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Invited review

Carotenoids and human health

A.V. Rao [a,*], L.G. Rao [b]

[a] Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, 150 College Street, Toronto, Ontario M5S 3E2, Canada
[b] Department of Medicine, Calcium Research Laboratory, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

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Abstract

Oxidative stress is an important contributor to the risk of chronic diseases. Dietary guidelines recommend increased consumption of fruits and vegetables to combat the incidence of human diseases such as cancer, cardiovascular disease, osteoporosis and diabetes. Fruits and vegetables are good sources of antioxidant phytochemicals that mitigate the damaging effect of oxidative stress. Carotenoids are a group of phytochemicals that are responsible for different colors of the foods. They are recognized as playing an important role in the prevention of human diseases and maintaining good health. In addition to being potent antioxidants some carotenoids also contribute to dietary vitamin A. There is scientific evidence in support of the beneficial role of phytochemicals in the prevention of several chronic diseases. Although the chemistry of carotenoids has been studied extensively, their bioavailability, metabolism and biological functions are only now beginning to be investigated. Recent interest in carotenoids has focused on the role of lycopene in human health. Unlike some other carotenoids, lycopene does not have pro-vitamin A properties. Because of the unsaturated nature of lycopene it is considered to be a potent antioxidant and a singlet oxygen quencher. This article will review carotenoids in general and lycopene in particular for their role in human health.

Keywords: Carotenoids; Human health; Lycopene; Oxidative stress; Chronic diseases; Antioxidants

Contents

* Corresponding author. Tel.: +1 416 978 3621; fax: +1 416 978 5882.
E-mail address: v.rao@utoronto.ca (A.V. Rao).

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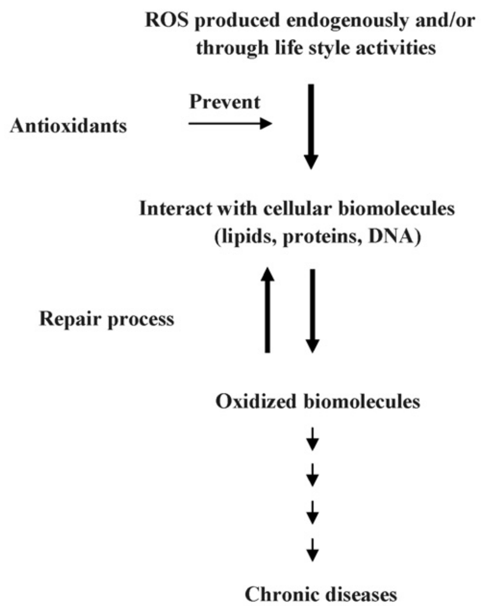

Fig. 1. Oxidative stress, antioxidants and chronic diseases.

1. Introduction

There is convincing scientific evidence in support of the association between diet and chronic diseases. Based on such evidence, dietary guidelines have been formulated around the world for the prevention of chronic diseases such as cancer, cardiovascular disease, diabetes and osteoporosis. One of the main recommendation of these dietary guidelines is to increase the consumption of plant based foods including fruits and vegetables that are good sources of carotenoids and other biologically active phytochemicals. Fruits and vegetables mediate their beneficial effects via several mechanisms that include metabolism, immune modulation and hormonal induction. However, in recent years oxidative stress, induced by reactive oxygen species (ROS) that are generated by normal metabolic activity as well as lifestyle factors such as smoking, exercise and diet, have been implicated in the causation and progression of several chronic diseases. Antioxidants that can mitigate the damaging effects of ROS have been the focus of recent research. The role of oxidative stress and antioxidants in chronic diseases is shown in Fig. 1. Carotenoids, in view of their antioxidant properties have received considerable interest by researchers, health professionals and regulatory agencies. This review will focus on the role of carotenoids in human health in general and lycopene in particular which has been researched extensively in recent year for its role in the prevention of chronic diseases.

2. Carotenoids

Carotenoids are a family of pigmented compounds that are synthesized by plants and microorganisms but not animals. In plants, they contribute to the photosynthetic machinery and protect them against photo-damage. Fruits and vegetables constitute the major sources of carotenoid in human diet [1–3]. They are present as micro-components in fruits and vegetables and are responsible for their yellow, orange and red colors. Carotenoids are thought to be responsible for the beneficial properties of fruits and vegetables in preventing human diseases including cardiovascular diseases, cancer and other chronic diseases [4,5]. They are important dietary sources of vitamin A [4]. In recent years the antioxidant properties of carotenoids has been the major focus of research [4]. More than 600 carotenoids have so far been identified in nature. However, only about 40 are present in a typical human diet. Of these 40 about 20 carotenoids have been identified in human blood and tissues. Close to 90% of the carotenoids in the diet and human body is represented by β-carotein, α-carotein, lycopene, lutein and cryptoxanthin [6].

