Chemistry, Distribution, and Metabolism of Tomato Carotenoids and Their Impact on Human Health

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Recent epidemiological studies have suggested that the consumption of tomatoes and tomato-based food products reduce the risk of prostate cancer in humans. This protective effect has been attributed to carotenoids, which are one of the major classes of phytochemicals in this fruit. The most abundant carotenoid in tomato is lycopene, followed by phytoene, phytofluene, ζ-carotene, γ-carotene, β-carotene, neurosporene, and lutein. The distribution of lycopene and related carotenoids in tomatoes and tomato-based food products has been determined by extraction and high-performance liquid chromatography-UV/Visible photodiode array detection. Detailed qualitative and quantitative analysis of human serum, milk, and organs, particularly prostate, have revealed the presence of all the aforementioned carotenoids in biologically significant concentrations. Two oxidative metabolites of lycopene, 2,6-cyclolycopene-1,5-diols A and B, which are only present in tomatoes in extremely low concentrations, have been isolated and identified in human serum, milk, organs (liver, lung, breast, liver, prostate, colon) and skin. Carotenoids may also play an important role in the prevention of age-related macular degeneration, cataracts, and other blinding disorders. Among 25 dietary carotenoids and nine metabolites routinely found in human serum, mainly (3R,3′R,6′R)-lutein, (3R,3′R)-zeaxanthin, lycopene, and their metabolites were detected in ocular tissues. In this review we identified and quantified the complete spectrum of carotenoids from pooled human retinal pigment epithelium, ciliary body, iris, lens, and in the uveal tract and in other tissues of the human eye to gain a better insight into the metabolic pathways of ocular carotenoids. Although (3R,3′R,6′R)-lutein, (3R,3′R)-zeaxanthin, and their metabolites constitute the major carotenoids in human ocular tissues, lycopene and a wide range of dietary carotenoids have been detected in high concentrations in ciliary body and retinal pigment epithelium. The possible role of lycopene and other dietary carotenoids in the prevention of age-related macular degeneration and other eye diseases is discussed. Exp Biol Med 227:845–851, 2002

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Numerous epidemiological studies have suggested an association between the high intake of carotenoid-rich fruits and vegetables and a reduced risk of cancer (1–3). Fruits and vegetables contain in excess of 40 carotenoids that are routinely absorbed and metabolized by humans (4, 5). Intake of tomato and tomato-based food products contributes to the absorption of a wide range of carotenoids in human serum and tissues. The prominent carotenoid in tomatoes is the red pigment lycopene that is also among the major carotenoids found in human serum. A prospective cohort study by Giovannucci *et al.* (6) indicated that intake of lycopene-rich foods (e.g., tomato sauce, tomatoes, and pizza) was inversely associated with risk of prostate cancer whereas the overall intake of fruits and vegetables were not related. The nutritional significance of lycopene has also been demonstrated in an *in vivo* study of colon cancer involving rodents (7). Levy *et al.* (8) have shown that lycopene is more potent than α- and β-carotene in inhibiting the cell growth of various human cancer cell lines. One hypothesis for the biological activity of carotenoids in disease prevention is based on the antioxidant ability of these compounds that can quench singlet oxygen and other oxidizing species and protect the cells from oxidative damage. In early 1990, we first reported on the detection of the oxidation products of lycopene and lutein in human plasma (4). Because these carotenoids were also abundant in fruits and vegetables associated with a reduced risk of cancers in epidemiological studies, we proposed metabolic pathways for the formation of their oxidation products and concluded that lycopene and lutein can serve as potentially useful chemopreventive agents (9). Although

lycopene has no vitamin A activity, it has been shown to possess strong antioxidant activity *in vitro* (10). In 1998, we reported on the synthesis and characterization of two oxidation products of lycopene detected in human plasma and tomato-based foods (11) and proposed possible pathways for the formation of the oxidative metabolites of this carotenoid (12). Here, we present a review of the distribution of lycopene and related tomato carotenoids in fruits, vegetables, tomato-based food products, human serum, and tissues and discuss the chemistry and metabolic transformation of these compounds in humans.

