

Absorption, metabolism, and functions of β -cryptoxanthin

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β -Cryptoxanthin, a carotenoid found in fruits and vegetables such as tangerines, red peppers, and pumpkin, has several functions important for human health. Most evidence from observational, in vitro, animal model, and human studies suggests that β -cryptoxanthin has relatively high bioavailability from its common food sources, to the extent that some β -cryptoxanthin-rich foods might be equivalent to β -carotene-rich foods as sources of retinol. β -Cryptoxanthin is an antioxidant in vitro and appears to be associated with decreased risk of some cancers and degenerative diseases. In addition, many in vitro, animal model, and human studies suggest that β -cryptoxanthin-rich foods may have an anabolic effect on bone and, thus, may help delay osteoporosis.

INTRODUCTION

β -Cryptoxanthin is an oxygenated carotenoid with a chemical structure similar to, but more polar than, β -carotene. Although β -carotene is present in large amounts in numerous fruits and vegetables, β -cryptoxanthin is found at high concentrations in only a small number of foods. Table 1 lists the foods with the highest concentrations of β -cryptoxanthin.¹⁻³

As with other carotenoids, the amount of β -cryptoxanthin in fruits and vegetables seems to depend on cultivar, stage of maturity, growing conditions, storage methods, and season.⁴⁻⁹ Many of the best sources of β -cryptoxanthin are citrus fruits. Not surprisingly, concentrations of β -cryptoxanthin in citrus fruits and in human plasma are highest during the ripening season, in late fall and winter.^{10,11}

Many β -cryptoxanthin-rich foods (such as tangerines and peaches) are eaten raw or juiced, but others (such as pumpkin and butternut squash) are baked or added to mixed dishes. Food processing decreases β -cryptoxanthin concentrations in foods. However, food processing and cooking may increase or decrease the bioaccessibility (i.e., the amount of the nutrient that could be absorbed from the food by a human or other

organism) of β -cryptoxanthin in the food. Milder, shorter cooking methods generally improve bioaccessibility because they soften and disrupt cell walls and denature proteins that can bind β -cryptoxanthin.^{4,5,12-14} However, harsh or prolonged processing, such as refining, drying, or prolonged boiling, can isomerize or destroy carotenoids.^{4,5,12-14}

Despite being found in a limited number of foods that are not staples of the diet, β -cryptoxanthin is a common carotenoid in human blood. In the United States, it is generally the fourth most abundant carotenoid.^{3,4,15,16}

ABSORPTION OF β -CRYPTOXANTHIN

Mechanism

To be absorbed, β -cryptoxanthin must be freed from its food matrix, emulsified into oil droplets, and taken up by cells of the intestinal lining. Few studies have focused on the absorption and metabolism of β -cryptoxanthin. However, like other carotenoids, β -cryptoxanthin seems to be absorbed into the intestine by 2 mechanisms. At low physiological concentrations, it is absorbed mainly by facilitative transport, assisted by enzymes such as scavenger receptor class B type 1 (SR-B1), an epithelia

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transporter also involved in cholesterol and lipid uptake,^{17,18} and cluster determinant 36.¹⁶ At high pharmacological doses, this active transport mechanism is supplemented by passive diffusion.^{19–21}

Most *in vitro*, animal model, and human studies suggest that β -cryptoxanthin is better absorbed from its major food sources than are other common carotenoids. For example, a comparison of the apparent bioavailability (the fraction of the nutrient that becomes absorbed and available for use or storage) of retinoid-forming carotenoids (β -cryptoxanthin, α -carotene, and β -carotene) showed that β -cryptoxanthin was more bioavailable in every population studied.²² This is supported by other studies that found β -cryptoxanthin from orange fruits to be more bioavailable than β -carotene-rich foods.^{23,24}

There are several reasons why the absorption of β -cryptoxanthin from dietary sources might be greater

than that of most other common carotenoids. SR-B1 preferentially facilitates the absorption of xanthophylls (such as β -cryptoxanthin and lutein) over carotenes (such as α - and β -carotene).²⁵ In addition, the position of a carotenoid incorporated into a mixed micelle depends on its hydrophobicity: the less polar the carotenoid, the more likely it is to be located in the interior of the micelle, where it is less available for absorption. β -Cryptoxanthin is more hydrophilic than other important carotenoids such as lycopene, β -carotene, and α -carotene^{3,4} and is thus believed to have relatively higher absorbability due to its presence on the outer surface of micelles and its higher solubility in the aqueous environment of the intestine. Indeed, the percentage of β -cryptoxanthin incorporated into micelles during *in vitro* digestion is 3 times greater than that of β -carotene under similar conditions.²⁶

Carotenoids are crystalline in form and are dissolved within oil droplets in the chromoplasts of yellow and orange fruits such as papaya, tangerines, and sweet potatoes.^{27,28} Considerable evidence shows they are extracted and digested more easily than carotenoids bound to pigment-protein complexes within the chloroplasts of leafy green vegetables.^{4,23,24,27,29} The addition of oil or fat increases the bioaccessibility of most carotenoids in foods,^{3,4,30,31} though there is limited information available on this for β -cryptoxanthin.