2.1. Chemistry and dietary sources

All carotenoids posses a polyisoprenoid structure, a long conjugated chain of double bond and a near bilateral symmetry around the central double bond, as common chemical features [7].

Different carotenoids are derived essentially by modifications in the base structure by cyclization of the end groups and by introduction of oxygen functions giving them their characteristic colors and antioxidant properties. Structures of some common carotenoids are shown in Fig. 2.

Due to the presence of the conjugated double bonds, carotenoids can undergo isomerization to *cis-trans* isomers. Although the trans isomers are more common in foods and are more stable very little is known about the biological significance of carotenoid isomerization in human health.

Although carotenoids are present in many common human foods, deeply pigmented fruits, juices and vegetables constitute the major dietary sources with yellow-orange vegetables and fruits providing most of the β-carotein and α-carotein, orange

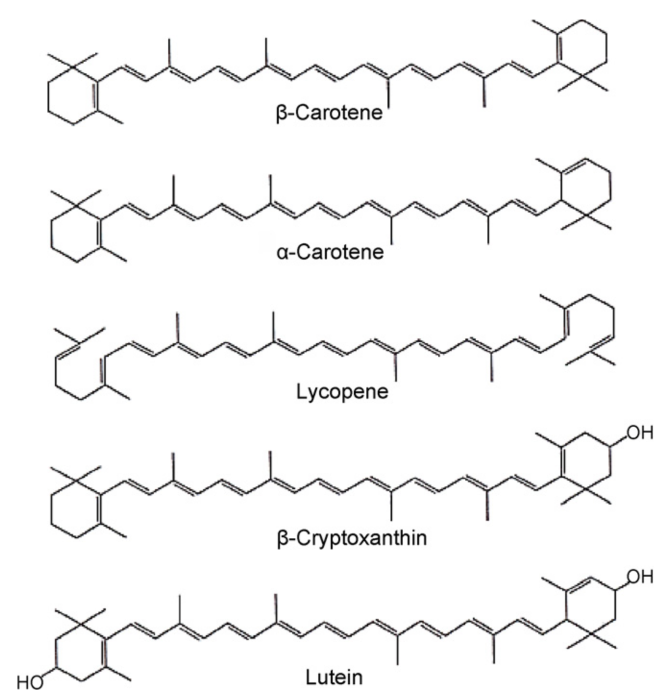

Fig. 2. Structure of some major dietary carotenoids.

Table 1
Examples of major contributors of carotenoids in North American diet

Carotenoid	Food source	Amount
β-Carotene	Apricot, dried	17600
	Carrots, cooked	9771
	Spinach, cooked	5300
	Green Collard	5400
	Canteloupe	3000
	Beet Green	2560
	Broccoli, cooked	1300
	Tomato, raw	520
α-Carotene	Carrots, cooked	3723
Lycopene	Tomatoes, raw	3100
	Tomato juice	10000
	Tomato paste	36500
	Tomato ketchup	12390
	Tomato sauce	13060
β-Cryptoxanthin	Tangerine	1060
	Papaya	470
Lutein	Spinach, cooked	12475
	Green collard	16300
	Beet, green	7700
	Broccoli, cooked	1839
	Green peas, cooked	1690

fruits providing α-cryptoxanthin, dark green vegetables providing lutein and tomatoes and tomato products lycopene [1,8]. Table 1 shows typical food sources and amounts of carotenoids present. In the case of lutein and zeaxanthin, they are also present in high concentrations in egg yolks [2]. Due to the unsaturated nature of the carotenoids they are subject to changes due mainly to oxidation. However, other factors such as temperature, light and pH can also produce alterations that can influence the color of foods as well as their nutritional value [9]. In general carotenoid content of foods is not altered to a great extent by common household cooking methods such as microwave cooking, steaming and boiling but extreme heat can result in oxidative destruction of carotenoids [10]. Although several nutrient data basis provide estimations of the daily intake of carotenoids by humans these values vary considerably due to the sensitivity and specificity of different analytical methods that are used in the detection of these phytochemicals. Also consideration is often times not given to seasonal variations and methods of processing of foods containing carotenoids [3]. In spite of the recognition of the beneficial role of carotenoids in human health they are not considered as essential nutrients and as such do not have a dietary reference intake (DRI) value assigned to them.

