

## REVIEW

# Bioavailability of Dietary Carotenoids: Intestinal Absorption and Metabolism

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### Abstract

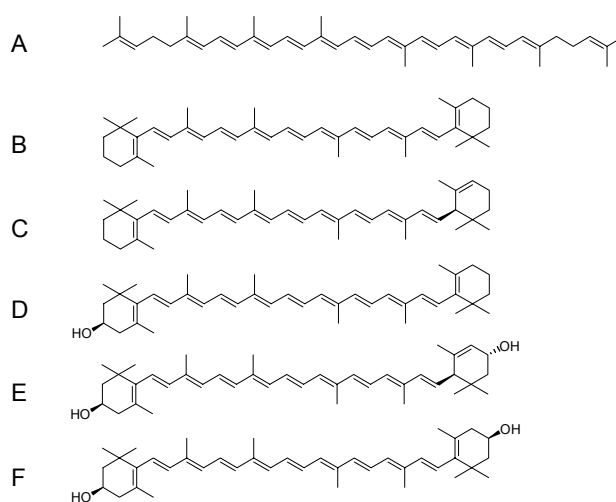
Various carotenoids with diverse structures are present in foods and have been reported to have beneficial effects on human health. Owing to their hydrophobicity, however, poor solubilization in the aqueous milieu of the digestive tract restricts their intestinal absorption. Fats and oils were found to increase the solubilization of carotenoids into mixed-micelles, which would therefore enhance their bioavailability. The uptake of carotenoids solubilized in the micelles by intestinal cells are thought to be mediated by simple diffusion and/or facilitated diffusion through scavenger receptors. Lipids that constituted the mixed-micelles affected the uptake of carotenoids. In particular, lysophosphatidylcholine significantly enhanced uptake. Highly polar carotenoids, meanwhile accumulated in mice but not in humans, suggesting discriminate absorption and metabolism in the latter. The metabolism of provitamin A carotenoids is well known to be mediated by the central cleavage enzyme. Recently, another cleavage enzyme was found to cleave various carotenoids asymmetrically into apocarotenoids. Xanthophylls were found to be oxidized to unstable keto-carotenoids in mice. These metabolic conversions are thought to affect the levels of bioavailable carotenoids in tissues. In this article, the solubilization into mixed-micelles, intestinal absorption and oxidative metabolism of carotenoids are reviewed to understand the factors that determine the bioavailability of carotenoids ingested from fruit and vegetables.

**Discipline:** Food

**Additional key words:** antioxidant, bioaccessibility,  $\beta$ -carotene, carotenoid, lutein

## Introduction

Carotenoids are a group of isoprenoids synthesized by plants and microorganisms. Most carotenoids have a long carbon chain skeleton with a series of conjugated carbon-carbon double bonds (Fig. 1.). This conjugated polyene structure endows carotenoids with warm colors from yellow to red as well as antioxidant activity. Carotenoids are crucial for plants' photosynthetic apparatus due to their function as light harvesting antenna pigments and antioxidants. Small molecules derived from carotenoids also work as hormones such as abscisic and trisporic acids in plants and fungi, respectively. In animals, carotenoids must be ingested in the diet because *de novo* synthesis of carotenoids is lacking in animals, except for some arthropods. Carotenoids are utilized for pigmentation of ornaments in birds and other animals. Vitamin A, small molecules derived from provitamin A carotenoids, also plays an essential role in cell differentiation, morphogenesis and vision in vertebrates.



**Fig. 1. Major carotenoids in human plasma**

A, lycopene; B,  $\beta$ -carotene; C,  $\alpha$ -carotene; D,  $\beta$ -cryptoxanthin; E, lutein; F, zeaxanthin.

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In addition to these physiological functions, carotenoids have been thought to prevent degenerative diseases such as cancer, atherosclerosis and age-related macular degeneration in humans, due to their potential to suppress oxidative lesions by scavenging peroxy radicals and quenching singlet oxygen. Other various biological activities of carotenoids such as immune enhancement, anti-inflammation, and anti-obesity are also thought to benefit human health.