Absorbed β -cryptoxanthin can either be converted to retinal in the enterocytes or packaged into chylomicrons and excreted into lymph.^{20,32} These chylomicrons can then be secreted into the bloodstream, where they can be transported into cells. During fasting states, approximately 75% of plasma β -carotene and lycopene is associated with low-density lipoprotein and about 25% with high-density lipoprotein. Oxygenated xanthophylls,

Table 1 Common foods rich in β -cryptoxanthin^a

Food	β -Cryptoxanthin ($\mu\text{g}/100\text{ g of food}$)
Butternut squash	3471
Persimmons	1447
Hubbard squash	1119
Hot chili peppers	1103
Tangerines (canned; raw)	775; 407
Papaya	589
Sweet red peppers	490
Rose hips	483
Sweet pickles	271
Carrots	199
Kumquats	191
Orange juice	169
Sweet corn	161
Oranges	116

^aData from the USDA/ARS National Nutrient Database For Standard Reference, Release 27 (2014).¹

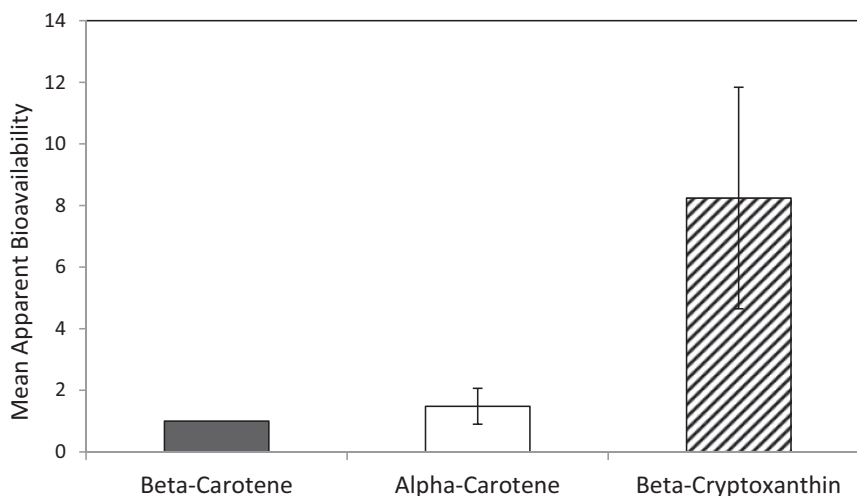


Figure 1 Apparent bioavailability of alpha-carotene and beta-cryptoxanthin from typical diets relative to the bioavailability of beta-carotene from the same diet (\pm SEM). Data from 9 food frequency questionnaires of 5824 individuals and 4 food record studies of 113 individuals; Burri et al. (2011).²²

such as β -cryptoxanthin, are more evenly distributed between low-density lipoprotein and high-density lipoprotein.^{20,32,33} Chylomicron remnants are transported to the liver, where some β -cryptoxanthin is converted into retinal and, subsequently, into retinol and retinyl esters.^{20,33}

Bioaccessibility and bioavailability

β -Cryptoxanthin appears to be much better absorbed than other carotenoids.^{22–24} A comparison of apparent bioavailability between different provitamin A carotenoids showed that β -cryptoxanthin-rich foods had 725% greater bioavailability than β -carotene-rich foods (Figure 1).²²

The absorption of β -carotene from food varies greatly, for reasons that include the food matrix, the presence or absence of fat, and human factors such as health status or genetic differences.^{34–38} The absorption of β -cryptoxanthin is probably influenced by many of the same factors that influence the absorption and bioavailability of other carotenoids: it appears to depend on the nutritional status, genetics, and digestive health of the subject, the amount and type of carotenoids present, the food matrix, and the presence of fat and other nutrients in the diet.^{3,4,10,20,32,33} Within foods, many carotenoids are bound to proteins that must be denatured by bile acids.^{3,4} Very low-fat diets can decrease carotenoid digestion and absorption, but the effect of fat in the diet is inconsistent and appears to be small.^{38–40}

β -Cryptoxanthin may be less affected by these conditions than other carotenoids. In a study comparing carotenoid plasma levels in chronic cholestatic patients with those in age-matched control subjects, β -cryptoxanthin was the only carotenoid not significantly lower in the control group,⁴¹ which may suggest that β -cryptoxanthin is more effectively absorbed and transported despite fat malabsorption or compromised liver function.

The bioaccessibility of free and esterified β -cryptoxanthin seems to be identical.^{42,43} This suggests that humans are capable of efficiently cleaving various β -cryptoxanthin esters in the body, resulting in the existence of only free-form β -cryptoxanthin in the body.

A human study that directly compared the bioavailability of carotenoids from carrot, tomato, and papaya in 16 nonsmoking men and women showed that β -carotene bioavailability from papaya was 3 times greater than carotenoid bioavailability from tomatoes or carrots, and lycopene bioavailability from papaya was 2.6 times greater than that from carrots or tomatoes, suggesting that food matrix impacts bioavailability, with carotenoids in fruit being more bioavailable.⁴⁴ Furthermore, β -cryptoxanthin from papaya was 2.9 times more bioavailable than β -carotene from papaya, potentially indicating that the β -cryptoxanthin molecule itself was more bioavailable than

β -carotene. Thus, observational, in vitro, and human intervention studies suggest that β -cryptoxanthin has greater bioaccessibility and bioavailability than other common carotenoids such as β -carotene, α -carotene, and lycopene.

TISSUE STORAGE AND EXCRETION OF β -CRYPTOXANTHIN

Few studies have investigated the tissue storage and excretion of β -cryptoxanthin, and there is essentially no information on this from human studies,^{3,4,20} mostly because the metabolism of carotenoids in humans is atypical. Unlike most animals, humans absorb some carotenoids whole from the food matrix, with the rest being hydrolyzed by pancreatic enzymes.^{3,4,20} Animals that metabolize carotenoids similarly to humans are rare.^{45,46} The best small animal models of carotenoid metabolism appear to be the Mongolian gerbil and the ferret.

