Chapter 3
Tomato (Lycopene and β-Carotene) and Cancer

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Abstract Consuming fruits and vegetables regularly is able to decrease the risks of cancer, increase longevity and improve the quality of life. Among them, tomatoes are particularly interesting for their potential anticancer activity. In fact, the main carotenoids in tomatoes, namely lycopene and β-carotene, are responsible for the anti-cancer and anti-tumoral activities, particularly against prostate and gastric cancers. These carotenoids had an anti-proliferative activity against cancer cells by inhibiting cell viability and angiogenesis, activating apoptosis and decreasing metastasis. This chapter highlights the biochemical properties and mechanisms of action of lycopene and β-carotene and their preventive and curative effects on different types of cancer and discusses the main findings of epidemiological, animal and clinical studies.

Keywords Tomato · Lycopene · β-carotene · Anticancer activity · Antioxidant · Bioavailability · Pro-vitamin A

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1 Introduction

To guarantee a balanced diet, it is mandatory to ensure a regular daily intake of fruits, vegetables and non-refined cereals with a modest consumption of red meat, poultry, fish, sugar and dairy products (De Alvarenga et al. 2018). In fact, it has been proved that consuming fruits and vegetables can significantly decrease risks related to chronic diseases, increase longevity and improve the quality of life. A diet based on fruits and vegetables could be effective to prevent cardiovascular diseases, osteoporosis, diabetes and various types of cancer (Rao and Rao 2007). Several cancer institutes and health organizations have recommended to increase the dietary intake of citrus, fruits and vegetables (mainly yellow and green ones and those with high contents of vitamins A and C) in order to reduce cancer risks (Barber and Barber 2002). Fruits and vegetables owe their beneficial role to health promoting compounds such as vitamins, minerals and phytochemicals, particularly polyphenols and carotenoids. Tomatoes are one of the richest fruits in carotenoids and lycopene is considered to be the most prevalent one, being pursued by β-carotene. Several studies based on *in vitro*, animal and clinical investigations, with considerable results, revealed that carotenoids are in charge for the biological activity of tomato fruit (Desmarchelier et al. 2018). These activities are related to the provitamin A activities characteristic of some carotenoids like β-carotene, α-carotene and β-cryptoxanthin and the well-established antioxidant effect of tomato carotenoids, mainly lycopene. Carotenoids also show biological activities which are not related to their antioxidant power, such as modulator agents of inflammation or ligands for nuclear receptor (Desmarchelier et al. 2018). The biological activities of tomatoes and tomato-based products were essentially associated with lycopene, in combination with other carotenoids present in fresh tomatoes and the other nutrients and molecules present in processed tomato-based products and meals (Frohlich et al. 2006; Desmarchelier et al. 2018).

Thanks to their various biological activities, carotenoids provided by a tomato rich diet, whether consumed directly or through tomato-based products, act as a natural drug for curing and preventing cancers. The Mediterranean diet, for example, is abundantly based on tomatoes and derivatives due to their availability throughout the year and their affordability. This diet has proven health benefits, especially in preventing chronic and degenerative troubles due to its high content on phytochemicals. This observation was approved by a prospective cohort study dealing with the prevention of cardiovascular diseases using the Mediterranean diet (De Alvarenga et al. 2018). Moreover, Canene-Adams et al. (2007) studied the effect of tomato intake on preventing and treating cancer and found that rats consuming tomatoes 5 to 7 times per week had a decrease of 30 to 40% in risk related to prostate cancer. Even though the beneficial effect of tomato consumption on human health was evidenced through several studies, the results of clinical assays remain controverted and this may be related to many factors such as sampling method, subject attributes (age, gender, chronic diseases, etc.) and the method used to quantify the anticancer activity in the clinical assay.

In this context, the present chapter aims at highlighting the anticancer activity of tomato fruit with a special focus on lycopene and β-carotene, the two entities mostly responsible for this biological activity. The mechanisms of action of these phytochemicals on curing and preventing cancers are particularly developed. The results of mainly epidemiological, animal and clinical studies are summarized and their limits are highlighted.

2 Tomatoes: Botanical Aspect, Composition and Main Properties

Tomato (*Lycopersicon esculentum* Mill., from its old nomenclature *Solanum lycopersicum* L.) is a member of the *Solanaceae* family, the genus of *Solanum* and the section of *Lycopersicon*. Tomato is characterized by relevant traits like its fleshy fruit, sympodial branching and compound leaves (Naika et al. 2005; Costa and Heuvelink 2018). Fruit shape could be round, oval or flattened depending on the variety and the fruit color can change from green to red as a function of ripeness stage. Tomato is an annual plant that grows in various climate conditions from temperate to tropical but it requires cool and dry climate for high quality fruits. Tomato is originated in South America and was brought to Europe by Spanish then introduced to Asia, Africa and Middle East (Naika et al. 2005). Tomato has immense economic importance as it is a short duration crop with high production yield, leading to a continuous expansion of tomato cultivation area. This latter reached 4.3 million hectares in 2014, mostly held in China, India, USA, Turkey and Egypt. In the same year, the global production of tomatoes amounted to 171 million tons and this production was mostly carried out by China, European Union, India, USA and Turkey (Costa and Heuvelink 2018).

Tomatoes are considered to be the second most valuable crop in the world, after potatoes, and are essential for human nutrition and diet. In fact, tomatoes can be eaten in different forms whether fresh or processed (puree, juice, paste, pickled or dried). They can also be consumed as tomato-based products such as ketchup, sauce, soup or complex dishes. The largest worldwide tomato consumer is China, followed by European Union, Mediterranean Africa, USA, Mexico and Canada (Costa and Heuvelink 2018).