2.2. *Metabolism and bioavailability*

Other than β-carotein and lycopene the absorption of other major carotenoids is not well know. Several factors influence the absorption of carotenoids. Food processing and cooking that cause mechanical breakdown of the tissue releasing the carotenoids improves their absorption [11–13]. They are absorbed into the gastrointestinal mucosal cells and appear unchanged in the circulation and tissues [12,14]. In the intestine the carotenoids are absorbed by passive diffusion after being incorporated into the micelles that are formed by dietary fat and bile acids. The micellular carotenoids are then incorporated into the chylomicrons and released into the lymphatic system. They are then incorporated into the lipoprotein at the site of the liver and released into the blood stream. Carotenoids are absorbed differentially by different tissues. Little is known about the mechanisms of tissue absorption of carotenoids at this time. The major site of tissue storage of carotenoids is the adipose tissue [14,15].

2.3. *Bioactivity and disease prevention*

Based on epidemiological studies a positive link is suggested between higher dietary intake and tissue concentrations of carotenoids and lower risk of chronic diseases [2,3,16]. β-Carotein and lycopene have been shown to be inversely related to the risk of cardiovascular diseases and certain cancers where as lutein and zeaxanthin to the disorders related to the eye [2,17]. The antioxidant properties of carotenoids have been suggested as being the main mechanism by which they afford their beneficial effects. Recent studies are also showing that carotenoids may mediate their effects via other mechanisms such as gap junction communication, cell growth regulation, modulating gene expression, immune response and as modulators of Phase I and II drug metabolizing enzymes [4,18,19,20]. However, carotenoids such as α- and β-carotein and β-cryptoxanthin have the added advantage of being able to be converted to Vitamin A and its related role in the development and disease prevention. The role of carotenoids in the prevention of chronic diseases and their biological actions are summarized in Fig. 3.

Several *in vitro*, animal and human experiments have demonstrated the antioxidant properties of carotenoids such as β-carotein and lycopene. When human dermal fibroblasts (FEK4) were exposed to UVA exposure, β-carotein was able to suppress the up-regulation of heme oxygenase-1 gene expression in a dose dependent manner [16]. It is interesting to observe that β-carotein has also been reported to act as a pro-oxidant

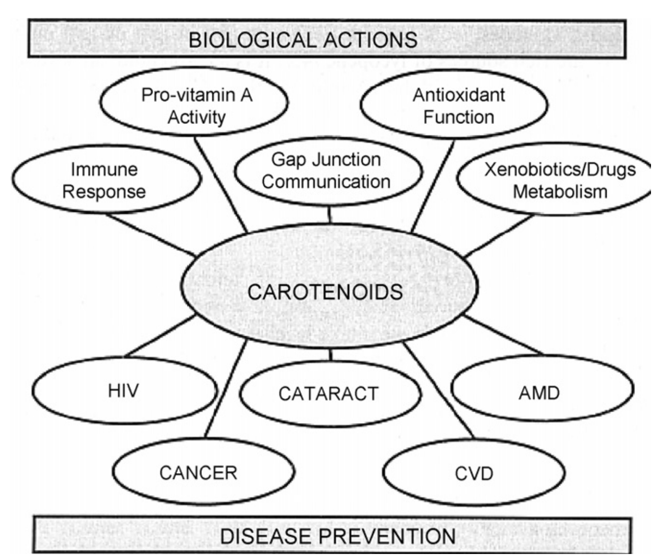

Fig. 3. Role of carotenoids in the prevention of chronic diseases.