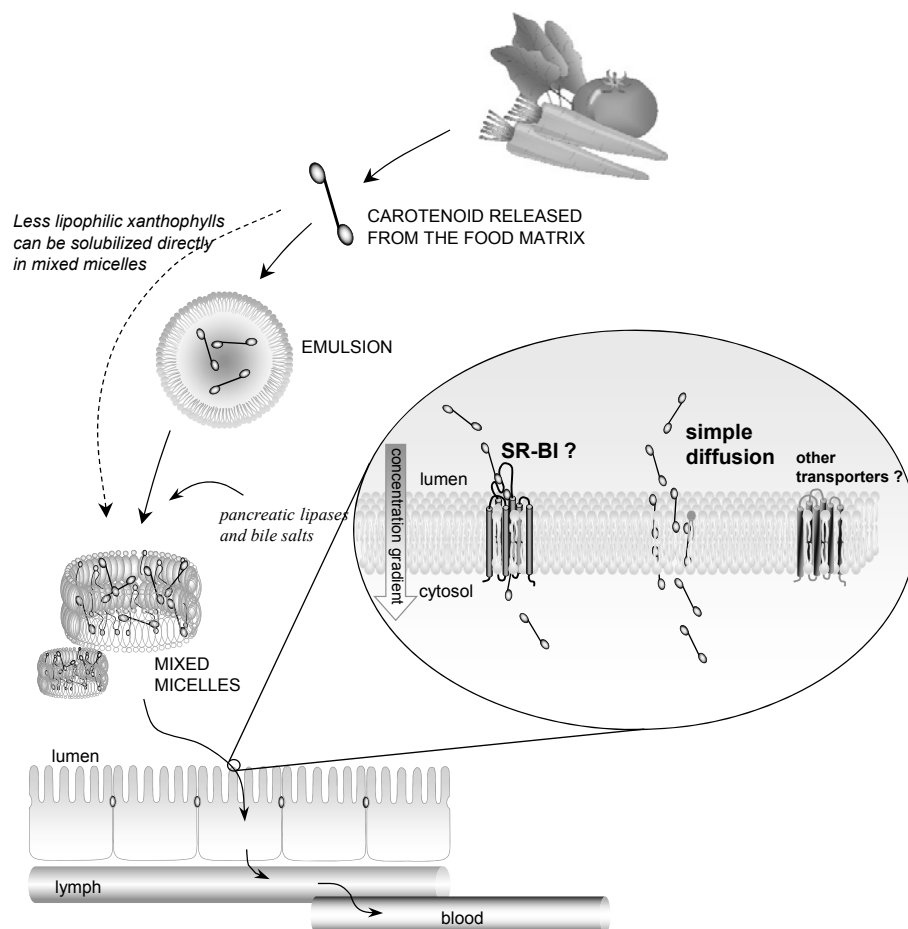
More than 600 carotenoids with diverse structures are present in nature and about 40 of which are ingested in the human diet. Despite the health benefits of dietary carotenoids, they are less bioavailable than other lipophilic nutrients, primarily due to extreme hydrophobicity. In general, the bioavailability of functional food ingredients in diets is one of the key factors affecting actual biological effectiveness. Ingestion of diets with higher content of functional ingredients does not necessarily mean higher intestinal absorption and accumulation in the human body. Thus, it is worth elucidating the various factors that affect the bioavailability of functional food ingredients. The bioavailability of dietary carotenoids depends on several steps: release from the food matrix, solubilization in the digestive tract, absorption in intestinal epithelia, and metabolism (Yonekura et al.

2007). In this paper, these steps critical to bioavailability are reviewed by introducing our recent research on dietary carotenoids.

## Solubilization

At an early stage of digestion, carotenoids must be released from food matrices. However, carotenoids present in vegetables are generally difficult to release due to rigid cell walls. In this sense, carotenoids in ripe fruit are more readily released than those in fresh vegetables. Destruction of food matrices by cooking and processing enhances the release of carotenoids and substantially improves their bioavailability in vegetables.

In subsequent steps, the carotenoids released must be effectively dispersed in the digestive tract, and finally, solubilized in mixed-micelles. Most carotenoids have a highly hydrophobic skeleton consisting of conjugated polyene and are solid but not oily at body temperature, which means that carotenoids hardly disperse in the aqueous milieu of digesta. The efficacy of dispersion and solubilization significantly affect bioavailability, because solubilization is a prerequisite for absorption by intestinal epithelia (Fig. 2).