Tomatoes owe their nutritional attributes to their composition on nutrients and phytochemicals. They present high amounts of vitamins, minerals and fibers and are considered as the main source of carotenoids. In fact, tomato is a natural source of vitamin A, thiamine (B1), riboflavin (B2), pantothenic acid (B3), ascorbic acid (C), folic acid, α-tocopherol (E), biotin, and niacin (Ibrahim et al. 2019).

Today, various types of tomato fruits are available (grape, cherry, plum, cocktail, round and salad) with different colors (red, yellow, green, orange, brown, black, pink, purple) and with different amounts of phytonutrients. Carotenoids and nutrients contents in tomato fruits depend on their variety and the environmental conditions where they have been cultivated. It has been proved that cherry, cluster and

round tomatoes contain the highest amount of lycopene among 40 varieties of tomato. Moreover, orange tomatoes present higher amounts of vitamin A and carotenoids when compared to red ones. However, lycopene content in yellow tomatoes is 10 times lower than that in red tomatoes (Dorais et al. 2008). Till today, traditional and molecular methods are used by researchers and companies to enhance lycopene and other carotenoids contents in tomato fruit (Dorais et al. 2008; Bogacz-Radomska and Harasym 2018).

Processing and cooking of tomatoes have an effect on the content of phytochemicals whether in a positive way by improving their bioavailability or in a negative way because of thermal degradation, oxidation, loss of nutrient and the formation of toxic compounds (De Alvarenga et al. 2018). Tomato phytochemicals, mainly carotenoids, polyphenols and ascorbic acid, confer to this fruit an interesting antioxidant activity responsible for the observed health benefits. In fact, the mentioned antioxidants help the human body fight free radicals which may lead to undeniable biological activities principally preventing and curing cancers and several neurodegenerative and cardiovascular diseases (Ibrahim et al. 2019).

3 Carotenoids

Carotenoids are hydrophobic molecules synthesized by plants as secondary metabolites or by some microorganisms and algae. Animals are unable to synthetize carotenoids and thus need a daily intake in their diet (Jaswir et al. 2011). Carotenoids are generally characterized by their pigmentation which can range from red to yellow, nevertheless, there are also some colorless carotenoids (like phytoene and phytofluene) (Desmarchelier and Borel 2017). Carotenoids are responsible for light absorption and prevention of cells photo-oxidation during photosynthesis and regulation of membrane fluidity (Barber and Barber 2002; Jaswir et al. 2011). There are more than 750 carotenoids naturally available but, in human diet, we can find about 40 kinds of carotenoids which are basically lycopene, β-carotene, lutein, β-cryptoxanthin, α-carotene, and zeaxanthin (Desmarchelier and Borel 2017; Reboul 2019).

The monomer of carotenoids is isopentenyl diphosphate, which contains 40 atoms of carbon, and carotenoids are represented by the formula $C_{40}H_{56}O_n$, where n ranged from 0 to 6. These chemical entities are derived from phytoene, where geranylgeranyl pyrophosphate (GGPP) undergoes a reductive dimerization following dehydrogenation, cyclization, hydroxylation, oxidation and epoxidation reactions (Jaswir et al. 2011). Most of carotenoids are all-*trans* molecules, but heat treatment may induce *cis*-trans isomerization (Desmarchelier and Borel 2017; Reboul 2019). A mixture of methanol, hexane and acetone solvents can extract carotenoids (Ibrahim et al. 2019). Carotenoid extraction from fruits and vegetables progresses through the steps described in Fig. 3.1. Sometimes, the raw material can be subjected to fermentation to increase the efficiency of carotenoids extraction (Bogacz-Radomska and Harasym 2018). Although their extraction process is simple and easy, the yield of carotenoids extraction is too low and not profitable. In addition, natural carotenoids are very sensitive to external factors so it is very hard to

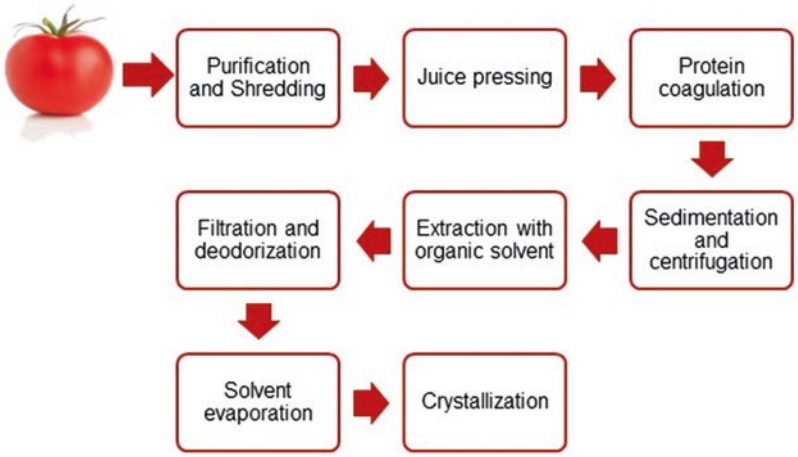

Fig. 3.1 Carotenoid extraction steps from tomato fruit

standardize the dye tones and composition. These drawbacks could be avoided using synthetic carotenoids which are more resistant thanks to pure colorless sugars, proteins or mineral salts, and more commercially viable as they require a small amount of raw material (Bogacz-Radomska and Harasym 2018).