under certain situations. β-carotein at a concentration of 0.2 μM augmented UVA-induced haem oxygenase-1 induction indicating a pro-oxidant effect [21]. Similarly, in another study β-carotein at a concentration of 10 μM increased the production of ROS and the levels of cellular oxidized glutathione in leukaemia and colon adenocarcinoma cell lines *in vitro* [22]. The pro-oxidant effect of β-carotein was also demonstrated in rats that showed increased activity of phase I enzymes in liver, kidney and intestine as well as increased oxidative stress [23]. Recently reported human studies also support the pro-oxidant properties of β-carotein. Supplementation of β-carotein at pharmacological levels increased lung cancer incidences in smokers in the Alpha-Tocopherol Beta-Carotene (ATBC) trial [24] and increased mortality from CVD in a group of smokers, former smokers and asbestos exposed individuals in the β-carotein and retinol efficiency trial (CARET) [25]. These observations suggest a possible biphasic response of β-carotein that promotes health when taken at dietary levels, but may have adverse effects when taken in higher amounts. Although the relevance of the outcome of the human studies and the details of the study designs are still being debated among the scientists, the concerns regarding pro-oxidant property of β-carotein that may enhance the risk of lung cancer and CVD among smokers has prompted a moratorium on further intervention studies using β-carotein. Over a long period of time β-carotein was used as a 'gold standard' model to study the relationship between oxidative stress and chronic diseases. The focus of research has now shifted to another carotenoid antioxidant lycopene. The evidence in support of lycopene in disease prevention and biological activity will be reviewed in the following section of this article.

3. Lycopene

3.1. Structure and occurrence

Lycopene, a member of the carotenoid family of phytochemicals is a lipid soluble antioxidant that is synthesized by many plants and microorganisms but not by animals and human [4]. It is a highly unsaturated open straight chain hydrocarbon consisting of 11 conjugated and 2 unconjugated double bonds [26–28]. It is responsible for the red color of many fruits and vegetables such as the tomatoes. Unlike some other carotenoids lycopene lacks the terminal β-ionic ring in its structure and provitamin A activity. Because of the presence of double bonds in the structure of lycopene, it can exist in both the *cis* and *trans* isomeric forms. In nature, lycopene is present primarily in the all trans isomeric form [29]. However, it can undergo mono or poly isomerization by light, thermal energy and chemical reactions to its cis-isomeric forms (Fig. 4). It is a highly stable molecule. However, it can undergo oxidative, thermal, and photodegredation [3]. Studies have shown lycopene to be stable under the conditions of thermal processing and storage [30]. A recent publication showed 5-*cis* lycopene to be most stable isomer followed by the all-*trans*, 9-*cis*, 13-*cis*, 15-*cis*, 7-*cis* and 11-*cis*. 5-*cis* lycopene was also shown to have the highest antioxidant properties followed by 9-*cis*, 7-*cis*, 13-*cis*, 11-*cis* and the all-*trans* isomers [31].

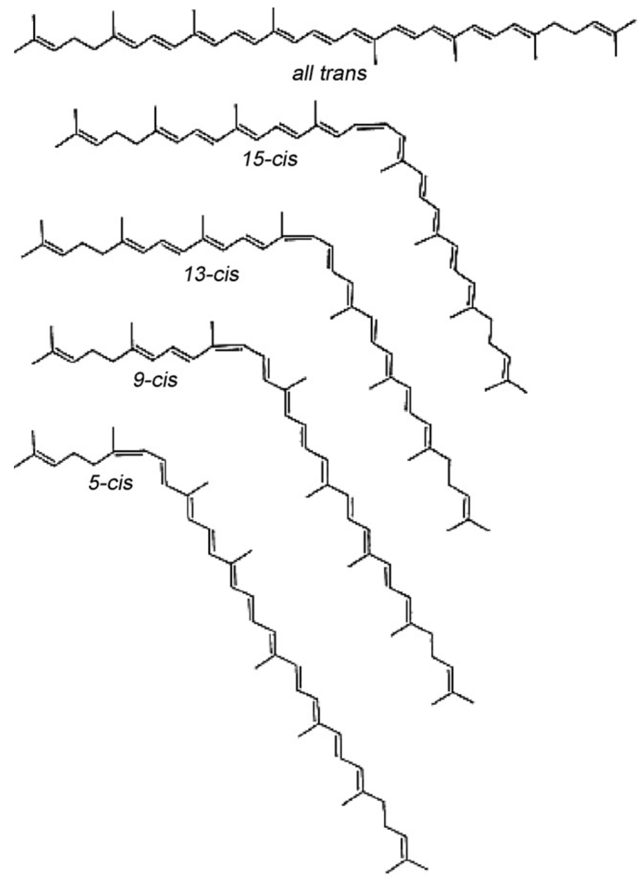

Fig. 4. All *trans* and *cis*-isomeric forms of lycopene.