**Fig. 2. Scheme of dietary carotenoid absorption**

(From Yonekura and Nagao 2007, © 2007 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

Carotenoids released from food matrices are dispersed with the aid of bile, which contains bile salts and phosphatidylcholine. Thereafter, carotenoids are solubilized in mixed-micelles, which are formed through hydrolysis of lipids emulsified in digesta by lipolytic enzymes in pancreatic juice. The mixed-micelles comprise bile acids, cholesterol, lysophosphatidylcholine, fatty acid and monoacylglycerol. A portion of the dietary carotenoids solubilized in the mixed-micelles is taken up into the intestinal epithelia, meaning solubilization of carotenoids in the mixed-micelles is an important process for bioavailability. In other words, bioaccessibility, which is defined as the ratio of solubilized carotenoids relative to the total carotenoid ingested, is a crucial for bioavailability.

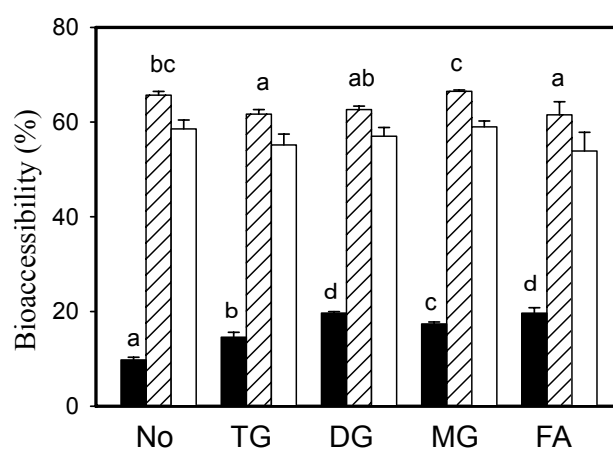
Fats and oils have been known to increase the bioavailability of lipophilic micronutrients, while several reports have demonstrated that intake of fats and oils enhanced the bioavailability of dietary carotenoids. One reason for this enhancement is the increased bioaccessibility of carotenoids by dispersing carotenoids in the digestive tract. Nagao et al. evaluated the effects of fats and oils on the bioaccessibility of carotenoids in vegetables using a simulated-digestion system (Nagao et al. 2013). Blended spinach leaves were digested with several lipids, and solubilized amounts of  $\beta$ -carotene, lutein and  $\alpha$ -tocopherol were determined by HPLC. The bioaccessibility of  $\beta$ -carotene was enhanced by adding lipids in the following order: trioleoylglycerol < monooleoylglycerol < dioleoylglycerol and oleic acid (Fig. 3). It should be noted that the hydrolyzates of triacylglycerol were more effective in enhancing the bioaccessibility of  $\beta$ -carotene than triacylglycerol per se. Among free fatty acids, unsaturated long-chain fatty acids enhanced the bioaccessibility of  $\beta$ -carotene in spinach leaves more efficiently than medium-chain fatty acids. These results indicated that the amphiphilic properties of triacylglycerol hydrolyzates are responsible for solubilizing  $\beta$ -carotene. This was also supported by the fact that medium-chain triacylglycerol was less effective than long-chain triacylglycerol, although the former has higher solubility of carotenoids than the latter. The solubility of carotenoids in triacylglycerol was less important for solubilization into the mixed-micelles. Long-chain free fatty acids formed from triacylglycerols would enhance solubilization more effectively than medium-chain fatty acids. Under the tested conditions, the solubilizing  $\beta$ -carotene was markedly enhanced, but not those of lutein and  $\alpha$ -tocopherol. In general, less hydrophobic carotenoids and other lipophilic vitamins would be more easily solubilized in the mixed-micelles without adding lipids, which means their solubilization by lipids would be less remarkable.

