belcher, Bisphenol A is released from polycarbonate drinking bottles and mimics the neurotoxic actions of estrogen in developing cerebellar neurons, Toxicol. Lett. 176 (2008) 149–156.
[328] W.M. Abdel-Waha, Thymoquinone attenuates toxicity and oxidative stress induced by bisphenol A in liver of male rats, Pak. J. Biol. Sci. 17 (2014) 1152–1160.
[329] H. Masuno, T. Kidani, K. Sekiya, K. Sakayama, T. Shiosaka, H. Yamamoto, K. Honda, Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes, J. Lipid Res. 43 (2002) 676–684.
[330] S. Agarwal, A.V. Rao, Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study, Lipids 33 (10) (1998) 981–984.
[331] J.R. Mein, F. Lian, X.D. Wang, Biological activity of lycopene metabolites: implications for cancer prevention, Nutr. Rev. 66 (12) (2008) 667–683.
[332] W. Stahl, H. Sies, Carotenoids and flavonoids contribute to nutritional protection against skin damage from sunlight, Mol. Biotechnol. 37 (2007) 26–30.
[333] C. Liu, R. Wang, B. Zhang, C. Hu, H. Zhang, Protective effects of lycopene on oxidative stress, proliferation and autophagy in iron supplementation rats, Biol. Res. 46 (2013) 189–200.
[334] U.K. Sharma, R. Kumar, R. Ganguly, A. Gupta, A.K. Sharma, A.K. Pandey, Cinnamaldehyde, an active component of cinnamon provides protection against food colour induced oxidative stress and hepatotoxicity in albino Wistar rats, Vegetos 31 (2018) 123–129.
[335] H.B. Lee, M.R. Yu, J.S. Song, H. Ha, Reactive oxygen species amplify protein kinase C signaling in high glucose-induced fbronectin expression by human peritoneal mesothelial cells, Kidney Int. 65 (2004) 1170–1179.
[336] A.C. Bandeira, R.C. da Silva, J.V.J. Rossoni, V.P. Figueiredo, A. Talvani, S.D. Cangussu, F.S. Bezerra, D.C. Costa, Lycopene pretreatment improves hepatotoxicity induced by acetaminophen in C57BL/6 mice, Bioorg. Med. Chem. 16 (2016) 31052–31055.
[337] A. Yefsah-Idres, Y. Benazzoug, A. Otman, A. Latour, S. Middendorp, N. Janel, Hepatoprotective effects of lycopene on liver enzymes involved in methionine and xenobiotic metabolism in hyperhomocysteinemic rats, Food Funct. 15 (2016) 2862–2869.
[338] G. Marchesini, M. Brizi, A.M. Morselli-Labate, G. Bianchi, E. Bugianesi, A.J. McCullough, G. Forlani, N. Melchionda, Association of nonalcoholic fatty liver disease with insulin resistance, Am. J. Med. 107 (1999) 450–455.

[339] E. Fabbrini, B.S. Mohammed, F. Magkos, K.M. Korenblat, B.W. Patterson, S. Klein, Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease, Gastroenterology 134 (2008) 424–431.
[340] T. Wilkins, A. Tadkod, I. Hepburn, R.R. Schade, Nonalcoholic fatty liver disease: diagnosis and management, Am. Fam. Phys. 88 (2013) 35–42.
[341] M. Masarone, A. Federico, L. Abenavoli, C. Loguercio, M. Persico, Non-alcoholic fatty liver: epidemiology and natural history, Rev. Recent Clin. Trials 9 (2014) 126–133.
[342] J.H. Tinkler, F. Bohm, W. Schalch, T.G. Truscott, Dietary carotenoids protect human cells from damage, J. Photochem. Photobiol. B 26 (1994) 283–285.
[343] F. Bohm, J.H. Tinkler, T.G. Truscott, Carotenoids protect against cell membrane damage by the nitrogen dioxide radical, Nat. Med. 1 (1995) 98–99.
[344] H.Y. Gao, J. Huang, H.Y. Wang, X.W. Du, S.M. Cheng, Y. Han, L.F. Wang, G.Y. Li, J.H. Wang, Protective effect of Zhuyeqing liquor, a Chinese traditional health liquor, on acute alcohol-induced liver injury in mice, J. Inflamm. 10 (2013) 3.
[345] W. Jiang, M.H. Guo, X. Hai, Hepatoprotective and antioxidant effects of lycopene on non-alcoholic fatty liver disease in rat, World J. Gastroenterol. 22 (2016) 10180–10188.
[346] A. Wender, G. Tiegs, Leukotriene D4 mediates galactosamine/endotoxin-induced hepatitis in mice, Biochem. Pharmacol. 36 (1867) 1867–1871.