A study in the Mongolian gerbil (*Meriones unguiculatus*), showed that most β -cryptoxanthin was stored in the liver,⁴⁷ with adipose tissue and blood being the other important storage sites. High concentrations of carotenoids per gram of tissue are also found in the adrenal gland. These results are similar to findings for β -carotene^{3,4,20,33,48–51} and other common carotenoids such as lycopene and phytoene.^{52,53} Another similarity is the primary route of excretion, the feces.^{3,4,20,33,48–53} The tissue distribution of β -cryptoxanthin was similar to that in male rats, except that the rat may have higher concentrations in the spleen and brain.⁵⁴ The results suggested that β -cryptoxanthin concentrations in gerbil tissues are saturable, because concentrations did not differ between the groups given the highest dosages of β -cryptoxanthin, except in the pancreas and in the intestines, where they are excreted. In this, too, β -cryptoxanthin appears to be similar to β -carotene.^{3,4,33,37}

The only long-lived metabolites of β -cryptoxanthin in the gerbils were retinoids (retinol and retinyl esters). Other possible metabolites, such as β -apo-10'-carotenal, β -ionone, 3-hydroxy- β -apo-10'-carotenal, 3-hydroxyretinol, and 3,4-didehydroretinol, were not found in any tissue. More studies on the absorption, metabolism, and excretion of β -cryptoxanthin are needed. The available studies suggest that, once absorbed, β -cryptoxanthin is stored in similar tissues as β -carotene and does not seem to form detectable amounts of potentially bioactive metabolites such as apocarotenals, 3-hydroxyretinol, or 3,4-didehydroretinol.

CONCENTRATIONS OF β -CRYPTOXANTHIN IN BLOOD, BREAST MILK, AND TISSUES

β -Cryptoxanthin concentrations in humans are not tightly regulated. Instead, they vary proportionally with

dietary intake.^{3,4,20,33,55–57} No large-scale national or international studies have focused on determining the dietary intake of β -cryptoxanthin. However, intake of β -cryptoxanthin has been measured along with intakes of other common carotenoids in the diet or blood in a variety of populations worldwide. Most dietary surveys report that oranges, orange juice, and tangerines are the major dietary sources of β -cryptoxanthin.^{1,3,15,20,55–57} β -Cryptoxanthin consumption varies widely by country, with unusually high consumptions in Spain and Japan,^{10,58,59} where tangerines are common in the diet, and very low consumption in most developing countries, including Bangladesh.⁶⁰

Plasma β -cryptoxanthin concentrations correlate with total intake of fruits and vegetables, as is typical for carotenoids.^{3,4,22,61–63} Studies show that correlations between dietary intakes and plasma concentrations of β -cryptoxanthin are similar to those for most carotenoids, in the range of $r = 0.2–0.5$.^{61–63}

Concentrations of carotenoids in human breast milk depend mainly on diet and lactation stage,^{64–66} with colostrum (days 4–6 postpartum) containing higher concentrations than more mature milk. Concentrations of β -cryptoxanthin in breast milk vary widely between countries, ranging from 0.012 to 0.080 $\mu\text{mol/L}$ (0.26–2.3 nmol/g lipid).⁶⁴ Interestingly, concentrations of retinol in breast milk were correlated with β -cryptoxanthin concentrations in Australia, Chile, Japan, and the United Kingdom, but not in the other countries studied (including the United States and Canada). There are few studies of β -cryptoxanthin concentrations in human tissues, but β -cryptoxanthin appears to accumulate in adipose tissue in humans,⁶⁷ as it does in gerbils and rats.^{47,54} It has also been detected in human brain.⁶⁸

β -CRYPTOXANTHIN AS A SOURCE OF RETINOL

Mechanisms of retinol formation

It was established many years ago that β -cryptoxanthin forms retinol (vitamin A).^{69–72} Despite this, research on the mechanism of retinol formation from carotenoids has focused almost exclusively on β -carotene. In fact, no recent research has focused on the mechanisms by which β -cryptoxanthin forms retinol. However, some studies of β -carotene metabolism include data on β -cryptoxanthin.^{73–76} These studies suggest that the same enzymes involved in β -carotene cleavage to retinal can also cleave β -cryptoxanthin. Generally, the kinetics of these reactions differ, suggesting that β -carotene is the preferred target of these enzymes. However, because the same enzymes that cleave β -carotene to retinal also

cleave β -cryptoxanthin with relatively good efficiencies, it is probable that β -cryptoxanthin forms retinol by the same mechanisms used for β -carotene.

There are a few mechanisms by which β -cryptoxanthin might form retinol. For example, β -cryptoxanthin is known to be centrally cleaved by β -carotene 15,15' oxygenase 1 (BCO1) into retinal, which is hydrolyzed to retinol. BCO1 catalyzes the cleavage of all retinoid-forming carotenoids, including β -cryptoxanthin, into retinal.^{25,73,74,76} This reaction occurs primarily in the enterocytes but can also occur in other tissues, such as the liver.^{33,73,74,76} BCO1 has a slightly alkaline pH optimum and is dependent upon ferrous iron.^{33,73,74} It is found in mucosal and glandular cells of the stomach, small intestine, colon, liver cells, exocrine pancreas, prostate, endometrium, mammary tissues, kidney tubular cells, skin epithelium, and skeletal muscle. BCO1 appears to be the most important enzyme cleaving β -carotene to retinol. It also cleaves β -cryptoxanthin to form retinal and 3-hydroxyretinal.^{33,73,74} This potential mechanism is shown in Figure 2.