Other food components also affect the bioaccessibility of dietary carotenoids. Dietary fibers have been thought to decrease bioaccessibility by binding bile acids. Phytosterols

may also inhibit solubilization of carotenoids into mixed-micelles. Accordingly, many factors are involved in solubilizing dietary carotenoids. Processing and cooking foods, and correctly combining food materials should be elaborated to enhance the bioaccessibility of carotenoids. The development of new cultivars aiming to increase the bioaccessibility of carotenoids is also desirable to ensure the health benefit of certain carotenoid-rich fruit and vegetables.

### Intestinal absorption

Carotenoids solubilized in mixed-micelles are taken up by the epithelial cells of the jejunum and incorporated into the chylomicron. Thereafter, the carotenoid-containing chylomicron particles are secreted into the lymph and circulated within the body (Fig. 2). The transfer of carotenoids from mixed-micelles to intestinal cells was thought to be mediated by simple diffusion dependent on the concentration gradient across the cellular membrane. When carotenoids solubilized in the mixed-micelles compatible with those formed in the intestine were incubated with human intestinal Caco-2 cells, a positive relationship was found between the hydrophobicity of carotenoids and the amount of carotenoid taken up by

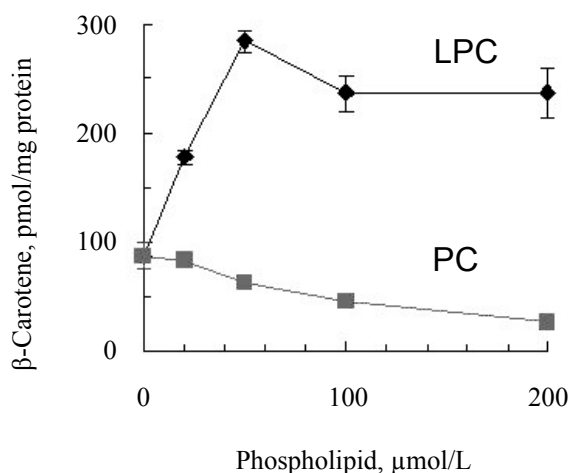


**Fig. 3. Effects of acylglycerols and fatty acid on the bioaccessibility of  $\beta$ -carotene, lutein and  $\alpha$ -tocopherol in spinach**

Spinach homogenate was digested in vitro without lipid (No) or with the following lipids: trioleoylglycerol (TG), dioleoylglycerol (DG), monooleoylglycerol (MG) and oleic acid (FA). The bioaccessibility of  $\beta$ -carotene (closed bar), lutein (hatched bar) and  $\alpha$ -tocopherol (open bar) was evaluated. Bars represent means and SD of data from each triplicate digestion from a single experiment, selected from three independent experiments with similar results. The values of  $\beta$ -carotene and lutein not sharing a common letter differ significantly among the lipids by the Tukey-Kramer test ( $P < 0.05$ ), while those of  $\alpha$ -tocopherol are not significantly different. (From Nagao et al. 2013, © Japan Society for Bioscience, Biotechnology and Agrochemistry)

the cells (Sugawara et al. 2001). This relationship would support a simple diffusion mechanism, because lipophilic substances can move across the lipid bilayer of a cellular membrane more readily than polar substances.

The constituents of the mixed-micelles, in which carotenoids are solubilized, would significantly affect the uptake of carotenoids by intestinal cells. In particular, the presence of lysophosphatidylcholine in the micelles was found to increase the uptake of carotenoids by Caco-2 cells, while phosphatidylcholine suppressed the uptake as shown in Fig. 4 (Sugawara et al. 2001). Pancreatic phospholipase A<sub>2</sub> hydrolyzes one of the two fatty ester bonds of phosphatidylcholine derived from bile and food to produce less lipophilic lysophosphatidylcholine in the intestinal tract. Accordingly, lysophosphatidylcholine would have a physiologically relevant function in promoting the intestinal uptake of lipophilic nutrients. The promoting effect of lysophosphatidylcholine was correlated with the chain length of fatty acid moiety, with longer chain species showing a higher promoting effect. Unlike ordinary phosphatidylcholine with a long-chain fatty acid, medium-chain phosphatidylcholine, which is not present in biological tissues, showed a promoting effect equivalent to long-chain lysophosphatidylcholine (Yonekura et al. 2006). Medium-chain phosphatidylcholine has hydrophile-lipophile balance equivalent to long-chain lysophosphatidylcholine, but at a higher level than long-