Lycopene and Related Tomato Carotenoids in Foods

Tomatoes and tomato-based food products are the major source of lycopene and a number of other carotenoids, such as phytoene, phytofluene, ζ-carotene, γ-carotene, β-carotene, and neurosporene (4, 5, 13). Other commonly consumed fruits in the United States that contain lycopene are pink grapefruit and papaya. Apricots (fresh, canned, dried) also contain low concentrations of lycopene and related carotenoids (14). Among these foods that are the major source of hydrocarbon carotenoids, only β-carotene, α-carotene, and γ-carotene are precursors of vitamin A (Fig. 1). Because the reduced risk of prostate cancer has been specifically correlated with the high consumption of tomato-based food products (6), this protective effect has been largely attributed to lycopene. Although lycopene is the major carotenoid in these foods, the presence of a wide range of other carotenoids in tomato-based food products cannot be overlooked. It is quite likely that lycopene in combination with other related tomato carotenoids mentioned above may be responsible for the observed biological activity. In 1995, Tonucci *et al.* (15) reported on the qualitative and quantitative distribution of carotenoids in name-brand and store-brand tomato-based food products purchased in three major U.S. cities. These foods were extracted and analyzed by high-performance liquid chromatography (HPLC) according to the methodology developed by Khachik *et al.* (5, 13). The results from this study are summarized in Table I. Also included in Table I are data on other lycopene-containing foods (pink grapefruit, papaya, apricot) as well as those with similar carotenoid profiles (oranges, mandarin oranges, squash). The carotenoids in these foods have been recently analyzed and quantified by HPLC by the author (F.K.). Although lycopene has, to some extent, been investigated for its biological properties in the prevention of carcinogenesis, other major hydrocarbon carotenoids listed in Table I have not received much attention. Therefore, the contribution of other related tomato carotenoids besides lycopene to the chemoprevention of prostate cancer remains unclear.

Distribution of Tomato Carotenoids in Human Serum, Milk, and Tissues

To date, 25 carotenoids and nine metabolites have been identified and characterized in the extracts from human serum and milk (16–18). A complete list of dietary carotenoids and their metabolites that have been detected in human serum and breast milk is provided in Table II. These are 34 carotenoids consisting of 25 dietary [13 *all-E (trans)*- and 12 *Z (cis)*- compounds] and nine carotenoid metabolites [1 *Z (cis)*- and 8 *all-E (trans)*-compounds]. Two of these metabolites originate from lycopene and five from lutein and zeaxanthin. In addition, two non-enzymatic dehydration products of lutein that are presumably formed in the human digestive system as a result of the presence of acids are listed among these metabolites (19). Therefore, all the dietary carotenoids listed in Table I also are found in high to relatively low concentrations in human serum and milk. Carotenoids in tomato-based food products belong to the class of hydrocarbons, and among these, only lycopene and the vitamin A active carotenoids undergo metabolic conversion. The metabolic transformation of lycopene in humans will be discussed later.