A second mechanism involves the enzyme β -carotene-9',10'-oxygenase 2 (BCO2). This enzyme cleaves many carotenoids asymmetrically into retinal and β -10'carotenals, which can be metabolized into short-chain carbonyl compounds or retinoic acid.^{33,74,75,77,78} BCO2 cleaves a wide variety of carotenoids, including β -carotene, β -cryptoxanthin, lutein, and lycopene, eccentrically to an apocarotenal that can be cleaved to retinal.^{33,74,75,77,78} BCO2 (CMO2) cleaves β -cryptoxanthin in the ferret, but its cleavage activity toward β -cryptoxanthin is lower than that toward zeaxanthin or lutein (Figure 2).⁷⁵ A third possible mechanism involves BCO2 cleaving β -cryptoxanthin into an apocarotenal, which is then cleaved to retinal by BCO1.^{33,75,77} So far, all mechanistic studies have shown that β -cryptoxanthin is a somewhat poorer substrate for BCO1 than is β -carotene.^{25,33,73,75,76} A typical comparison of the reaction kinetics for β -carotene and β -cryptoxanthin is shown in Figure 3, which shows that the kinetics of BCO1 is substantially faster when β -carotene is the substrate.

The mechanistic results summarized in this section suggest that, once absorbed, β -cryptoxanthin is a poorer substrate for carotenoid cleavage enzymes than is β -carotene. However, the amount of retinol that can be provided by a provitamin A carotenoid depends on several things, such as the structure of the carotenoid, the food matrix in which it occurs, and the health and physiological status of the person involved.⁷⁹

In vitro, epidemiological, animal model, and human studies suggest that β -cryptoxanthin is much better absorbed from at least some of its major food sources than is β -carotene. Thus, both the mechanisms

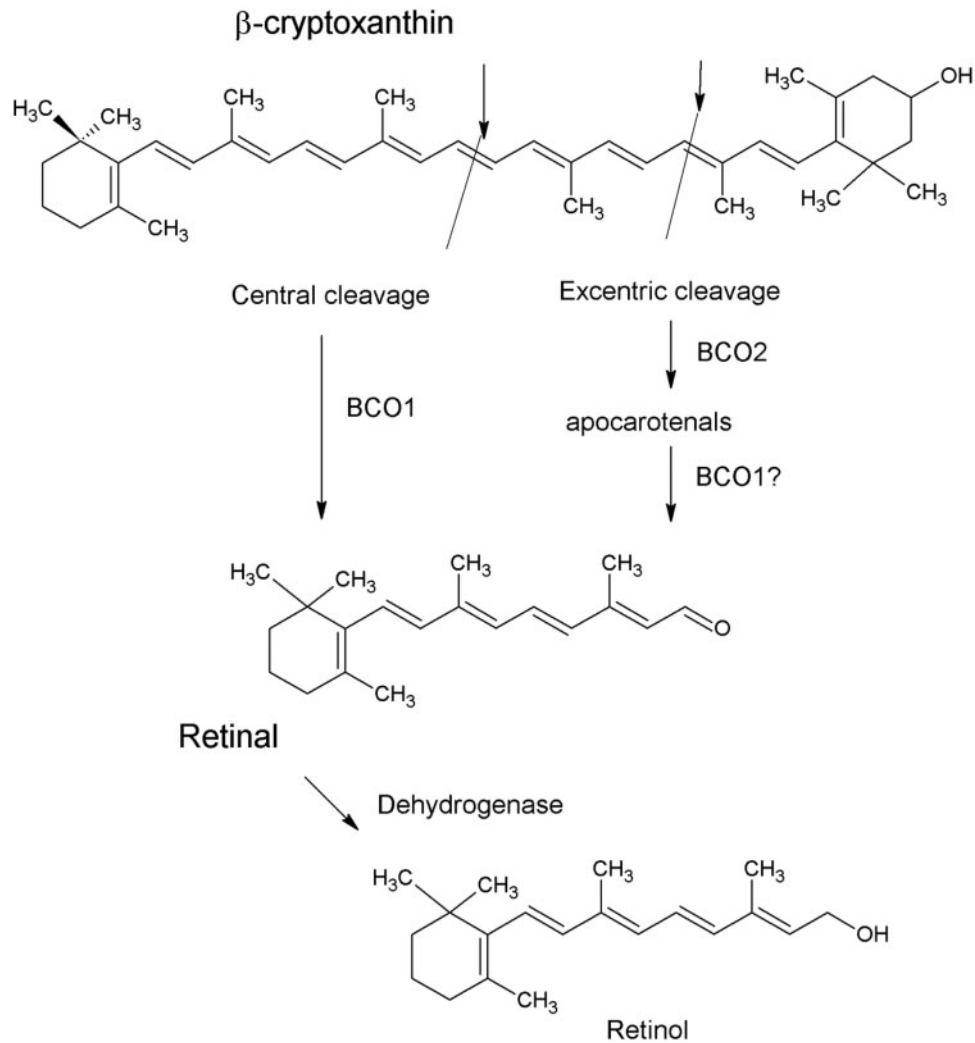


Figure 2 Schematic of probable mechanisms of retinol formation from β-cryptoxanthin.

by which β-cryptoxanthin is absorbed from food and the mechanisms by which β-cryptoxanthin is cleaved to form retinol are likely to be important.

Factors influencing the formation of retinol from β-cryptoxanthin

Few studies have focused on determining the factors that influence the formation of retinol from β-cryptoxanthin. However, research on β-carotene should provide some insight into these factors. The amount of retinol formed from carotenoids varies greatly from person to person, with 30%–50% of people converting very little β-carotene to retinol.^{80–82} The reasons why some people (called “low-” or “non-responders”) absorb and convert less carotenoid to retinol are complex and multifactorial, and are related to characteristics of the carotenoid, diet, person, and environment.⁷⁹ However, recent evidence suggests that an important reason for

this variability is genetic polymorphisms, especially of the genes for BCO1 or SR-B1.