**Fig. 4. Effect of micellar phospholipid content on micellar carotenoids absorption by Caco-2 cells**

Differentiated Caco-2 cell monolayers (20-22 day-old) were incubated in DMEM medium containing micelles comprising 1 μmol/L β-carotene, 2 mmol/L sodium taurocholate, 100 μmol/L monoolein, 33.3 μmol/L oleic acid and various amounts of phosphatidylcholine (PC) or lysophosphatidylcholine (LysoPC) for 2 h. The data represent the mean ± SD of three wells. Replicate experiments demonstrated a similar trend. (modified from Sugawara, et al. 2001, © 2001 American Society for Nutrition)

chain phosphatidylcholine. These results suggest that the amphiphilic nature of long-chain lysophosphatidylcholine enhances uptake by acting on the lipid-bilayer structure in the plasma membrane.

Fatty acids and monoacylglycerols, which are constituents of mixed-micelles, were also found to affect the uptake of carotenoids by Caco-2 cells (Kotake-Nara et al. 2012). Moreover, various phospholipids with different polar head groups affected the uptake (Kotake-Nara et al. 2010). Thus, lipophilic substances derived from diets would be incorporated into mixed-micelles and might affect the uptake of dietary carotenoids. Apart from the constituents of mixed-micelles, soluble fibers were found to decrease the uptake of carotenoids by Caco-2 cells, possibly by enhancing the viscosity of the media and thereby suppressing the diffusion of the micelles to the cells (Yonekura et al. 2009). Accordingly, food components ingested together with carotenoids would affect the uptake of carotenoids by intestinal cells. Selecting appropriate food materials and combinations would improve the bioavailability of dietary carotenoids by enhancing their cellular uptake as well as their solubilization into mixed-micelles.

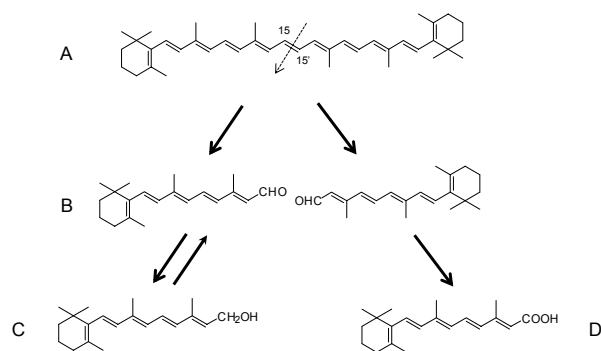
In addition to the simple diffusion mechanism for cellular uptake of carotenoids into intestinal epithelia, scavenger receptor class B type 1 (SR-B1) and cluster determinant 36 (CD36) have recently been found to mediate facilitated diffusion, based on in vitro study using human intestinal cells (Borel et al. 2013, During et al. 2005). The in vivo intestinal absorption of β-carotene was lower in SR-B1 knockout mice than wild-type mice fed a high-fat and high-cholesterol diet (van Bennekum et al. 2005). However, even in the knockout mice, the absorption of β-carotene was not completely abolished, which means absorption mediated by other receptors or simple diffusion cannot be ruled out, and it is likely that several absorption pathways by different mechanisms work together with SR-B1-mediated absorption (Fig. 2). Significant interindividual differences in carotenoid accumulation have been known to occur in human plasma. Recently, it was suggested that plasma levels of several provitamin A carotenoids are associated with genotypes of genes encoding SR-B1 and CD36 in human subjects (Borel et al. 2013). Genetic variants of the proteins that mediate facilitated diffusion might be partly responsible for interindividual differences in carotenoid bioavailability. Special dietary programs are desirable for individuals with genotypes indicating a poor response in terms of the intestinal uptake of dietary carotenoids.