Colored fruits and vegetables contain significant amounts of carotenoids, and tomatoes are particularly an interesting source of these phytochemicals. Among tomato carotenoids, lycopene and β-carotene are the most prevalent ones and are the most effective antioxidant and active compounds. Other carotenoids are significantly available in tomatoes, namely lutein, α-carotene, δ-carotene and γ-carotene. Carotenoid contents vary significantly among tomato species and cultivars. Moreover, the techniques used for cultivation, the location, the period of harvest and the stage of ripeness may highly influence the nutrient and phytochemical composition of tomatoes (Desmarchelier et al. 2018; Ibrahim et al. 2019). Carotenoids are considered as intracellular products and can be detected in the membranes of mitochondria, chloroplasts or endoplasmic reticulum where they are generally associated with lipids or found as hydrophobic structures like membranes (Jaswir et al. 2011).

Carotenoids are distinguished by their antioxidant activity which could be involved in other biological activities such as the prevention of cellular damage. Carotenoids take part in the human antioxidant defense system and can quench singlet oxygen in the same way as tocopherols (Jaswir et al. 2011). In fact, carotenoids present an intrinsic mechanism of defense using oxidative weapons with an unpaired electron called free radicals. This mechanism includes two enzymes, which are glutathoine peroxidase and superoxide dismutase. In this case, carotenoids transfer the unpaired electron of oxygen free radicals putting it into an excited triplet state. Afterward, energy in excess may be converted into heat and, in this case, the carotenoid remains intact and will be able to participate in other reactions of free radical scavenging. Otherwise, the energy in excess may be dissipated by discoloring the carotenoid leading to its decomposition. This process depends on how many double bonds are present in carotenoid structure and the higher is the

carbon-carbon double bonds the more efficient is the carotenoid (Barber and Barber 2002).

The biological activities of carotenoids depend on their intake and circulating levels as well as their bioavailability. Carotenoid bioavailability is a complex phenomenon including several factors such as diet features (intake of fats, fibers, etc.), processing methods and the characteristics of the concerned subjects (age, sex, diseases, etc.). Previous studies demonstrated that single-nucleotide polymorphisms are involved in tomato carotenoids bioavailability (Desmarchelier et al. 2018). Carotenoids are particularly sensitive to high temperatures which is an important factor that induce oxidation, in addition to light and oxygen. Oxidation is considered to be the major cause of carotenoids loss. Nevertheless, cooking process can improve the bioaccessibility of carotenoids by disrupting carotenoid-protein complexes, modifying the integrity of the matrix, increasing carotenoid extraction from food matrix and promoting carotenoid isomerization (De Alvarenga et al. 2018). Carotenoids can be combined with other nutrients and compounds such as coix seed oil and olive oil in order to enhance their bioavailability and bioactivity. However, it has not yet been proven that the mentioned combined systems could be economically viable and suitable for food applications.

Carotenoids belong to lipid family and, once ingested by the body, their destiny follows the gastrointestinal digestion, absorption by enterocytes and distribution in blood circulation of the other lipidic molecules (Desmarchelier et al. 2018). First of all, carotenoids are degraded from food matrix under the effect of digestive enzymes, then transferred using pancreatic lipase, to mixed micelles. This step is called micellization. Secondly, bioaccessible carotenoids are assimilated by enterocytes where this assimilation is facilitated by several proteins. For example, scavenger receptor class B member 1 is a protein, which participate in provitamin A, lycopene, lutein, zeaxanthin, phytoene and phytofluene uptake. These proteins could favor chylomicrons assembly and secretion and thus increase the gradient of carotenoids between the intestinal lumen and absorptive cells (Desmarchelier et al. 2018).

Today, carotenoids are not only exploited as food, feed and nutraceutical ingredients but also in pharmaceutical field after developing structurally diverse carotenoids. From industrial and commercial point of view, carotenoids are applied as natural colorants, dietary supplements, animal feed supplements and even as nutraceuticals for cosmetic and pharmaceutical applications (Jaswir et al. 2011).

4 Lycopene

4.1 Chemistry

The most prevalent carotenoid within red ripe tomatoes is obviously lycopene, which constitutes about 80–90% of its total carotenoids (Dorais et al. 2008). This phytochemical confers to tomato and several other fruits namely guava, watermelon, pink grapefruit and papaya their red color (Barber and Barber 2002). Lycopene content ranges from 0.1μg/g in green tomatoes to 50μg/g in red ripe

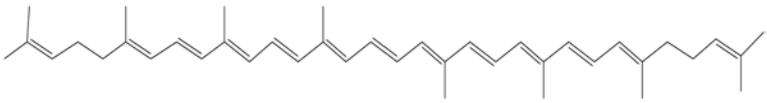

Fig. 3.2 All-*trans* isomer of lycopene

tomatoes and can reach 70μg/g in overripe softened tomatoes (based on fresh weight) (Dorais et al. 2008).

Lycopene is an extremely hydrophobic carotenoid with a linear chemical structure containing 13 conjugated double bonds (Fig. 3.2). Lycopene structure is free from β-ionone ring, which make it deprived of provitamin A activity (Barber and Barber 2002). Lycopene double bonds allow it to isomerize and various *cis* and *trans* isomers can consequently be obtained. Lycopene is considered to be stable during cooking, even though susceptible to isomerization. All-*trans* isomers, the most commonly found in raw materials, are considered to be the most thermodynamically stable (Barber and Barber 2002).