[347] Y. Endo, T. Kikuchi, M. Nakamura, Ornithine and histidine decarboxylase activities in mice sensitized to endotoxin, interleukin-1 or tumour necrosis factor by D-galactosamine, Br. J. Pharmacol. 107 (1992) 888–894.
[348] A. Manabe, C.C. Cheng, Y. Egashira, T. Ohta, H. Sanada, Protective effect of *Picrorhiza kurroa* on mitochondrial glutathione antioxidant system in D-galactosamine-induced hepatitis in rats, J. Nutr. Sci. Vitaminol. 42 (1996) 121–132.
[349] C.C. Tsai, S.T. Kao, C.T. Hsu, C.C. Lin, J.S. Lai, J.G. Lin, Ameliorative effect of traditional Chinese medicine prescriptions on alpha naphthylisothiocyanate and carbon-tetrachloride induced toxicity in rats, Am. J. Chin. Med. 25 (1997) 185–196.
[350] H.L. Hu, R.D. Chen, Changes in free radicals, trace elements and neurophysiological function in rats with liver damage induced by galactosamine, Biol. Trace Elem. Res. 34 (1992) 19–25.
[351] N. Chikhi, N. Holic, G. Guellaen, Y. Laperche, Gamma-glutamyl transpeptidase gene organization and expression: a comparative analysis in rat, mouse, pig and human species, Comp. Biochem. Physiol. B 122 (1999) 367–380.
[352] I. Paduraru, A. Saramet, G.H. Danica, Antioxidant action of a new flavonoic derivative in acute carbon tetrachloride intoxication, Eur. J. Drug Metab. Pharmacokinet. 21 (1996) 1–16.
[353] Y. Wang, L.M. Ausman, A.S. Greenberg, R.M. Russell, X.D. Wang, Dietary lycopene and tomato extract supplementations inhibit nonalcoholic steatohepatitis-promoted hepatocarcinogenesis in rats, Int. J. Cancer 126 (2010) 1788–1796.
[354] L.P. Toledo, T.P. Ong, A.L. Pinho, A. Jordao Jr., H. Vanucchi, F.S. Moreno, Inhibitory effects of lutein and lycopene on placental glutathione *S*-transferase positive preneoplastic lesions and DNA strand breakage induced in Wistar rats by the resistant hepatocyte model of hepatocarcinogenesis, Nutr. Cancer 47 (2003) 62–69.
[355] P. Astorg, S. Gradelet, R. Berges, M. Suschetet, Dietary lycopene decreases the initiation of liver preneoplastic foci by diethylnitrosamine in the rat, Nutr. Cancer 29 (1997) 60–68.
[356] S.D. Aust, B.A. Swingen, The role of iron in enzymatic lipid peroxidation., in: W.A. Pryor (Ed.), Free Radicals in Biology, vol. 5, Academic, New York, 1982, , pp. 1–28.
[357] A. Agarwal, A. Hamada, S.C. Esteves, Insight into oxidative stress in varicocele-associated male infertility: part 1, Nat. Rev. Urol. 9 (2012) 678–690.
[358] P. Gharagozloo, R.J. Aitken, The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy, Hum. Reprod. 26 (2011) 1628–1640.
[359] M. Kelkel, M. Schumacher, M. Dicato, M. Diederich, Antioxidant and anti-proliferative properties of lycopene, Free Radic. Res. 45 (8) (2011) 925–940.
[360] P. Palan, R. Naz, Changes in various antioxidant levels in human seminal plasma related to immunofertility, Arch. Androl. 36 (1996) 139–143.
[361] A. Goyal, G.H. Delves, M. Chopra, B.A. Lwaleed, A.J. Cooper, Can lycopene be delivered into semen via prostasomes? In vitro incorporation and retention studies, Int. J. Androl. 19 (2006) 528–533.

[362] A. Agarwal, L.H. Sekhon, The role of antioxidant therapy in the treatment of male infertility, Hum. Fertil. (Camb.) 13 (2010) 217–225.
[363] A. Goyal, M. Chopra, B.A. Lwaleed, B. Birch, A.J. Cooper, The effects of dietary lycopene supplementation on human seminal plasma, BJU Int. 99 (2007) 1456–1460.
[364] A. Zini, M. San Gabriel, J. Libman, Lycopene supplementation in vitro can protect human sperm deoxyribonucleic acid from oxidative damage, Fertil. Steril. 94 (2010) 1033–1036.