Humans ingest no less than 40 carotenoids from common fruit and vegetables. However, the major carotenoids found in human tissues are limited to the following few: β-carotene, α-carotene, lycopene, β-cryptoxanthin, lutein and zeaxanthin (Fig. 1). Despite the fact highly polar xanthophylls like neoxanthin and violaxanthin are ubiquitously

distributed in green leafy vegetables, they and their metabolites have never been found in tissues of human subjects with normal dietary habits. Indeed, Asai et al. evaluated the plasma carotenoids of healthy subjects who ingested a stirred spinach dish containing neoxanthin (3.0 mg) and violaxanthin (6.5 mg) every day for lunch for 1 week (Asai et al. 2008). While levels of plasma lutein and  $\beta$ -carotene significantly increased, levels of neoxanthin, violaxanthin and their possible metabolites remained below the quantification limits. Conversely, in previous animal studies, neoxanthin and its metabolites accumulated in mouse plasma at a level comparable to  $\beta$ -carotene and lutein, although the response of the latter two carotenoids was lower in mice than in humans (Asai et al. 2004, Baskaran et al. 2003). These results suggest that humans accumulate carotenoids selectively, possibly by discriminative uptake and/or re-excretion by intestinal cells and metabolism in the body, in contrast with mice. Human beings and other primates are also unique species in that they accumulate carotenoids at a high level (Slifka et al. 1999). The selective accumulation acquired by humans during evolution can be neither fortuitous nor meaningless, but must be relevant to human health. Physiological roles and underlying mechanisms behind the discriminate accumulation of carotenoids in humans are worth investigating.

## Metabolism

In addition to intestinal absorption, post-absorption distribution and metabolism also affect the bioavailability of carotenoids. The metabolism of carotenoids in mammals has not been revealed except for conversion to vitamin A. It is well known that provitamin A carotenoids such as  $\beta$ -carotene,  $\alpha$ -carotene, and  $\beta$ -cryptoxanthin are converted to

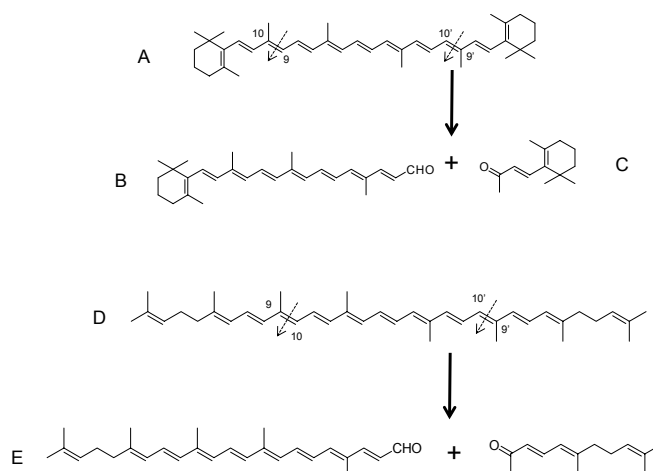


**Fig. 5. Conversion of provitamin A carotenoid to vitamin A by central cleavage**

$\beta$ -Carotene (A) is cleaved to two retinal (B) molecules, which is further reduced to retinol (C) or irreversibly oxidized to retinoic acid (D).

vitamin A by a central cleavage enzyme, namely,  $\beta$ -carotene 15,15'-oxygenase in intestinal epithelia and other tissues (During et al. 1996, Nagao et al. 1996, Nagao et al. 1994, Olson et al. 1965) as shown in Fig. 5. Recently, an asymmetric cleavage enzyme has been found to be coded in the genome of mammals. This new cleavage enzyme can cleave the double bond at C9 and C9' of lutein and lycopene as well as provitamin A carotenoids to a pair of cleavage products with different chain length (Kiefer et al. 2001) as shown in Fig. 6. Although the asymmetric cleavage of provitamin A is thought to be involved in another pathway to vitamin A synthesis, its physiological roles remain to be clarified. Naturally, these cleavage enzyme activities affect the carotenoid levels in tissues. Indeed, cows that had defects in the asymmetric cleavage enzyme showed high levels of  $\beta$ -carotene in plasma and milk (Berry et al. 2009). Similarly, a missense mutation in the gene of the central cleavage enzyme was found in a human subject with hypercarotenemia (Lindqvist et al. 2007). Thus, it has been suggested that polymorphisms of cleavage enzyme genes significantly affect carotenoid levels in tissues of individual subjects (Wang et al. 2013).