4.2 Bioavailability

In the human body, lycopene is absorbed and then distributed in the plasma lipoproteins. The limited bioavailability of this lipophilic carotenoid is mainly attributed to the high resistance of chloroplasts, where lycopene is found, to gastric and intestinal digestion (Schweiggert et al. 2014). Lycopene serum levels vary among populations and individuals (e.g. dietary intake, structure of the food matrix source, age, food processing, mastication, dietary composition, hormonal and pharmaceutical status) (Clinton 2005). In fact, thermal processing may increase the lycopene availability by improving the accessibility of lipophilic compounds to form lipidic micelles with dietary lipids and bile acids (Jaswir et al. 2011). It has been proven that lycopene presents as *cis*-isomers in processed tomato products (e.g., catsup, tomato juice, tomato puree) is more bioavailable and better absorbed by humans than lycopene from fresh and unprocessed tomatoes (Tan et al. 2010). Indeed, lycopene contents in cooked tomatoes, tomato sauce, ketchup, and fresh tomatoes are 3.7, 6.2, 9.9–13.4, and 0.8–7.4 mg lycopene/100 g (Barber and Barber 2002). Lycopene absorption and bioavailability was improved when consumed with fat as it is a fat-soluble compound (Clinton 2005).

Lycopene is found in *trans*-form in crystalline aggregates in fresh red tomatoes, while it is present as tetra-*cis* isomers in lipid dissolved globular matrices in tangerine tomatoes. The accumulation of tetra-*cis* form of lycopene in place of all-*trans* form in tangerine tomatoes is due to the absence of specific isomerase able of isomerizing poly*cis* to all-*trans*-lycopene and confers orange color to tomatoes (Isaacson et al. 2002). As demonstrated by clinical studies, *cis*-isomers of lycopene were easily absorbed by human intestinal cells and then more bioaccessible than the all-*trans* lycopene, probably due to the higher solubility of the former in the bile acid micelles, their presence in lipid-dissolved globular structures and their better intracellular

stability (Boileau et al. 2002; Unlu et al. 2007; Cooperstone et al. 2015). Cooperstone et al. (2015) reported in a randomized, crossover clinical trial that lycopene bioavailability in orange tomato juice was 8.5 times greater than that in red tomato juice and concluded that orange tomatoes are a rich source of lycopene, causing great levels of lycopene in plasma. More recently, Cooperstone et al. (2017) confirmed the higher lycopene availability from orange tomatoes in an animal model study where mice fed with orange tomato powder, which contained about three time less total lycopene than red tomato powder, displayed increased plasma and skin lycopene concentrations reaching 286–500 nmol/L and 0.23–2 nmol/g, respectively.

4.3 Biological Activities and Modes of Action

Lycopene is known as the most effective antioxidant among tomato carotenoids especially because of its potent singlet oxygen quenching activity and peroxyl radicals scavenging. In its excited state, lycopene has not enough energy to set off the excitation of other molecules leading to the generation of reactive species. Thus, a single lycopene molecule is able to quench more than one free radical (Jaswir et al. 2011). Lycopene is obviously an effective antioxidant and singlet oxygen quencher because of its unsaturated structure (Rao and Rao 2007). Lycopene owe these particularly interesting activities to the double bonds present in large number within its chemical structure, which is correlated to the antioxidant activity efficacy (Dorais et al. 2008; Barber and Barber 2002). For this reason, lycopene was found to be two times more effective than β-carotene as a nitrogen dioxide scavenger (Barber and Barber 2002).

Thanks to its antioxidant activity, lycopene is particularly efficient against cancer incidence and many carcinogenesis studies have been performed with the purpose of bringing out the anticancer activity of this phytochemical and highlighting its mechanisms of action (Fig. 3.3). The presence of lycopene in human blood at high concentrations was revealed to be effective in fighting oxidative damage and mutagens occurring to DNA, cellular proteins and lipids and leading to several types of cancers (Barber and Barber 2002; Ibrahim et al. 2019). Lycopene prevents oxidative damage of cells through the scavenging of oxygen free radicals, like peroxyl radicals, and through the interaction with reactive oxygen species, like hydrogen peroxide and nitrogen dioxide (Barber and Barber 2002). In case of gastric cancer, it has been shown that lycopene prevented oxidative injury through the stimulation of both levels and activities of glutathione (GSH), glutathione-S-transferase (GST) and glutathione peroxidase (GPx) enzymes and thus, the anticancer activity of lycopene can be linked to the enhancement of the antioxidant activity of enzymes as well as the reduction of oxidative damage in gastric mucosa (Kim and Kim 2015). Moreover, lycopene potential anticancer activity may be associated with the regulation of cell-cell communication and the alteration of cell signaling (Barber and Barber 2002).

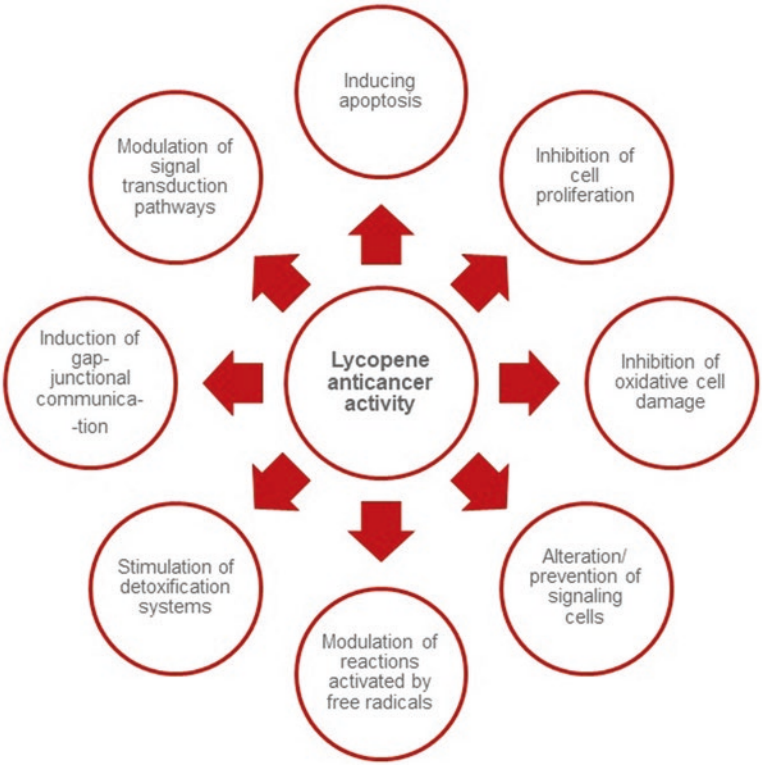

Fig. 3.3 Some proposed mode of action underlying the lycopene anticancer activity