[365] A. Ateşşahin, I. Karahan, B. Türk, S. Gür, S. Yilmaz, A.O. Ceribaşi, Protective role of lycopene on cisplatin-induced changes in sperm characteristics, testicular damage and oxidative stress in rats, Reprod. Toxicol. 21 (2006) 42–47.
[366] G. Türk, A. Ateşşahin, M. Sönmez, A. Yüce, A.O. Ceribaşi, Lycopene protects against cyclosporine A-induced testicular toxicity in rats. Theriogenology 67 (4) (2007) 778–785, https://doi.org/10.1016/j.theriogenology.2006.10.013.
[367] D. Durairajanayagam, A. Agarwal, C. Ong, P. Prashast, Lycopene and male infertility, Asian J. Androl. 16 (2014) 420.
[368] A.V. Rao, S. Agarwal, Role of lycopene as antioxidant carotenoid in the prevention of chronic diseases: a review, Nutr. Res. 19 (1999) 305–323.
[369] G. Krishnamoorthy, K. Selvakumar, P. Elumalai, P. Venkataraman, J. Arunakaran, Protective role of lycopene on polychlorinated biphenyls (aroclor 1254)-induced adult rat sertoli cell dysfunction by increased oxidative stress and endocrine disruption, Biomed. Prev. Nutr. 1 (2011) 116–125.
[370] I. Oborna, K. Malickova, H. Fingerova, J. Brezinova, P. Horka, et al., A randomized controlled trial of lycopene treatment on soluble receptor for advanced glycation end products in seminal and blood plasma of normospermic men, Am. J. Reprod. Immunol. 66 (2011) 179–184.
[371] A.J. Hamada, B. Montgomery, A. Agarwal, Male infertility: a critical review of pharmacologic management, Expert Opin. Pharmacother. 13 (2012) 2511–2531.
[372] M.P. Rosato, G. Centoducati, M.P. Santacroce, N. Iaffaldano, Effects of lycopene on in vitro quality and lipid peroxidation in refrigerated and cryopreserved Turkey spermatozoa, Br. Poult. Sci. 53 (2012) 545–552.
[373] S.K. Choi, J.S. Seo, Lycopene supplementation suppresses oxidative stress induced by a high fat diet in gerbils, Nutr. Res. Pract. 7 (2013) 26–33.
[374] M.N. Bucak, M.B. Ataman, N. Başpınar, O. Uysal, M. Taşpınar, A. Bilgili, C. Öztürk, Ş. Güngör, M.E. İnanç, E. Akal, Lycopene and resveratrol improve post-thaw bull sperm parameters: sperm motility, mitochondrial activity and DNA integrity, Andrologia 47 (5) (2015) 545–552.
[375] E. Tvrdá, A. Kováčik, E. Tušimová, D. Paál, A. Mackovich, J. Alimov, N. Lukáč, Antioxidant efficiency of lycopene on oxidative stress-induced damage in bovine spermatozoa, J. Anim. Sci. Biotechnol. 7 (1) (2016) 50.
[376] N. Mohanty, S. Kumar, A. Jha, R. Arora, Management of idiopathic oligoasthenospermia with lycopene, Indian J. Urol. 18 (2001) 57–61.
[377] M.G. Mangiagalli, P.A. Martino, T. Smajlovic, L. Guidobono Cavalchini, S.P. Marelli, Effect of lycopene on semen quality, fertility and native immunity of broiler breeder, Br. Poult. Sci. 51 (2010) 152–157.
[378] M.G. Mangiagalli, V. Cesari, S. Cerolini, F. Luzi, L. Toschi, Effect of lycopene supplementation on semen quality and reproductive performance in rabbit, World Rabbit Sci. 20 (2012) 141–148.
[379] H.A. Aly, H.A. El-Beshbishy, Z.M. Banjar, Mitochondrial dysfunction induced impairment of spermatogenesis in LPS-treated rats: modulatory role of lycopene, Eur. J. Pharmacol. 677 (2012) 31–38.
[380] S. Devaraj, S. Mathur, A. Basu, H.H. Aung, V.T. Vasu, et al., A dose-response study on the effects of purified lycopene supplementation on biomarkers of oxidative stress, J. Am. Coll. Nutr. 27 (2008) 267–273.
[381] P.D. Sarkar, T. Gupt, A. Sahu, Comparative analysis of lycopene in oxidative stress, J. Assoc. Physicians India 60 (2012) 17–19.
[382] J.L. Rowles III, K.M. Ranard, J.W. Smith, R. An, J.W. Erdman Jr., Increased dietary and circulating lycopene are associated with reduced prostate cancer risk: a systematic review and meta-analysis, Prostate Cancer Prostatic Dis. 20 (4) (2017) 361.