SR-B1 has a role in transporting carotenoids in and out of cells.¹⁷ Single-nucleotide polymorphisms of genes regulating SR-B1 (such as *SCARB1*) are associated with altered plasma carotenoid levels.^{17,18,33} Expression of *SCARB1* and *BCO1* genes in intestinal cells has been shown to be affected by intestinal transcription factor ISX, which in turn is influenced by retinoic acid through the binding of retinoic acid receptors (RARs). ISX is a retinoic acid-sensitive gatekeeper that controls carotenoids. Expression of *ISX* increases when retinoic acid is present, which in turn decreases *SCARB1/BCO1* expression.³³ Single-nucleotide polymorphisms in *SCARB1* were related to β-cryptoxanthin plasma concentrations. For example, concentrations were 40% higher in male carriers of allele A in *SCARB1* exon 1 than in men with the GG genotype and were 28% lower in women possessing a T allele at *SCARB1* exon 8 than in female CC carriers.⁸³

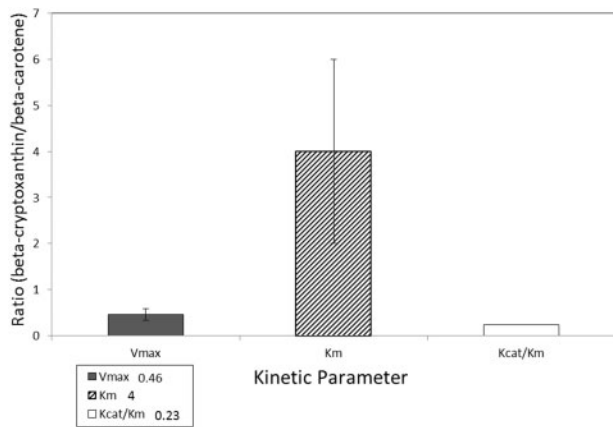


Figure 3 Ratio of β -carotene 15,15' oxygenase 1 (BCO1) kinetic parameters (V_{max} , K_m , K_{cat}/K_m) for β -cryptoxanthin/ β -carotene. Data from an in vitro study by Dela Sena et al. (2013).⁷⁶

Single-nucleotide polymorphisms appear to be common in the *BCO1* gene.^{33,83–88} Most studies on genetic modifications have focused on β -carotene, but several have examined β -cryptoxanthin as well as other carotenoids. These studies have found that some, but perhaps not all, of the genetic polymorphisms that influence β -carotene metabolism also influence β -cryptoxanthin metabolism.^{84,86,87} The genetic polymorphisms identified so far do not appear to influence β -cryptoxanthin concentrations as much as they influence β -carotene concentrations.^{85,87} These results suggest that the amount of retinol formed from β -cryptoxanthin will vary from person to person, in part because of differences in genetics; however, these differences in genetics may not be as important for β -cryptoxanthin as they are for β -carotene.

Single-nucleotide polymorphisms also influence the *BCO2* gene, though the importance of this gene to β -cryptoxanthin cleavage is not known and is likely to be small.^{77,78} A second important influence on the amount of retinol formed from carotenoids is the food matrix, which exerts its influence primarily at the carotenoid absorption step.^{22–24} Recently, scientists have begun to study the effects of the food matrix on the amount of retinol formed from β -carotene-rich foods. These studies are summarized in Figure 4, which shows the conversion ratios determined for β -carotene-rich foods.^{89,90} The conversion ratio for β -cryptoxanthin was calculated from data from a study of β -cryptoxanthin in humans, described below.⁶⁰ When available, the range of the conversion estimates is shown, with the thin black bar denoting the range between the low and the high estimates.

Essentially, β -carotene in oil is a better source of retinol than β -carotene in fruit, and β -carotene from fruit or from biofortified foods tends to be a better source of retinol than β -carotene from most

vegetables.⁹¹ Furthermore, studies suggest that physiological concentrations (below 6 mg) form more retinol per milligram than do supraphysiological concentrations. Although information on β -cryptoxanthin is very limited, research shows that the absorption of β -cryptoxanthin is likely influenced similarly to that of β -carotene, i.e., by the food matrix and dosage.^{44,47,92}

Animal studies comparing the bioefficacy of carotenoids for maintaining retinol status

Mongolian gerbils (*Meriones unguiculatus*) are accepted as the best small animal model for human carotenoid digestion.^{45,46} In gerbils, β -cryptoxanthin-rich maize was found to be as good as or better than β -carotene-rich maize in maintaining retinol status.^{92–94} Furthermore, gerbils fed 7 maize genotypes (3 with high concentrations of β -carotene and 4 with high concentrations of β -cryptoxanthin) that were equalized for retinol activity (assuming a 1:1 retinol activity equivalency between β -carotene and β -cryptoxanthin) maintained retinol status. The β -cryptoxanthin-rich maize maintained retinol status equally as well as the β -carotene-rich maize.⁹²

In another study, gerbils were fed a low-retinoid, low-carotenoid diet supplemented with freeze-dried fruit (banana, mango, orange, tangerine, papaya) or a vitamin A supplement. Gerbils received a theoretical retinol intake of 32–37 nmol/d from fruit compared with 17 nmol/d from the vitamin A supplement.⁹⁵ All fruit treatments except banana maintained retinoid concentrations in blood and liver, irrespective of whether the most abundant carotenoid was β -carotene or β -cryptoxanthin. These results suggest that β -cryptoxanthin-rich foods are comparable to β -carotene-rich foods in their ability to maintain vitamin A status in the gerbil.