In fact, lycopene may inhibit cancer development by limiting cell proliferation through the inhibition of regulatory proteins phosphorylation, making the cell cycle stop at G0/G1 phase (Palozza et al. 2004; Gupta et al. 2018). In addition, lycopene demonstrated an efficient effect of blocking insulin-like growth factor type 1 (IGF-1) responsible for the proliferation of various cell lines of tumors, and the lower levels of IGF1 were related to higher intake of tomatoes (Karas et al. 2000; Barber and Barber 2002). The inhibition of IGF-1-induced cell growth was linked to the inhibition of IGF signaling, as confirmed by the reduction in IGF-I stimulation of tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1) and binding capacity of activating protein-1 (AP-1). The effect of lycopene on inhibiting IGF-1 was correlated with the enhancement of the number of cell surface-associated insulin-like growth factor-binding proteins (IGFBPs) which negatively modulate the receptor function (Karas et al. 2000). Moreover, lycopene decreased the incidence of mammary tumors whether induced spontaneously or chemically in animal models. In fact, it has been proved that lycopene prevents AP-1 signaling in mammary cells (Gupta et al. 2018). Lycopene is also effective in preventing and inhibiting cancers by inducing cell apoptosis. It has been shown that lycopene as well as its auto-oxidant

products caused apoptosis in human leukemia cells. In fact, lycopene is involved in apoptosis through B-cell lymphoma 2 (Bcl-2) and this action is somehow linked to the antioxidant power of lycopene (Karas et al. 2000; Palozza et al. 2004; Gupta et al. 2018).

Clinton (2005) concluded that, even though the consumption of lycopene based products may only decrease overall cancer risk by 30, 20 or even 10%, the efforts dedicated to establish complex array of risk factors and preventive interventions could be motivated by the cost of health care system particularly in screening, diagnosis and therapy and also by the pain caused by the disease and its involvements. The same author suggested that combining tomato products with efficient chemopreventive and dietary compounds could effectively intervene in the prevention of cancer.

5 β-Carotene

5.1 Chemistry

β-carotene is a lipid soluble secondary metabolite, presenting the structure of a tetraterpene. It is synthesized by plants and presents a molecular weight of about 536 Da (Zahra et al. 2016). It is derived from acyclic structure and presents a long chain made of conjugated double bonds (Bogacz-Radomska and Harasym 2018). β-carotene is generally present in all-*trans* isomer, shown in Fig. 3.4. The high temperature induces the isomerization of β-carotene double bonds and lead to the enhancement of the resulting color (Bogacz-Radomska and Harasym 2018).

β-carotene is present in fruits and vegetables, particularly in orange carrots, pumpkins, spinach, and tomatoes. This carotenoid accounts for around 7% of total carotenoids present in tomato fruit (Dorais et al. 2008).

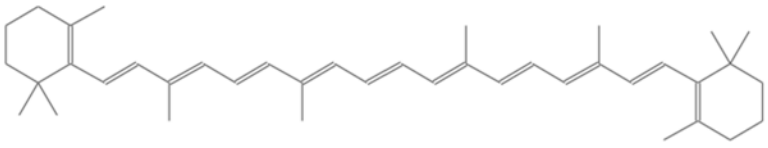

Fig. 3.4 All-*trans* β -carotene

5.2 Bioavailability

β-carotene is considered as a provitamin A carotenoid and its bioavailability depends on many factors such as the food matrix nature, the presence of other nutrients in the meal, β-carotene dose, processing, and genetic, health, and nutritional status of individuals. Desmarchelier et al. (2018) revealed that six genes were shown to have single nucleotide polymorphisms, which may explain the observed differences in β-carotene bioavailability between persons. High β-carotene intake led to a decrease the conversion of this carotenoid to vitamin A in the intestines. Indeed, a two-fold increase in β-carotene dietary dose produced an increase in plasma vitamin A not exceeding 36% (Novotny et al. 2010). Dietary fat intake and ultra-processed foods promote intestinal absorption of β-carotene (Haskell 2012). β-carotene bioaccessibility and bioavailability in tomato paste was greater than that of lycopene due to the higher solubility of β-carotene into micelles and their various structural location in tomato matrix. Incorporation of tomato peels in tomato paste increased β-carotene bioavailability (Reboul 2019). Bugianesi et al. (2004) reported in a crossover clinical trial that human plasma β-carotene levels remained unchanged after ingestion of two test meals based on fresh or cooked cherry tomatoes.

5.3 Biological Activities and Modes of Action

β-carotene is considered to be a highly efficient scavenger of singlet oxygen and is a potent dietary precursor of vitamin A as it is converted into retinal through enzymatic reaction, and ultimately into retinol, namely vitamin A (Jaswir et al. 2011; Zahra et al. 2016). Thanks to its chemical properties and biological activities, β-carotene is applied in food, cosmetic and pharmaceutical fields where it is used as orange-red pigment or as active ingredient against oxidation and UV radiation (Bogacz-Radomska and Harasym 2018).