Tomatoes and tomato-based foods account for more than 85% of all the dietary sources of lycopene [32]. Lycopene content of some common tomato-based foods is shown in Table 2 [33,34].

3.2. Absorption and tissue distribution

Lycopene absorption from dietary sources is influenced by several factors including the break up of the food matrix containing lycopene, cooking temperatures and the presence of lipids and other lipid soluble compounds including other carotenoids. Absorption of lycopene is similar to other lipid soluble compounds and is absorbed across the gastrointestinal tract via a chylomicron mediated mechanism [12].

In general, 10–30% of the dietary lycopene is absorbed by humans [13,35]. It is absorbed equally efficiently from different sources of lycopene including tomato sauce, tomato juice and

Table 2
Lycopene content of common fruits and vegetables

Fruits and vegetables	Lycopene (μg/g wet weight)
Tomatoes	8.8–42.0
Water melon	23.0–72.0
Pink guava	54.0
Pink grapefruit	33.6
Papaya	20.0–53.0
Apricot	<0.1

tomato oleoresin capsules [13,36]. Other studies have shown that lycopene is absorbed more efficiently from processed tomato products compared to raw tomatoes. The increased absorption of lycopene from processed tomato products is attributed to the presence of cis-isomers of lycopene [37].

Absorbed lycopene is distributed throughout the body via the circulatory system. Lycopene is the most predominant carotenoid in human plasma with a half life of about 2–3 days [38]. Although the most prominent geometric isomers of lycopene in plants are the all-*trans*, in human plasma, lycopene is present as an isomeric mixture containing 50% of the total lycopene as *cis* isomer [39]. When animals were fed lycopene containing predominantly the all trans isomeric form, serum and tissue lycopene showed the presence of cis lycopene [40]. Similar results were also observed in human serum. Testes, adrenal glands, prostate, breast and liver were shown to have the highest levels of lycopene in humans [27,40]. Lycopene in the tissues undergoes oxidation and metabolism. Several oxidized form of lycopene and polar metabolites have recently been isolated and identified [26]. The biological significance of these findings is not clear at present and is the subject of many studies.

3.3. Metabolism and mechanisms of action

Very little is known about the *in vivo* metabolism of lycopene. In an *in vitro* study using post-mitochondrial fraction of rat intestinal mucosa two types of metabolic products of lycopene, cleavage products and oxidation products were identified. Identified among the cleavage products were: 3-keto-apo-13-lycopenone and 3,4-dehydro-5,6-diihydro-15-apo-lycopenal. The oxidation products included: 2-ene-5,8-lycopenal-furanoxide, lycopene-5,6.5′,6′-diepoxide, lycopene-5,8-furanoxide isomer (I), lycopene-5,8-epoxide isomer (II), and 3-keto-lycopene-5′,8′-furanoxide. In another study lycopene was shown to be cleaved to acycloretinal, acycloretinoic acid, and apolycopenals in a non enzymatic manner. Only a few metabolites, such as 5,6-dihydroxy-5,6-dihydro lycopene, have been detected in human plasma [26,41,42]. It is suggested that lycopene may undergo *in vivo* oxidation to form epoxides which then may be converted to the polar 5,6-dihydoxy-5,6 dihydro-lycopene through metabolic reduction.

The antioxidant property of lycopene has been the main focus of research to study its biological role. However, it has also been shown to exert its effect via other mechanisms that include gene function regulation, gap-junction communication, hormone and immune modulation, carcinogen metabolism and metabolic pathways involving phase II drug-metabolizing enzymes [43–46]. An extensive review of both the antioxidant mechanisms and other molecular mechanisms has recently been reviews [33,47].

3.4. Prevention of chronic diseases

3.4.1. Cancer

The evidence in support of lycopene in the prevention of chronic diseases comes from epidemiological studies [48–53] as well as tissue culture studies using human cancer cell lines [54–56], animal studies [40,57–60] and also human clinical trials [32,61,62–64].