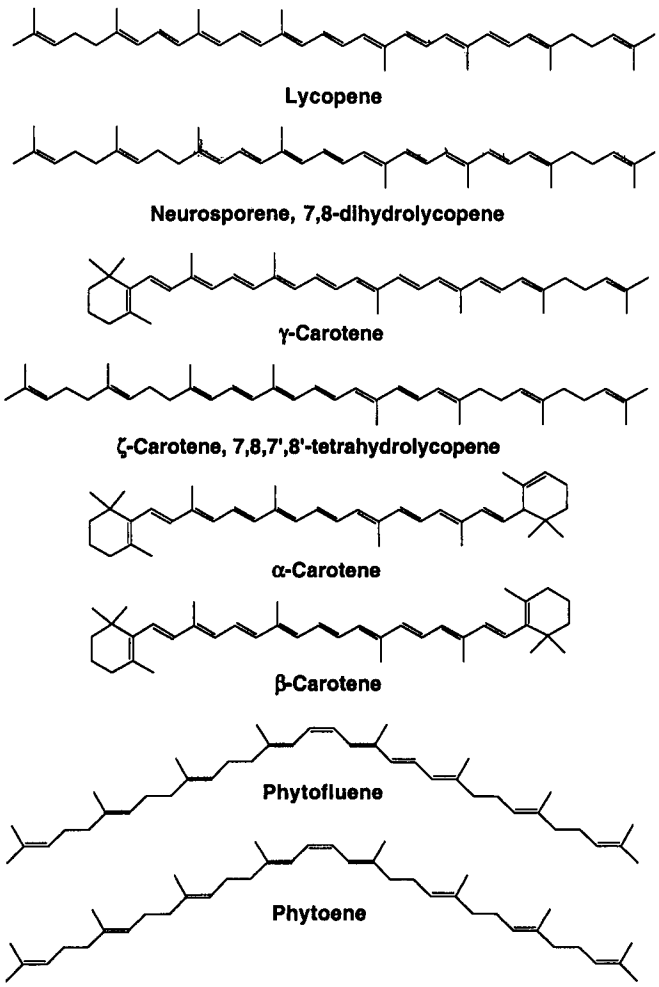

Figure 1. Chemical structures of carotenoids in tomatoes and tomato-based food products.

The presence of carotenoids in various human organs and tissues were reported as early as 1990 (20–24). However, we have reported the detection of a more comprehensive list of dietary carotenoids and their metabolites in μg-ng/g of tissue in human liver, lung, breast, cervix, and skin

Table I. Concentration of Carotenoids in Tomatoes, Tomato-Based Food Products, and Several Fruits and Vegetables With Similar Carotenoid Profiles

Foods	Concentration of carotenoids (mg/100 g)[a,b]									
	Lycopene	α-Carotene	β-Carotene	γ-Carotene	Neurosporene	ζ-Carotene	Phytofluene	Phytoene	Lutein	Zeaxanthin
Tomato paste	55.45	–[c]	1.27	9.98	6.95	0.84	3.63	8.36	0.34	–[c]
Tomato sauce	17.98	–[c]	0.45	3.17	2.48	0.29	1.27	2.95	trace	–[c]
Catsup	17.23	–[c]	0.59	3.03	2.63	0.33	1.54	3.39	–[c]	–[c]
Tomato puree	16.67	–[c]	0.41	2.94	2.11	0.25	1.08	2.40	0.09	–[c]
Spaghetti sauce	15.99	–[c]	0.44	3.02	3.15	0.34	1.56	2.77	0.16	–[c]
Tomato juice	10.77	–[c]	0.27	1.74	1.23	0.18	0.83	1.90	0.06	–[c]
Vegetable juice	9.66	0.21	0.83	–[d]	N.D.	–[d]	0.69	1.71	0.08	–[c]
Tomato	9.27	–[c]	0.23	1.50	1.11	0.21	0.82	1.86	0.08	–[c]
Grapefruit, pink	3.36	–[c]	2.34	1.38	0.38	–[c]	0.01	0.02	–[c]	–[c]
Papaya	2.52	0.02	0.22	0.01	0.05	0.19	0.44	0.68	0.02	0.02
Vegetarian vegetable soup	1.93	0.41	1.50	–[d]	–[d]	–[d]	0.31	0.60	0.16	–[c]
Minestrone soup	1.48	0.21	0.92	–[d]	–[d]	–[d]	0.17	0.28	0.15	–[c]
Vegetable beef soup	0.31	0.46	1.51	–[d]	–[d]	–[d]	0.19	0.35	0.11	–[c]
Apricots										
Fresh	0.01	0.02	1.59	0.08	–[c]	0.04	0.36	0.59	0.09	–[c]
Canned	0.07	0.14	4.76	0.12	–[c]	0.02	0.82	1.01	0.17	–[c]
Dried	0.86	1.60	8.56	0.13	–[c]	0.14	2.00	2.27	0.36	–[c]
Orange	–[c]	0.02	0.06	0.004	0.01	0.10	0.06	0.08	0.35	0.25
Orange, mandarin	–[c]	0.05	0.08	0.05	0.01	0.12	0.14	0.11	0.07	0.06
Squash, butternut	–[c]	1.85	5.21	0.36	0.14	0.72	0.20	0.55	2.38	0.28