As an antioxidant agent, β-carotene quenches the free radicals present in human cell membranes, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) and thus inhibits the oxidation of some fats under certain conditions (Ringer et al. 1991). In fact, this phytochemical scavenges free radicals following the process including radicals' incorporation into carotenoids, extraction of hydrogen and transfer of electron (Krinsky 2001). Thus, β-carotene protects lipidic membranes especially through its synergy with vitamins C and E (Zahra et al. 2016). However, it has been shown that β-carotene is not always effective in LDL protection against oxidative agents and this finding is depending on population characteristics, diet and other unknown factors (Bogacz-Radomska and Harasym 2018).

Thanks to its role as a vitamin A precursor, β-carotene undergoes a symmetrical cleavage by β-Carotene-15,15′-oxygenase (BCO1) leading to the production of two molecules of retinaldehyde. β-carotene cleavage can also be ensured by another enzyme called β-carotene-9′, 10′-oxygenase (BCO2) but this cleavage is performed

in an asymmetric manner and produces apocartenal and β-ionone ring, which will be further converted into retinaldehyde (Zahra et al. 2016). Retinaldehyde is later oxidized by enzymes from retinaldehyde dehydrogenase family and produces all-*trans* retinoic acid, which is the vitamin A active form (Zahra et al. 2016).

β-carotene is considered as a health promoting phytochemical with antioxidant and anticancer activities (Bai et al. 2019) and low β-carotene plasma levels could lead to death (Zahra et al. 2016). β-carotene could increase longevity, reduce osteoporosis risks and prevent oxidative stress on bone (Rao and Rao 2007). High consumption of β-carotene may decrease the incidence of different diseases namely cataract formation, macular degeneration, cardiovascular diseases and several types of cancers (Zahra et al. 2016). It also presents an antimutagenic activity and could provoke apoptosis and stop cell cycle.

In fact, some studies reported that β-carotene could be efficient in blocking the growth of malignant cells thanks to its pro-apoptotic effect. In case of human cervical cancer, β-carotene may cause chromatin condensation, which is a characteristic phenomenon of apoptosis. Moreover, it has been reported that the initiation of the mentioned cancer can be prevented thanks to the induction of cervical dysplastic cells apoptosis through the down-regulation of the protein related to the receptor of epidermal growth factor (EGF) (Muto et al. 1995; Palozza et al. 2004). In human leukemia, undifferentiated HL-60 cells were more vulnerable to β-carotene pro-apoptotic action than the differentiated ones. Thus, it has been confirmed that the cell type may influence the pro-apoptotic properties of β-carotene due to the difference in carotenoid incorporation by the cells. In addition to leukemia cells, β-carotene was effective in inducing apoptosis of adenocarcinoma of human colon. However, carotenoid inhibitory concentrations were very different in these two types of cancer cells. It has been stated in previous studies that β-carotene apoptotic activity could be perceived at the concentration range of 2–20μM (Palozza et al. 2004).

Even though consuming fruits and vegetables particularly rich in β-carotene was linked to a significant decrease in cancer risks, many researches have not associated cancer prevention to β-carotene anticancer activity. Some studies have demonstrated that subjects consuming β-carotene from non-natural sources showed an increased mortality rate with an increased cancer incidence. In fact, it has been confirmed that β-carotene should be taken in a balanced diet based on fruits and vegetables and not through supplements containing only β-carotene because the beneficial effect of this phytochemical requires the presence of other compounds, which can facilitate its absorption by the body and enhance its biological activity. β-carotene interacts with the other chemicals present in natural fruits and vegetables synergistically and thus, an increased longevity and decreased cancer incidence were observed. However, it is difficult to quantitatively measure these observed health benefits and prove the synergistic relationship among the different dietary phytochemicals (Dickman 2019).

6 Epidemiologic Studies

Epidemiologic studies have linked increased fruit, vegetable and carotenoid intake with decreased risk of cancer development in the lung (Neuhouser et al. 2003), the cervix (Goodman et al. 2007), the prostate (Tan et al. 2016), the pancreas (Chen et al. 2016), the breast tissue (Tamimi et al. 2009), the anal canal (Shvetsov et al. 2010), the liver (Montella et al. 2011) and the ovaries.

Lung cancer is among the most serious cancer types with approximately two million cases in 2018 (World Health Organization 2018). Wright et al. (2010) reported an important increase in lung cancer rates in male smokers supplemented with β-carotene and attributed this result to tumor development in the airway epithelial cells of these smokers. Likewise, in a multicenter, double-blind chemoprevention trial, Neuhouser et al. (2003) reported that persons with increased risk of getting lung cancer and supplemented with β-carotene and retinol did not take advantage of *active substances* in fruits and vegetables and no protective effect on risk for developing lung cancer was found. Many hypotheses including the modulating activity of phase 1 enzymes by high dose of supplemental β-carotene and its potential adverse effect on the bioavailability of other bioactive phytochemicals were given. Recently, Hashim et al. (2014) performed a mortality analysis, using a database, which comprises clinical measurements of asbestos exposed workers, to evaluate the relation between β-carotene concentrations in serum without supplementation and mortality in these workers. Serum β-carotene concentration, strongly correlated with fruit and vegetable consumption, is considered as a nutritional status or a healthy diet indicator. Despite the reducing effect of high serum β-carotene concentrations on overall mortality of asbestos-exposed workers, no correlation was found with overall cancer or lung cancer mortalities.