Human study of β -cryptoxanthin conversion to retinol

Only one study in humans has attempted to compare the conversion of β -carotene and β -cryptoxanthin to retinol.⁶⁰ In this single-site, parallel, randomized, placebo-controlled study that evaluated the absorption of β -carotene from orange sweet potato and the absorption of β -cryptoxanthin from tangerines, the effects of these foods on retinoids and carotenoids in plasma and breast milk were compared.⁶⁰ Lactating women with marginal vitamin A status were recruited from Mirpur, Bangladesh, an area with poor socioeconomic status. Participants received a food and either a vitamin A (retinyl acetate) or a placebo corn oil capsule twice a day, 6 days a week, for 3 weeks. The amount of β -carotene

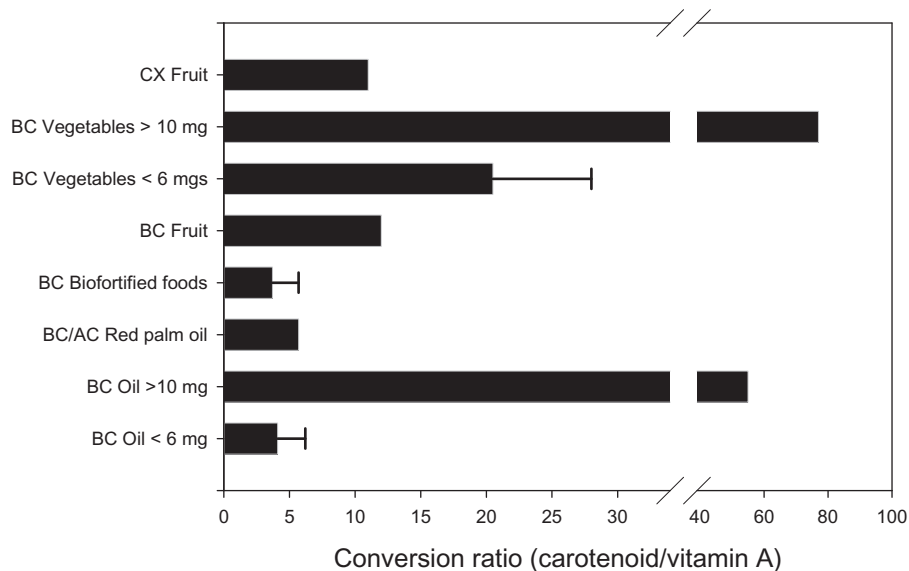


Figure 4 Effects of the food matrix on the conversion ratio of carotenoid to vitamin A. Bars represent the mean conversion ratio of carotenoid from the food indicated. Abbreviations: AC, α -carotene; BC, β -carotene; CX, β -cryptoxanthin. Data from literature reviews by Haskell (2012)⁸⁹ and Van Loo-Bouman et al. (2014).⁹⁰

supplied by sweet potatoes (12 mg) was more than twice that of the β -cryptoxanthin supplied by tangerines (5.3 mg), while the positive control group consumed 0.5 mg of vitamin A.

Plasma β -carotene increased 250% in the sweet potato group, while plasma β -cryptoxanthin increased 830% in the tangerine group. Thus, the relative absorption of β -cryptoxanthin was 4 times greater than that of β -carotene. Breast milk retinol increased significantly only in the vitamin A supplement group: 36%, or, when correcting for fat, 16%. When breast milk fat was taken into account, retinol levels in all but the vitamin A supplement group tended to decrease. Changes in breast milk retinoid concentrations (nmol/g fat) in the carotenoid treatment groups were not significantly different from those in the control group. Interestingly, though, the final breast milk retinoid concentrations in the tangerine group were also not significantly different from those in the vitamin A supplement group ($P = 0.12$). β -Carotene increased significantly in the sweet potato group, while β -cryptoxanthin in the tangerine group showed a large significant increase of 447%. Little is known about how well infants can convert carotenoids to retinol, but large increases in β -cryptoxanthin concentrations in breast milk might be beneficial to the infant.

Although sweet potato interventions providing similar concentrations of β -carotene have resulted in increased retinol status in some populations,^{89,90} this study found no significant change in status. The sweet potato group showed a nonsignificant increase in breast milk retinol concentrations, as did the tangerine group. The placebo control group had a nonsignificant decrease of 14% from baseline (Figures 5A and B).

Another recent study using sweet potatoes in this same population also failed to demonstrate increased retinol status,⁹⁶ for unknown reasons. Taken together, these studies might mean that the conversion of carotenoids to retinol is limited in this population. The women in this study seemed to have low but adequate levels of iron (as assessed by concentrations of transferrin receptor, ferritin, and hemoglobin), but they might have had inadequate levels of protein, which might have resulted in poor carotenoid conversion.^{3,4,33} Additionally, foods in that study location are prepared in unhygienic conditions, and both mothers and infants have high exposure to disease. Unhygienic environments could increase enteropathy and chronic inflammation, which could decrease the effectiveness of carotenoid interventions.^{3,4,20} It is also possible that genetic polymorphism in this population might be important, since several common polymorphisms of the *BCO1* gene are associated with decreased conversion of β -carotene to retinol.^{84–88} Carotenoid-based interventions to improve retinoid status may be less effective in impoverished populations, where codeficiencies and comorbidities are often present together, especially in ethnically isolated population groups (as was the case in these studies in Bangladesh).^{60,96}

Although neither treatment was effective, β -cryptoxanthin from tangerines and β -carotene from sweet potatoes provided similar amounts of retinol (even though the amount of β -cryptoxanthin consumed was less than half the amount of β -carotene consumed, 5.3 mg/d vs 12 mg/d, and supposedly provided less than one-fourth of the retinyl equivalents). The relative apparent bioavailability of β -cryptoxanthin from tangerines was 10 times greater than that of β -carotene from sweet