[a] Data on tomatoes and tomato-based food products are tabulated from reference 15 with permission.
[b] Data on grapefruit, papaya, apricots, oranges, orange mandarin, and squash were determined by the author F.K. and have not been published elsewhere.
[c] Not detected.
[d] Carotenoids were not quantified because of co-elution of their HPLC peaks with the degradation products of chlorophylls.

(25, 26). These tissues were extracted and analyzed for carotenoids by HPLC using UV/Visible photodiode array detection. In addition to these tissues, we have also recently analyzed carotenoids in the extracts from human colon and prostate using the same methodology. The results as summarized in Table III indicate that all the dietary carotenoids that are present in human serum are also accumulated in these organs and tissues, particularly the liver. 2,6-Cyclolycopene-1,5-diols A and B are metabolites of lycopene that are also found at very low concentrations in tomato products. The presence of these compounds in human serum and tissues might be a result of the *in vivo* oxidation of lycopene. With regard to carotenoid distribution in lung tissue, the relatively high concentrations of lutein, β-cryptoxanthin, lycopene, β-carotene, phytofluene, and particularly phytoene are notable. Over the years, our extensive serum analysis of human subjects with various dietary regimens has revealed that the relative concentration of serum carotenoids is, to some degree, reflective of their ratio in foods. Therefore, the unusually high concentration of phytoene (Table III), relative to the other tomato carotenoids, may be due to a preferential uptake of this compound from serum by the lung tissues. Similarly, the high concentration of ζ-carotene and phytofluene in breast tissue relative to the other carotenoids is particularly interesting. Major carotenoids in cervical tissue appear to be lycopene, β-carotene, and phytofluene; surprisingly, no phytoene could be detected. In all cases the analysis of the extracts from various organs and tissues also revealed the presence of several unidentified apparent degradation products of carotenoids. The data shown in Table III must be considered tentative because these results are the average of a limited number of samples. Analysis of a large number of samples will be needed to establish the normal tissue concentration of specific carotenoids and their metabolites.

Lycopene and Its Metabolites in Human Ocular Tissues

One of the underlying hypotheses for the protective role of carotenoids in age-related Macular Degeneration (AMD) and cataracts has been based on the ability of these carotenoids to act as antioxidants that can protect the human retina from photo-oxidation. In 1997, we provided preliminary evidence for the photo-protective role of two dietary carotenoids, lutein and zeaxanthin, in human retina as antioxidants in the prevention of AMD (27). This was accomplished by isolating and identifying the chemical structure and measuring the concentrations of lutein, zeaxanthin, and their oxidation products in the retinas of 11 human donor eyes and that of one monkey. Although lutein, zeaxanthin, and a direct oxidation product of lutein were found to be the major carotenoids in the retina, 11 minor carotenoids were also identified. Included in the minor carotenoids was 2,6-cyclolycopene-1,5-diol A, which is the major oxidative metabolite of lycopene also found in human serum. Based on these findings, we proposed and postulated a series of reactions in which dietary (3R,3′R,6′R)-lutein and (3R,3′R)-zeaxanthin may be interconverted via their oxidation products to protect the macula against bright light and prevent AMD. More recently, we have identified and quantified lutein, zeaxanthin, and their oxidative metabolites in the pooled extracts from various tissues of the human eye (neu-

Table II. Dietary Carotenoids and Their Metabolites in Human Serum and Breast Milk