The results of a systematic review including 10 studies found a negative but insignificant relation between lycopene consumption and risk for developing ovarian cancer in elderly women (Li and Xu 2014). The presumed protective effect of lycopene is related to its great ability to quench singlet oxygen molecules and to scavenge peroxyl radicals. The authors attributed the insignificant obtained results in the meta-analysis to postmenopausal status of participants, histological types of ovarian cancer in included studies and the difficulty in quantifying lycopene intake. Furthermore, Tamimi et al. (2009) reported that high concentrations of α-carotene, lycopene, lutein and β-cryptoxanthin in plasma decreased breast cancer risk by up to 40% in women with high mammographic density.

A meta-analysis of the impact of β-carotene supplements on cancer prevention revealed no protective effect on cancer prevalence and mortality (Jeon et al. 2011). Likewise, no effect of β-carotene intake was found on prostate cancer survival, while α-tocopherol supplementation was linked to improved prostate cancer survival (Watters et al. 2009). Inconsistent findings on the correlation between dietary lycopene intake and prostate cancer were obtained from meta-analysis studies (Etminan et al. 2004; Chen et al. 2015). Haseen et al. (2009) claimed in their systematic review that lycopene reduced cancer-related symptoms in the few

intervention studies on the impact of lycopene on prostate cancer progression. In a prospective cohort study among male health practitioners, a strong inverse relation was found between high lycopene consumption and lethal prostate cancer and the authors hypothesized that lycopene-rich diet can inhibit angiogenesis by regulating vascular permeability factor, preventing aggressive prostate cancer (Zu et al. 2014). Although this trend was not observed in the meta-analysis conducted by Chen et al. (2015), an exposure-effect relationship was found between lycopene supplementation and circulating concentration and prostate cancer incidence.

7 Animal Studies

In an *in vitro* study performed by Elgass et al. (2012), the anti-angiogenic effect of lycopene using rat aortic rings was revealed. Indeed, a lycopene concentration of 1.15 mmol/l significantly decreased tubule length and network branching by 25 and 44%, respectively. In another study, Tan et al. (2016) demonstrated that tomato powder and lycopene beadlets, which produced lycopene serum concentrations in mice comparable to those detected in human serum, inhibited prostate oncogenesis in the transgenic adenocarcinoma of the mouse prostate system in a BCO2 genotype-specific manner. Indeed, loss of BCO2 gene might decrease the chemopreventive effect of lycopene, supporting the potential anticancer activity of lycopene cleavage metabolites. It was established that lycopene interacts with fructose-amino acids synergistically to inhibit the growth of rat prostate adenocarcinoma cells by more than 98% and the highest survival rate from prostate tumorigenesis was obtained in rats fed with tomato paste/ketosamines (>50 weeks) (Mossine et al. 2008). Likewise, combined administration of lycopene, selenium and vitamin E effectively inhibited prostate cancer cell growth and progression in lady transgenic mice (Venkateswaran et al. 2009). In male nude mice supplemented with lycopene, a significant inhibition of metastasis of lung cancer induced by human hepatoma cells was observed by Huang et al. (2008) who attributed this result to significant reduction in matrix metalloproteinase-2 and vascular endothelial growth factor levels as well as increase in interleukin-12 production. According to Luo and Wu (2011), lycopene provided to male Wistar rats with gastric cancer exhibited an anticancer activity, which may be related to improvement of immunity function and stimulation of antioxidant enzymes. In another study, lycopene prevented oxidative stress and polychlorinated biphenyls-induced apoptosis in Sertoli cells from albino rat testes. Indeed, lycopene supplementation decreased Bad and Bid expression and increased anti-apoptotic Bcl2 protein in testicular cells (Krishnamoorthy et al. 2013). Moreover, tomatoes had a defensive effect against UVB-induced skin tumors by reducing DNA inflammation in mice skin (Cooperstone et al. 2017).

8 Human Clinical Trials

Associations between tomatoes intake and decreased human cancers risk have been established in many epidemiological and clinical studies (Ford et al. 2011; Venier et al. 2012; Chen et al. 2015). Many mechanisms have been advanced to investigate the chemopreventive effects of bioactive constituents in tomato, such as lycopene and various phenolic compounds, against many cancers. These mechanisms could include inhibition of Reactive Oxygen Species (ROS), activation of apoptosis pathways, activation of cell growth arrest, increase of gap-junctional communication and inhibition of cell proliferation and viability (Sharoni et al. 2016). The considerable increase in prostate lycopene content in cancer patients may in part justify its protective action in lowering damage of prostate DNA and prostate cancer biomarkers (Basu and Imrhan 2007).

Although the relation between consumption of β-carotene and risk of prostate cancer was not established, high lycopene intake decreased this risk by 26% (Sharoni et al. 2011). Many clinical trials with high tomatoes consumption or high lycopene plasma levels have documented lycopene antioxidant potential and anticancer properties against cancer cells in prostate (Ford et al. 2011; Venier et al. 2012; Chen et al. 2015). Using different lycopene concentrations, Soares et al. (2013) showed that 10 μM of lycopene increased human malignant prostate cancer cell death by more than twofolds after 96 h treatment with significant increase in expression of BAX and CK18 genes and decrease in expression of Bcl-2 gene. In a recent study, Soares et al. (2019) treated two human cancer cells in prostate with lycopene extracted from various tomato-based products and evaluated its effect on viability, cycle progression and death of cells. They found that lycopene exhibited a significant anticarcinogenic activity against prostate cancer cell lines by inhibiting cell viability, inducing cell cycle arrest and increasing apoptosis. After 4 days of treatment, lycopene promoted growth arrest in G0/G1 and G2/M phases and achieved the highest increase rate in apoptotic cells. *In vitro* assays using three different human prostate cancer cells demonstrated that lycopene enhanced the anticancer properties of capsaicin and these two dietary agents were able to promote apoptosis by regulating Bax/Bcl-xl ratio and stimulating caspase cascade in androgen sensitive cells (Venier et al. 2012). Likewise, Jeong et al. (2019) demonstrated that lycopene promoted apoptosis in human pancreatic cancer cells by reducing intracellular and mitochondrial reactive oxygen species and downregulating NF-κB activity and NF-κB regulated genes. Moreover, Huang et al. (2013) demonstrated that lycopene anti-angiogenic activity may be explained by modulation of cytokine secretion and decrease of matrix metalloproteinase-2 activity in human peripheral blood mononuclear cells.