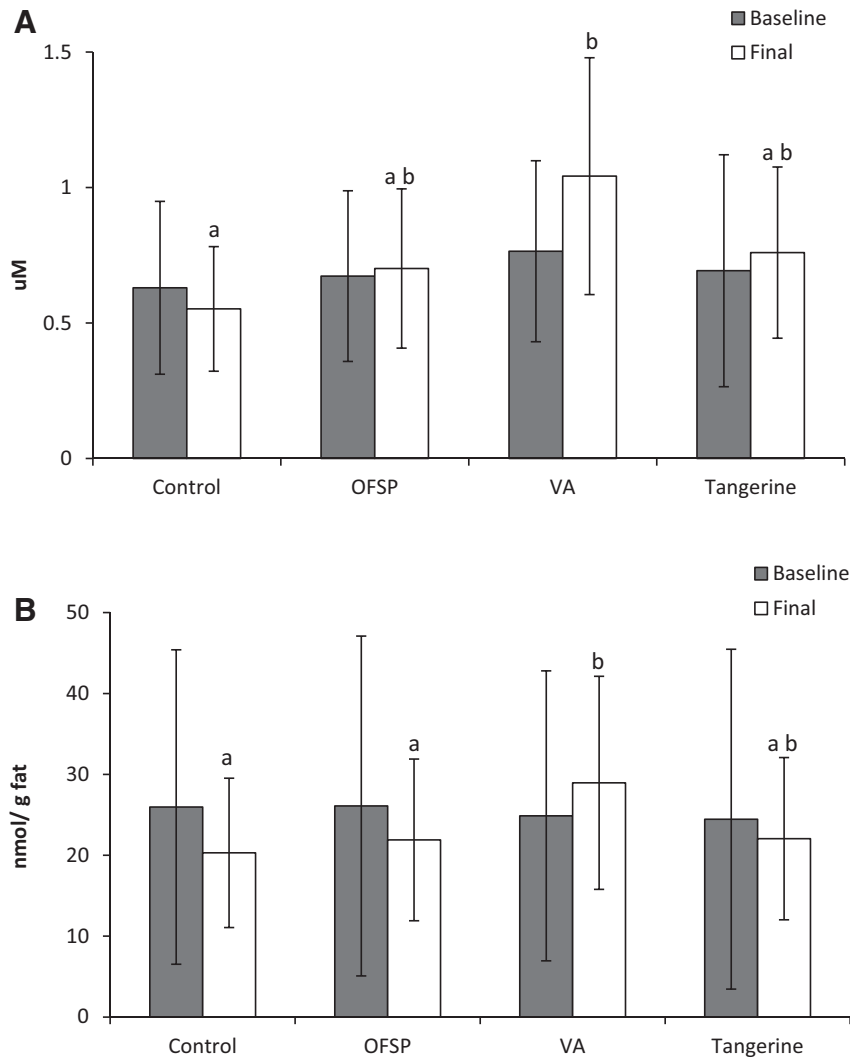


Figure 5 Concentrations of retinol in breast milk before and after tangerine and sweet potato interventions. (A) Concentrations ($\mu\text{M} \pm \text{SEM}$). (B) Concentration changes normalized for changes in milk fat concentration. Abbreviations: OFSP, treatment group fed orange-fleshed sweet potatoes; VA, treatment group given vitamin A supplement capsules. Data from a study of 135 lactating Bangladeshi women; Turner et al. (2013).⁶⁰

potatoes, and if breast milk results were corrected for the difference in the amount of carotenoids provided, then tangerines provided 5 times as much retinoid as sweet potatoes.

Clearly, more animal model and human studies are needed to determine the bioefficacy of β -cryptoxanthin-rich foods as retinoid sources. More studies on the absorption, metabolism, and retinyl equivalency of β -cryptoxanthin should be done, preferably with longer supplementation times in larger populations. Research on the metabolism of β -cryptoxanthin may be important scientifically and might also have practical implications in some areas of the world, specifically in Japan, where the consumption of β -cryptoxanthin is especially high and the amount of preformed retinol eaten is relatively low. Determining accurate values of the

conversion of β -cryptoxanthin-rich foods might improve the estimates of retinol intake in Japan as well as in other areas of the world where food sources of β -cryptoxanthin are commonly consumed.⁵⁹

β -CRYPTOXANTHIN AS AN ANTIOXIDANT

β -Cryptoxanthin can accept energy from singlet oxygen ($^1\text{O}_2$).^{3,4,97} The evidence that β -cryptoxanthin is an antioxidant in vitro at most physiological concentrations is persuasive.^{3,4,98–100} However, a recent review suggested that there is a difference between nonvitamin A-forming carotenoids (such as lycopene) and vitamin A-forming carotenoids (such as β -cryptoxanthin).¹⁰⁰ Nonvitamin A-forming carotenoids protected against DNA damage in almost all circumstances, but vitamin A-forming

carotenoids protected against DNA damage in some cases and enhanced DNA damage in others, especially when they were present at high concentrations.

There have been no *in vivo* studies of β -cryptoxanthin as an antioxidant. To act as an antioxidant *in vivo*, a carotenoid would need to be incorporated into the tissues in the correct location and at a suitable concentration relative to the oxidizing agent and the molecule that is to be protected.⁹⁷ The concentrations of β -cryptoxanthin in most mammalian tissues generally are low compared with those of other dietary antioxidants such as vitamins E and C^{20,33}; therefore, it is unlikely that β -cryptoxanthin is an important antioxidant for most people. However, more studies of both the antioxidant and pro-oxidant activity of β -cryptoxanthin would be useful.