Entry	Carotenoids	Chemical class
All-E (trans)-dietary carotenoids*		Hydrocarbons (carotenes)
1	α-carotene*	
2	β-carotene*	
3	γ-carotene*	
4	Lycopene	
5	Neurosporene	
6	ζ-carotene	
7	Phytofluene	
8	Phytoene	
9	α-cryptoxanthin	Monohydroxycarotenoids
10	β-cryptoxanthin*	
11	Lutein	Dihydroxycarotenoids
12	Zeaxanthin	
13	Lactucaxanthin	
Z (cis)-Dietary Carotenoids*		Hydrocarbons (carotenes)
14	9*Z*-β-carotene*	
15	13*Z*-β-carotene*	
16	*Z*-lycopenes	
17	*Z*-phytofluenes	
18	*Z*-β-cryptoxanthin*	Monohydroxycarotenoids
19	13*Z*, 13′*Z*-lutein	Dihydroxycarotenoids
20	9*Z*-lutein	
21	9′*Z*-lutein	
22	13*Z*-lutein + 13′*Z*-lutein	
23	9*Z*-zeaxanthin	
24	13*Z*-zeaxanthin	
25	15*Z*-zeaxanthin	
Z (cis)- and *all-E (trans)*-Carotenoid Metabolites		
26	3′-hydroxy-ε,ε-caroten-3-one	Monoketocarotenoids
27	3-hydroxy-β,ε-caroten-3′-one	
28	*Z*-3-hydroxy-β,ε-caroten-3′-one	
29	ε,ε-caroten-3,3′-dione	Diketocarotenoid
30	3-hydroxy-3′,4′-didehydro-β,γ-carotene	Monohydroxycarotenoids
31	3-hydroxy-2′,3′-didehydro-β,ε-carotene	
32	3′-epilutein	Dihydroxycarotenoids
33	2,6-cyclolycopene-1,5-diol A	
34	2,6-cyclolycopene-1,5-diol B	

* Asterisk denote carotenoids with vitamin A activity.

ral retina, retinal pigment epithelium [RPE/choroid], ciliary body, iris, lens; 28). Lycopene and a diverse range of carotenoids were also identified and quantified in the human ciliary body and RPE/choroid. The distribution of carotenoids in human ciliary body and RPE/choroid is shown in Table IV. These data suggest that carotenoids in human RPE/choroid may provide protection by antioxidant and light-screening mechanisms. This is because RPE/choroid is subjected to comparable light exposure level to neural retina, and carotenoids may play a role in the protection against light-induced oxidative damage. Moreover, the RPE/choroid may be an intermediate control and transfer point for lutein and zeaxanthin uptake by the neural retina from the circulating blood. The levels of carotenoids in the ciliary body are unexpectedly high because this heavily pigmented tissue is not exposed to particularly intense levels of light. It is, however, a metabolically active tissue responsible for aqueous humor formation. Enzymes of the carbonic anhydrase family found in the ciliary body are known to be susceptible to oxidative damage and inactivation (29); therefore, the presence of a diverse range of carotenoids, including lycopene in the human ciliary body, suggests that these pigments might function as antioxidants in this tissue. Whether carotenoids could be useful in the treatment of glaucoma remains to be explored. Our recent unpublished data have also revealed the presence of lycopene in the human iris but no detectable levels were found in the lens. The presence of carotenoids and their oxidation products in iris and lens is consistent with the hypothesized role of these compounds in the prevention and treatment of cataract.