In fish and birds, carotenoid metabolites that retain a polyene backbone have been identified, and both reductive and oxidative metabolic pathways have been proposed. In human plasma, several carotenoids that were not present in diets have been identified and are thought to be metabolites and/or reaction products with reactive oxygen species. No enzymatic reaction in any vertebrate had been identified, until Asai et al. demonstrated that mouse liver microsomes catalyzed the dehydrogenation of fucoxanthinol dependent on a coenzyme of NAD and subsequent isomerization to produce amarouciaxanthin A (Asai et al. 2004). Fucoxanthinol and amarouciaxanthin A were found in the tissues of mice fed with fucoxanthin, which is present in brown algae

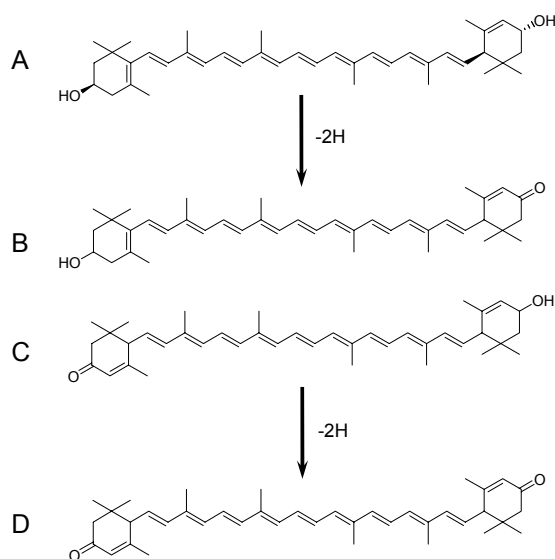


**Fig. 6. Asymmetric cleavage of carotenoids**

A,  $\beta$ -carotene; B,  $\beta$ -apo-10'-carotenal; C,  $\beta$ -ionone; D, lycopene; E, apo-10'-lycopenal.

such as konbu and wakame. Yonekura et al. also found lutein metabolites in mice fed with lutein (Yonekura et al. 2010). Metabolites such as 3'-hydroxy- $\epsilon,\epsilon$ -caroten-3-one and  $\epsilon,\epsilon$ -carotene-3,3'-dione were present as major carotenoids in the tissues of mice fed with lutein, suggesting the dehydrogenation of the hydroxyl group and double bond migration in lutein. These keto-carotenoids derived from lutein have already been reported in human tissues, suggesting metabolic activity in humans equivalent to that in mice. Therefore, these results suggest that mammals have metabolic activity to oxidize hydroxyl groups of xanthophylls to produce keto-carotenoids (Fig. 7). It is possible that these keto-carotenoids have unique biological activity, due to their  $\alpha,\beta$ -unsaturated carbonyl structure, which is known to be highly reactive with nucleophilic molecules like the thiol group of proteins. The keto-carotenoids are unstable, particularly under alkaline conditions. If the keto-carotenoids readily decompose in the body, the metabolism of keto-carotenoid formation can be assumed to eliminate xanthophylls from the body as the cleavage reactions decrease the carotenoid level. Accordingly, the metabolic activities for cleavage of polyene and oxidation in the hydroxyl group of carotenoids are important factors affecting their levels in tissues. Genetic variants in the activities of the responsible enzymes would result in interindividual differences in carotenoid bioavailability.

The various factors that affect the bioavailability of dietary carotenoids have been realized in terms of bioaccessibility, uptake by intestinal cells, and metabolism. Further studies are needed to improve the bioavailability from fruit and vegetables. Although processing and cooking enhance bioaccessibility significantly, it is important to find out which



**Fig. 7. Proposed oxidative pathway of lutein in mammals**

- A, lutein; B, 3-hydroxy- $\beta,\epsilon$ -caroten-3'-one,  
C, 3'-hydroxy- $\epsilon,\epsilon$ -caroten-3-one;  
D,  $\epsilon,\epsilon$ -carotene-3,3'-dione.

cultivars have the highest bioaccessibility, and to develop them by breeding. Further progress in research on how intestinal absorption and metabolism is related to genetics would facilitate dietary programs specifically designed for individuals with genetic variants hindering their response to dietary carotenoids.

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