[383] Y. Wang, R. Cui, Y. Xiao, J. Fang, Q. Xu, Effect of carotene and lycopene on the risk of prostate cancer: a systematic review and dose-response meta-analysis of observational studies, PLoS One 10 (9) (2015) e0137427.
[384] P. Chen, W. Zhang, X. Wang, K. Zhao, D.S. Negi, L. Zhuo, M. Qi, X. Wang, X. Zhang, Lycopene and risk of prostate cancer: a systematic review and meta-analysis, Medicine 94 (33) (2015).

[385] L.M. Alda, I. Gogoasa, D.M. Bordean, I. Gergen, S. Alda, C. Moldovan, L. Nita, Lycopene content of tomatoes and tomato products, J. Agroaliment. Process. Technol. 15 (4) (2009) 540.
[386] K.E. Senkus, L. Tan, K.M. Crowe-White, Lycopene and metabolic syndrome: a systematic review of the literature, Adv. Nutr. (2018).
[387] H.M. Cheng, G. Koutsidis, J.K. Lodge, A.W. Ashor, M. Siervo, J. Lara, Lycopene and tomato and risk of cardiovascular diseases: a systematic review and meta-analysis of epidemiological evidence, Crit. Rev. Food Sci. Nutr. 1 (2017) 1–8.
[388] J. Chen, Y. Song, L. Zhang, Effect of lycopene supplementation on oxidative stress: an exploratory systematic review and meta-analysis of randomized controlled trials, J. Med. Food 16 (5) (2013) 361–374.
[389] D. Ilic, M. Misso, Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review, Maturitas 72 (4) (2012) 269–276.
[390] D. Ilic, K.M. Forbes, C. Hassed, Lycopene for the prevention of prostate cancer, Cochrane Database Syst. Rev. 11 (2011).
[391] S. Zhao, P.A. Tuan, J.K. Kim, W.T. Park, Y.B. Kim, et al., Molecular characterization of carotenoid biosynthesis genes and carotenoids accumulation in *Lycium chinense*, Molecules 19 (2014) 11250–11262.
[392] M. Butnariu, Methods of analysis (extraction, separation, identification and quantification) of carotenoids from natural products. J. Ecosyst. Ecography 6 (2016) 193, https://doi.org/10.4172/2157-7625.1000193.
[393] M.V. Butnariu, C.V. Giuchici, The use of some nanoemulsions based on aqueous propolis and lycopene extract in the skin's protective mechanisms against UVA radiation, J. Nanobiotechnol. 9 (2011) 3.
[394] G.A. Armstrong, J.E. Hearst, Carotenoids2: genetics and molecular biology of carotenoid pigment biosynthesis, FASEB J. 10 (1996) 228–237.
[395] I.R. Bunghez, M. Raduly, S. Doncea, I. Aksahin, R.M. Ion, Lycopene determination in tomato by different spectral techniques (UV-VIS, FTIR and HPLC), Dig. J. Nanomater. Biostruct. 6 (3) (2011) 1349–1356.
[396] S. Prabhu, P.D. Rekha, A.B. Arun, Zeaxanthin biosynthesis by members of the genus uricauda, Pol. J. Microbiol. 63 (2014) 115–119.
[397] N. Corniani, E.D. Velini, F.M. Silva, N.P. Nanayakkara, M. Witschel, Noval bioassay for the discovery of inhibitors of the 2-c-methyl-D-erythritol4-phosphate (MEP) and terpenoid pathways. Leading to carotenoid biosynthesis, PLoS One 9 (2014) e103704.
[398] A. Altemimi, D.A. Lightfoot, M. Kinsel, D.G. Watson, Employing response surface methodology for the optimization of ultrasound assisted extraction of lutein and β-carotene from Spinach, Molecules 20 (2015) 6611–6625.
[399] D. Naviglio, T. Caruso, P. Iannece, A. Aragon, A. Santini, Characterization of high purity lycopene from tomato wastes using a new pressurized extraction approach. J. Agric. Food Chem. 56 (15) (2008) 6227–6231, https://doi.org/10.1021/jf703788c (Epub 2008 June 20).
[400] N. Aghel, Z. Ramezani, S. Amirfakhrian, Isolation and quantification of lycopene from tomato cultivated in Dezfoul, Iran, Jundishapur J. Nat. Pharm. Prod. 6 (1) (2011) 9–15.
[401] K. Frohlich, J. Conrad, A. Schmid, D.E. Breithaupt, V. Bohm, Isolation and structural elucidation of different geometrical isomers of lycopene. Int. J. Vitam. Nutr. Res. 77 (6) (2007) 369–375, https://doi.org/10.1024/0300-9831.77.6.369.