Proposed Metabolic Pathways of Lycopene in Humans

The proposed metabolic transformation of lycopene in humans is shown in Figure 2. These pathways were based on the identification of 2,6-cyclolycopene-1,5-diols A and B in extracts from human serum and milk (18) as well as the detailed studies of the chemical oxidation of lycopene with *m*-chloroperbenzoic acid (11, 12). Numerous oxidation reactions of lycopene with *m*-chloroperbenzoic acid have

Table III. Dietary Carotenoids and Their Metabolites in Human Tissues and Skin

Dietary carotenoids and their metabolites	Average concentration (ng/g) of carotenoids and their metabolites in human tissues[a] and skin[b]						
	Liver (n = 3)	Lung (n = 3)	Breast (n = 3)	Cervix (n = 3)	Prostate (n = 5)	Colon (n = 3)	Skin (n = 3)
Dietary carotenoids							
α-carotene	67	47	128	23.6	50	128	8
β-carotene + Z-isomers	470	226	356	125.3	163	256	26
γ-carotene	–[c]	–[c]	–[c]	–[c]	48	–[c]	20
Lycopene	352	300	234	95.0	374	534	69
ζ-carotene	150	25	734	57.2	187	134	13
Phytofluene	261	195	416	106.3	201	116	15
Phytoene	168	1275	69	–[c]	45	70	65
α-cryptoxanthin	127	31	23	4.0	32	21	–[c]
β-cryptoxanthin	363	121	37	24.3	146	35	–[c]
Lutein + Z-isomers	1701	212	90	23.8	128	452	26
Zeaxanthin + Z-isomers	591	90	14	–[c]	35	32	6
Metabolites							
2,6-cyclolycopene-1,5-diols A + B	576	20	42	–[c]	7	19	7
3′-hydroxy-ε,ε-caroten-3-one	527	22	15	–[c]	–[c]	12	–[c]
3-hydroxy-β,ε-caroten-3′-one	319	24	32	–[c]	–[c]	17	–[c]
ε,ε-caroten-3,3′-dione	314	–[c]	52	–[c]	–[c]	15	–[c]
3′-epilutein	96	11	10	–[c]	–[c]	27	–[c]

[a] Data were obtained from reference 25 with permission.
[b] Data were obtained from reference 26 with permission.
[c] Not detected.

Table IV. Average Concentration of Dietary Carotenoids in Pooled Extracts From Human Ciliary Body and RPE/Choroid

Dietary carotenoids	Average carotenoid concentration (ng/tissue)[a]	
	Pooled extracts from human ciliary body (≈0.20 g) (n = 30)	Pooled extracts from human RPE/choroid (≈0.20 g) (n = 20)
Dihydroxycarotenoids		
Lutein	10.93	18.27
Zeaxanthin	2.54	4.85
Monohydroxycarotenoids		
α-Cryptoxanthin	1.36	N.D.[b]
β-Cryptoxanthin	0.36	N.D.[b]
Hydrocarbon carotenoids		
Neurosporene	4.50	N.D.[b]
γ-Carotene	4.48	N.D.[b]
Lycopene	7.80	8.64
α-Carotene	1.60	2.97
β-Carotene	2.72	10.80
Total	36.29	45.53

[a] Data obtained from reference 28 with permission.
[b] N.D. = not detected.

clearly shown that this compound is first oxidized at the 1,2- and the 5,6-position to form lycopene 1,2-epoxide and lycopene 5,6-epoxide, respectively. Although lycopene 1,2-epoxide was found to be quite stable, lycopene 5,6-epoxide was extremely unstable and underwent cyclization to give a mixture of 2,6 cyclolycopene-1,5-epoxide A and B. Although lycopene epoxides and the rearrangement products of lycopene 5,6-epoxide have not been detected in human serum, their corresponding cyclic diols, 2,6-cyclolycopene 1,5-diols A and B, are present (18). These diols may be formed from acidic and/or enzymatic ring opening of their respective epoxides. The structures of the cyclic diols A and B in human serum have been confirmed by comparison of their HPLC-UV/Vis-MS profile with those of fully characterized synthetic compounds (11). The metabolites of lycopene identified in human serum consist of a novel five-membered ring end-group with three asymmetric centers at C-2, C-5, and C-6. Although the relative configurations at C-2, C-5, and C-6 for synthetic 2,6 cyclolycopene-1,5-diols A and B have been determined by ^{1}H and ^{13}C-NMR, the absolute configurations of these diols are not known at present. The origin of the metabolites of lycopene in human serum may be due to the presence of trace amounts of these compounds in tomato-based products. However, the concentration of 2,6 cyclolycopene-1,5-diols A and B in raw tomatoes and tomato-based products is extremely low and probably would not account for their presence in human serum. The origin of the lycopene metabolites in human serum is not very well understood at present. This is because 2,6-cyclolycopene-1,5-diols A and B and their precursors of 2,6-cyclolycopene-1,5-epoxides A and B are found in tomato paste and tomato juice in extremely low concentrations (12). Lycopene 5,6-epoxide is undoubtedly the precursor of the lycopene metabolites in human serum. Lycopene 5,6-epoxide and lycopene 1,2-epoxide can be formed by several processes because it is the instability of lycopene that makes this compound readily susceptible to oxidation. The oxidation of lycopene may be part of the natural me-