Of all the cancers. the role of lycopene in the prevention of prostate cancer has been studied the most. An inverse relationship between the consumption of tomatoes and the risk of prostate cancer was first demonstrated in a 1995 publication [65]. Lycopene was suggested as being the beneficial compound present in tomatoes. A follow up met analysis of 72 different studies in 1999 showed that lycopene intake as well as serum lycopene levels were inversely related to several cancers including prostate, breast, cervical, ovarian, liver and other organ sites [49]. Several other studies since then demonstrated that with increased intake of lycopene and serum levels of lycopene the risk of cancers were reduced significantly [33,34,48,66]. To study the status of oxidative stress and antioxidants in prostate cancer patients a study was undertaken [32]. Results showed significant differences in levels of serum carotenoids, biomarkers of oxidation and prostate specific antigen (PSA) levels in these subjects. Although there were no differences in the levels of β-carotene, lutein, cryptoxanthin, vitamin E and A between the cancer patients and their controls, levels of lycopene were significantly lower in the cancer patients. As expected the PSA levels were significantly elevated in the cancer patients who also had higher levels of lipid and protein oxidation indicating higher levels of oxidative stress in cancer patients. In the same study, serum PSA levels were shown to be inversely related to the serum lycopene [32]. Other carotenoids did not show similar inverse relationship. In more recently reported studies, lycopene was shown to decrease the levels of PSA as well as the growth of prostate cancer in newly diagnose prostate cancer patients receiving 15 mg of lycopene daily for 3 weeks prior to radical prostactomy [62,66]. In another study when tomato sauce was used as a source of lycopene, providing 30 mg lycopene/day for three weeks preceding prostatectomy in men diagnosed with prostate cancer, serum and prostate lycopene levels were elevated significantly [67]. Oxidative damage to DNA was reduced and serum PSA levels declined significantly by 20% with lycopene treatment. Although small in number, these observations raise the possibility that lycopene may be involved not only in the prevention of cancers but may play a role in the treatment of the disease.

Other than prostate cancer there is now growing evidence in support of the protective role of lycopene in cancers of other sights including breast, lung, gastrointestinal, cervical, ovarian and pancreatic cancers [49]. Tissue culture studies using human cancer cell lines have shown that their growth is inhibited significantly in the presence of lycopene in the growth media [47,68,69]. Similarly, several animal studies have also confirmed the inverse association between dietary lycopene and the growth of both the spontaneous and transplanted tumors [70,71]. Human dietary intervention studies are now beginning to be undertaken to study the role of lycopene in breast, ovarian and cervical cancers.

Overall, epidemiological studies, in vitro tissue culture studies, animal studies and now some human intervention studies are showing that increased intake of lycopene will result in increased circulatory and tissue levels of lycopene. In vivo lycopene can act as a potent antioxidant and protect cells against oxidative damage and there by prevent or reduce the risk of several cancers. Further studies are needed to get further proof and to gain better understanding of the mechanisms involved.

3.4.2. Cardiovascular disease

Several reports have now appeared in the literature in support of the role of lycopene in the prevention of CVD [72–74]. The strongest population-based evidence comes from a multicenter case-control study (EURAMIC) that evaluated the relationship between adipose tissue antioxidant status and acute myocardial infraction [75,76]. Subjects that included 662 cases and 717 controls were recruited from 10 different European countries. Results of this study showed a dose-response relationship between adipose tissue lycopene and the risk of myocardial infraction. Another study that compared the Lithuanian and Swedish populations showed lower lycopene levels to be associated with increased risk and mortality from coronary heart disease (CHD) [77]. Serum cholesterol level have traditionally been used as a biomarker for the risk of CHD. Oxidation of the circulating low density lipoprotein (LDL), that carries cholesterol into the blood stream, to oxidized LDL (LDL_{ox}) is also thought to play a key role in the pathogenesis of arteriosclerosis which is the underlying disorder leading to heart attack and ischemic strokes [78–80]. Lycopene was also shown to significantly reduce the levels of oxidized LDL (LDL_{ox}) in subjects consuming tomato sauce, tomato juice and lycopene oleoresin capsules as sources of lycopene [81]. In another small study, lycopene was shown to reduce serum total cholesterol levels and thereby lowering the risk of CVD [82].

Although epidemiological studies have provided convincing evidence in support of the protective role of lycopene in CVD. These observations need to be validated by conducting well controlled human intervention studies in the future. Important aspects of such studies will be to use well-defined subject populations, standardized outcome measures of oxidative stress and the disease, and lycopene ingestion that is representative of normal healthy dietary intakes.