Recently, Navarro-González et al. (2018) assessed gene expression variation of human hepatocytes obtained from liver tissues of overweight patients supplemented daily with 200 ml of tomato juice and found that this latter induced cellular apoptosis and regulated cell cycle progression due to lycopene accumulation in the liver. Moreover, tomato intake was found more effective in preventing hepatocarcinoma

than the intake of pure tomato compounds separately, suggesting the synergistic action of different tomato phytochemicals in prevention of liver cancer. Furthermore, Tanambell et al. (2019) reported that extracts from high-β-carotene tomatoes promoted proliferation of prostate cancer cells, while those from orange tomatoes (rich in tetra-*cis* lycopene) had anti-proliferative activity against prostate cancer cells. Moreover, tangerine tomatoes had greater anti-inflammatory activity than red and orange-colored tomatoes. It is worth noting that the observed *in vitro* anti-proliferative and anti-inflammatory properties should be validated with in vivo assays.

In a 24-month, randomized, double-blind trial, Keefe et al. (2001) evaluated the effect of daily β-carotene supplementation for women on the decrease of cervical intraepithelial neoplasia 2 and 3 lesions and measured levels of vaginal and serum micronutrients. β-carotene intake did not result in an improvement in cervical lesion regression, particularly for women infected with human papillomavirus, and the authors suggested that complex interactions between micronutrients might explain the obtained results. Li et al. (2005) reported in a randomized, double-blind clinical trial that β-carotene supplementation prevented prostate cancer in the participants with AA genotype, versus a placebo during 7 years.

Skin cancer is the most frequent cancer in the U.S. and worldwide, representing a major public health and economic problem. Every hour, more than 396 people are diagnosed with skin cancer and more than 2 people die of skin cancer in the U.S. (American Cancer Society 2019). Keratinocyte carcinomas, known as non-melanoma skin cancers, are the most frequent skin tumours that are associated with exposure to solar ultraviolet radiation. Human clinical results demonstrated that dietary tomato paste rich in lycopene prevented sunburn due to the photoprotective effect of carotenoid compounds stored in human skin (Stahl et al. 2001; Cooperstone et al. 2017). Consumption of a whole tomato provided a better photoprotective effect that supplement intake (Stahl et al. 2005).

9 Limitations of Cancer Studies and Future Trends

The obtained results of many epidemiologic and clinical studies lack consistency and coherence because of many factors including:

- Low statistical power of performed studies resulting mainly from small sized samples and effects
- Variability in dietary assessment methods and concerns related to their reproducibility and validity
- Supplements Interference with each other and with cancer treatments
- Heterogeneity in cancer screening among different populations or within the same patient
- Overdiagnosis of indolent cancers resulting in low impact on cancer prevalence and death rate reductions as well as in needless harmful treatments

– Late diagnosis of some cancers, such as lung cancers, until they are far advanced may result in undetected carcinomas in persons classified as noncases
– Wide variation of cancer risks among individuals depending on lifestyle, dietary and genetic factors.
– Variation of results with the form, dosage, composition, metabolism, bioavailability and timing of the administrated supplement, association with other supplements or phytochemicals as well as stage and molecular characteristics of cancer
– Incomplete control of some confounding factors (i.e., physical activity, alcohol
– intake levels, age, cancer subtypes)
– Biased data on self-reported nutrient intake (food frequency questionnaires)

10 Conclusion and Future Trends

Several *in vitro* studies have underlined the protective effects of lycopene and β-carotene on cancer. However, many others have been uncapable to successfully convert these results in related preclinical/clinical model systems. In fact, cancer and anticancer activity are complicated mechanisms that cannot easily be explained or underlined by simple models of biological reactions and mechanisms. This may be due to the fact that properties related to the biology, pharmacology and bioavailability of carotenoids, especially lycopene and β-carotene, are still not well understood and further studies on their pharmacokinetic properties are required.

Up today, several researches have shown the health advantages of lycopene and β-carotene intake, especially when brought naturally within an equilibrated diet. For this reason, the intake of tomato and tomato based products such as sauces and tomato puree have been widely encouraged. In addition, it has been established that the consumption of tomato in complex dishes increases lycopene and β-carotene availability. Thus, future research could be conducted to develop new formulations that guarantee an optimal carotenoid intake where several types of oils can be added to enhance intestinal absorption of carotenoids. As the beneficial effects of lycopene and β-carotene, when consumed within an equilibrated diet were established, more researches need to be performed in order to enrich food matrices with these carotenoids and to increase their bioavailability in natural food products where they already exist.

Even though the consumption of lycopene and β-carotene from food sources is highly recommended by the scientific community to reduce cancer risks, the health benefits of purified forms of lycopene and β-carotene remain poorly understood and further research should be designed to enhance our knowledge on the anticancer effects of these specific purified supplements. Moreover, molecular mechanisms and genetic interactions associated with the impact of tomato consumption on several types of cancer need to be refined.

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