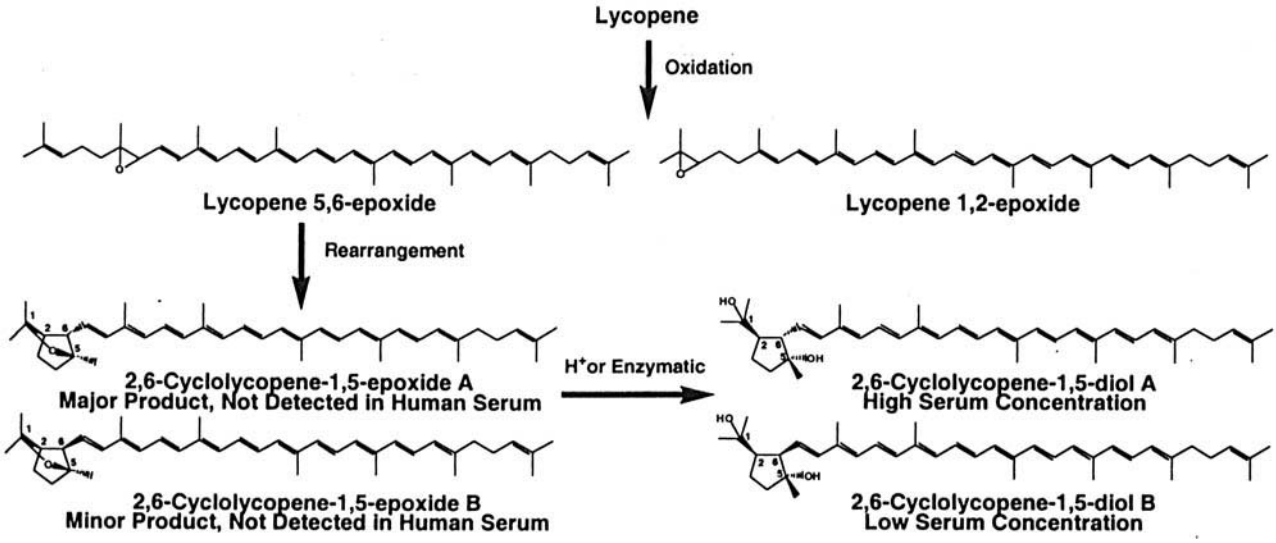

Figure 2. Proposed metabolic pathways for the formation of the oxidation of lycopene in humans.