3.4.3. Osteoporosis

Oxidative stress and antioxidants may contribute to the pathogenesis of the skeletal system including osteoporosis, the most prevalent metabolic bone disease [83]. Oxidative stress control the functions of both osteoclasts [84,85] and osteoblasts [86]. Endogenous [85,87] and synthetic [54] antioxidants counteract the effects of oxidative stress in these cells. Recent studies reported that antioxidants from natural sources, such as the lycopene from tomatoes, can also counteract the damaging effects of oxidative stress. The findings that lycopene has a stimulatory effect on the cell proliferation [88] and the differentiation marker alkaline phosphatase of osteoblasts [88,89], as well as its inhibitory effects on osteoclasts formation and resorption [90,91] are evidence of the involvement of lycopene in bone health and warranted further investigation in clinical studies.

Epidemiological studies have shown that oxidative stress is associated with osteoporosis and that antioxidants may counteract this effect. Certain antioxidants including vitamin C, E and beta-carotene may reduce the risk of osteoporosis [92–95] and counteract the adverse effects of oxidative stress on bone that are produced during strenuous exercise [94] and among smokers [92]. Osteoporotic women have been shown to have reduced levels of antioxidant vitamins and enzymes indicating a decrease in their antioxidant defences [96].

A recently published clinical study showed a direct correlation between serum lycopene and decrease in the risk of osteoporosis among postmenopausal women for the first time [97]. The relationship between serum lycopene, oxidative stress parameters and bone turnover markers in postmenopausal women were investigated. Study participants were asked to complete a seven-day food intake record prior to giving fasting blood samples. Oxidative stress parameters, total antioxidant capacity, serum lycopene and the bone turnover markers including bone alkaline phosphatase (bone formation) and cross-linked N-telopeptides of type I collagen (NTx) (bone resorption) were measured in the serum samples. Results showed a direct correlation between lycopene intake and serum lycopene levels. Increase in serum lycopene levels resulted in significant decreases in protein oxidation and NT_x values [97]. Based on these results an important role for lycopene mediated via its antioxidant property in reducing the risk of osteoporosis is suggested. Dietary intervention studies with varying levels of lycopene are currently being conducted with the objective of demonstrating the beneficial effects of lycopene in the prevention and management of osteoporosis.

3.4.4. Other human diseases

Since the recognition of lycopene as a potent antioxidant, and its preventive role in oxidative stress mediated chronic diseases, researchers are beginning to investigate its role in other human diseases. Hypertension is commonly referred to as the ‘silent killer’ since symptoms of this disorder are not observed until a more advanced and fatal stage of the diseases is reached. A causal relationship between oxidative stress and the incidence of hypertension is now recognized. The antioxidant property of lycopene has attracted scientific research into its protective role in hypertension. A recent study showed lycopene supplementation at the rate of 15 mg per day for 8 weeks to significantly decrease systolic blood pressures from the baseline value of 144 mmHg to 134 mmHg in mildly hypertensive subjects [98,99]. In another study a significant reduction in plasma lycopene was observed in the hypertensive patients compared to normal subjects [100]. When patients with liver cirrhosis, a condition closely associated with hypertension and disorders of the lymphatic circulation, were compared with matched controls a significant reduction in serum lycopene was observed along with other carotenoid antioxidants, retinol and vitamin E in the cirrhotic group [27,98]. Recognizing the importance of antioxidants in the management of hypertension a ‘dietary approach to control hypertension (DASH)’ diet is recommended that contains substantially higher levels of lycopene along with other carotenoids, polyphenols, flavanols, flavanones and flavan-3-ols [101].

Male infertility, a common reproductive disorder, is now being associated with oxidative damage of the sperm leading to loss of its quality and functionality. Significant levels of ROS are detectable in the semen of up to 25% of infertile men, whereas fertile men do not produce detectable levels of ROS in their semen [102,103]. A number of studies have reported the beneficial effects of vitamins C and E. and other antioxidants, including taurine [104], L-carnitine [105], coenzyme Q10 [106,107], and glutathione [108] on sperm quality. Researchers are beginning to investigate the role lycopene in protecting sperm from oxidative damage leading to infertility. Men with antibody-mediated infertility were found to have lower semen lycopene levels than fertile controls [109]. In another study infertile men consumed a daily dose of 8 mg lycopene in capsule form. After consuming lycopene for 12 months a significant increases in serum lycopene concentration and improvements in sperm motility, sperm motility index, sperm morphology and functional sperm concentration were observed. Lycopene treatment resulted in a 36% successful pregnancies. Other studies are now in progress and their results will further advance our knowledge of the beneficial role of lycopene in male infertility.

A recent review article elaborated on the possible role of lycopene in neurodegenerative diseases including Alzheimer's disease [110]. Due to high levels of oxygen uptake and utilization, high lipid content and low antioxidant capacity, human brain represents a vulnerable organ for oxidative damage. Although the role of antioxidant vitamins in neurodegenerative diseases have been reported in the literature, only a small number of studies have been reported for lycopene. Lycopene was shown to cross the blood brain barrier and be present in the central nervous system in low concentrations. Significant reduction in the levels of lycopene was reported in Parkinson's disease and vascular dementia patients [111]. In the Austrian Stroke Prevention study, lower serum lycopene and α-tocopherol levels were associated with increased risk of microangiopathy [112]. Lycopene was also suggested as providing protection against amyotrophic lateral sclerosis (ALS) disorder in humans [113]. When a population of elderly subjects were tested for functional capacity including the ability to perform self-care tasks, a significant positive correlation was observed between blood lycopene levels and functional capacity [114]. On the basis of the relationship between oxidative stress and neurodegenerative diseases and the potent antioxidant properties of lycopene it is logical to expect further intervention studies to be carried out in the future to address this important area of human health.

Incidence of emphysema, a disorder of the lungs is reported to be high is certain countries of the world. A recent study showed protective role of lycopene in the prevention of emphysema in a mouse model. At a recent conference on the role of processed tomatoes in human health, data was provided for the protective role of lycopene in the prevention of emphysema in a Japanese population. Undoubtedly, future research will also explore the role of lycopene in other human diseases including diabetes, ocular and skin disorders, rheumatoid arthritis, periodontal diseases and inflammatory disorders [33]. The antioxidant property of lycopene is also opening up new applications in pharmaceutical, nutraceutical and cosmoceutical products [115].

The scientific interest to explore innovative strategies for the prevention of human diseases underlines the common etiological and mechanistic nature of these diseases. The hypothesis that oxidation of cellular components as an initial event eventually leading to the incidence of several diseases brings the focus to the use of antioxidants. Examples of this hypothesis include oxidation of LDL leading to increases risk of CVD; oxidation of DNA as an early step in the progression of cancers; and protein oxidation resulting in possible alterations in the activity of several metabolic enzymes and influencing many disease conditions. Lycopene by acting as an antioxidant can prevent the progression of many human diseases at an early stage and improve the quality of life.

3.5. Daily intake level estimations and suggested levels of intake

Reports about the daily intake levels of lycopene have varied significantly due to the methods of estimation used. In general they range from 3.7 to 16.2 mg in the United States of America, 25.2 mg in Canada, 1.3 mg in Germany, 1.1 mg in United Kingdom and 0.7 mg in Finland [61]. However, it is important to note that close to half of the population in North America are estimated to consume less than 2 mg of lycopene per day. It is evident that the average intake levels of lycopene are lower than required to provide its beneficial effects. Although the beneficial effects of lycopene in the prevention of human diseases has been well documented it is not yet recognized as an essential nutrient. As a result there is no official recommended nutrient intake (RNI) level set by health professionals and government regulatory agencies. However, based on reported studies a daily intake level of 5–7 mg in normal healthy human beings may be sufficient to maintain circulating levels of lycopene at levels sufficient to combat oxidative stress and prevent chronic diseases [116]. Under the condition of disease such as cancer and cardiovascular diseases, higher levels of lycopene ranging from 35 to 75 mg per day may be required [63].

4. Summary and future directions

Historically, carotenoids have been know to have important beneficial properties for human health. Their biological role in the prevention and perhaps the treatment of human chronic diseases is now being studied and understood. Although the antioxidant properties of some carotenoids have been studied the most other mechanisms such as their pro-vitamin A activity; immune, endocrine and metabolic activities; and their role in cell cycle regulation, apoptosis and cell differentiation are also under intense scientific scrutiny. Future areas of research include their bioavailability, metabolism, mechanisms of action and safety. Epidemiological and other population studies have shown the importance of these phytochemicals in the prevention of human diseases. *In vitro* and animal studies have tested the hypothesis generated from the epidemiological observations. Although some human clinical trials are beginning to be undertaken there is a great need for well-designed human intervention studies that take into consideration study designs including subject selection, end point measurements and the levels of carotenoids being tested. It is only through such studies that our understanding of the important role played by carotenoids will be enhanced and help us develop complementary strategies for the prevention, treatment and management of diseases.

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