tabolism in tomatoes or this oxidation can also take place because of the exposure of tomato-based food products to severe heat during processing at relatively high temperatures. Alternatively, lycopene may undergo *in vivo* oxidation in humans as part of its normal metabolism to form these lycopene epoxides. Once lycopene 5,6-epoxide is formed, it can rearrange to 2,6-cyclolycopene-1,5-epoxides A and B in the acidic tomatoes; this reaction may also be catalyzed by certain enzymes in humans. Conversion of lycopene 5,6-epoxide to 2,6-cyclolycopene-1,5-epoxides A and B followed by hydrolysis to their corresponding diols may be non-enzymatic and take place in human stomach in the presence of acids. The presence of low concentration of some of the lycopene metabolites in tomatoes and human serum may also be related to the physiological function of lycopene as a radical scavenger. Unfortunately, the fact that 2,6-cyclolycopene-1,5-diols A and B and their precursor 2,6-cyclolycopene-1,5-epoxides A and B are also found in tomato products at low concentrations makes it difficult to differentiate between the various processes which may ultimately be responsible for the presence of these compounds in human serum and tissues. If the *in vivo* oxidation of lycopene in humans is indeed taking place, one would not expect to find the resulting epoxides in the serum. This is because, to date, our extensive analysis of the serum of human volunteers who consume large quantities of fruits and vegetables rich in carotenoid epoxides has not revealed the presence of these groups of carotenoids in humans (16–18). Therefore, the metabolic oxidation of lycopene in humans is more likely to involve enzymatic ring opening of 2,6-cyclolycopene-1,5-epoxides A and B to the observed diols. For example, the microsomal epoxide hydrolase has been reported to catalyze the *trans*-antiplanar addition of water to epoxides to give vicinal diols by involving an ester intermediate (30). Enzymes of this nature may also be responsible for the rearrangement of lycopene epoxides to 2,6-cyclolycopene-1,5-epoxides A and B as well as their respective diols A and B. However, if lycopene 5,6-epoxide is the initial product of the *in vivo* oxidation of lycopene in humans, the enzymatic conversion of this epoxide to the cyclic diols A and B, with or without the involvement of the cyclic epoxides A and B, need to be first established. In 1998, we reported a human bioavailability and metabolic study with lycopene supplements and provided preliminary evidence for the *in vivo* oxidation of lycopene to its observed metabolites in serum (31). Nonetheless, in the absence of human metabolic studies with isotopically labeled lycopene, that is, ^{13}C, the *in vivo* oxidation of lycopene in humans would be a difficult task to accomplish.

SUMMARY AND CONCLUSION

In this review we have presented epidemiological and experimental evidences that indicate tomato-based food products which contain lycopene and a diverse range of hydrocarbon carotenoids could play an important role as chemoprotective agents against cancer. The distribution of carotenoids in tomato-based food products, human serum, and prostate tissues suggest that lycopene as well as related tomato carotenoids, e.g. ζ-carotene, phytofluene, phytoene, γ-carotene, and neurosporene may be responsible for the observed protective effect against prostate cancer in epidemiological studies. A recent phase II randomized clinical trial of lycopene supplementation before radical prostatectomy clearly demonstrates the presence of all the serum carotenoids including the fore-mentioned tomato carotenoids in the benign prostate tissue (32). Therefore, it is quite likely that lycopene in concert with other tomato carotenoids may be responsible for the observed protective effect against prostate cancer. While the chemoprevention and early stage treatment of prostate cancer with purified lycopene in clinical trials should be investigated, the collective protective effect of other tomato carotenoids cannot be overlooked. Howver, because of the costs associated with such studies, it would be impractical to investigate each of the tomato carotenoids in a single clinical trial of prostate cancer. One approach would be to investigate the

efficacy of a mixture of carotenoids (multicarotenoid) in a clinical study that could be designed similar to those conducted with purified lycopene. The nature and composition of such a multicarotenoid can be based on the diverse range of carotenoids that are known to accumulate in the human prostate tissues and are listed in Table III.

In addition, lycopene and related tomato carotenoids are also present at biologically significant concentrations in human RPE/ choroid and ciliary body and may protect these tissues against oxidative damage to maintain the health and proper function of the human eye. Current investigations of the role of carotenoids in the prevention of AMD are focussed on lutein and zeaxanthin that are the only carotenoids found in the neural retina of the human eye. Meanwhile, the physiological functions of lycopene and a diverse range of other dietary carotenoids that are present in certain humam ocular tissues, remain unexplored.

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