β -CRYPTOXANTHIN AS A CANCER PREVENTIVE

A review of the literature on the relationship between carotenoids and cancer is beyond the scope of this review. Suffice it to say there is very strong epidemiological evidence for an association between low carotenoid intakes or low blood and tissue concentrations of carotenoids and higher risks of several types of cancers.¹⁰¹⁻¹⁰⁵ However, cancer trials in which high doses of pure β -carotene were administered orally to people at risk of lung cancer showed no preventive effect and sometimes were associated with an increased risk of cancer, perhaps because high-dose β -carotene acted as a pro-oxidant in smokers.^{106,107}

Most cancer prevention studies have focused on β -carotene or lycopene.¹⁰¹⁻¹⁰⁷ Only a few human studies have compared β -cryptoxanthin intakes or concentrations with cancer incidence. All were observational studies. Results were mixed¹⁰⁸⁻¹¹¹ but favored a protective role for β -cryptoxanthin in lung cancer. For example, a recent study linking dietary information from the National Health and Nutrition Examination Survey III (NHANES III) with the NHANES III Linked Mortality File compared 161 subjects who died of lung cancer with controls and found that higher baseline serum β -cryptoxanthin was associated with a lower risk of lung cancer death.¹¹¹

Recently, several laboratories have focused on identifying the mechanisms by which β -cryptoxanthin could prevent cancer.¹¹²⁻¹¹⁸ β -Cryptoxanthin appears to affect genetic regulation, antioxidant, and inflammatory markers *in vitro*. One promising area of research suggests that β -cryptoxanthin can increase the mRNA levels of RAR β ^{117,118} and that β -cryptoxanthin transactivates RAR-mediated transcription activity of the retinoic acid response element (RARE). When comparing the ability of several carotenoids as RAR agonists, β -cryptoxanthin outperformed all carotenoids in terms of dose-dependent

increases in β -galactosidase activity, a marker of agonist activity against RAR α and RAR γ .¹¹⁹ β -Cryptoxanthin may also be able to stimulate the differentiation of lung cancer cells and modulate immune response by Th2 cells via an RAR. Subsequent cell culture and animal studies investigated the chemopreventive effects of β -cryptoxanthin supplementation on lung cancer prevention. One cell culture study found that β -cryptoxanthin both inhibited lung cancer cell growth while inducing mRNA concentrations of RAR β in BEAS-2B cells and transactivated RAR-mediated transcription activity of RARE.¹²⁰ In another study, β -cryptoxanthin supplementation significantly decreased smoke-induced squamous metaplasia and inflammation in the lung and lowered tumor necrosis factor α concentrations in lung tissue cells and macrophages in ferrets.¹²¹ Lastly, a study in mice showed that β -cryptoxanthin supplementation reduced nicotine-promoted lung tumor multiplicity and volume, in addition to decreasing emphysema. Supplementation also restored nicotine-suppressed expression of lung Sirtuin 1 (SIRT1), p53, and RAR β and increased survival probability.¹²²

There is evidence β -cryptoxanthin may inhibit other types of cancer as well. β -Cryptoxanthin-supplemented ICR mice had a decreased incidence of preneoplastic and neoplastic lesions of the urinary bladder.¹²³ Furthermore, in a study in which F344 rats were provided varying doses of β -cryptoxanthin, the high-dose (25 ppm) group showed a decreased incidence of colon cancer.¹²⁴

Thus, besides evidence that β -cryptoxanthin may be involved in functions associated with cancer prevention, there is also some evidence linking moderate intakes of β -cryptoxanthin with cancer-preventive effects. Therefore, it would be useful to obtain information on the amounts of β -cryptoxanthin in the diet that might be beneficial or harmful as well as information on the relationship between β -cryptoxanthin and smoking, alcohol consumption, or other factors that might contribute to the risk of cancer. Further research to gather this basic information is needed before the importance of β -cryptoxanthin in cancer prevention can be established.

β -CRYPTOXANTHIN AND BONE HEALTH

Bone is a dynamic tissue, constantly forming and reforming. Good nutrition is essential for bone homeostasis, with vitamin D and calcium playing essential roles.¹²⁵ A series of cell culture and rodent studies suggest that β -cryptoxanthin may also be involved in bone health and homeostasis by promoting osteoclast formation and inhibiting osteoblast actions.¹²⁶⁻¹⁴¹ Most of these studies were summarized in 2012.¹⁴² Collectively,

they suggest that β -cryptoxanthin has an effect on bone health that is not duplicated by other carotenoids.

Moderate (probably physiological) concentrations of β -cryptoxanthin appeared to increase calcium content, protein content, and alkaline phosphatase activity in bone *in vitro*, changes that are inhibited by inhibitors of RNA polymerase II or protein synthesis, such as cycloheximide. Both calcium and alkaline phosphatase participate in the mineralization of bone. β -Cryptoxanthin also appeared to stimulate gene expression for proteins involved in bone formation and mineralization in osteoblasts, such as insulin-like growth factor 1 and transforming growth factor β 1, an effect possibly mediated by protein kinase C or mitogen-activated protein kinase (MAPK).¹³⁷ Transforming growth factor β 1 is involved in the differentiation of pre-osteoblasts to osteoblasts. Furthermore, β -cryptoxanthin stimulated runt-related transcription factor 2 (Runx2, also known as core-binding factor α 1 or CBF α 1), a key transcription factor associated with osteoblast differentiation.¹³⁰ Although retinoic acid, the active form of vitamin A, can also mediate bone formation, it did not always duplicate the actions of β -cryptoxanthin on gene expression in these studies.¹³²

In vitro, β -cryptoxanthin inhibited bone resorption induced by parathyroid hormone or prostaglandin E2 by preventing osteoclast cell formation by receptor activator of nuclear factor κ B ligand (RANKL).¹²⁷ β -Cryptoxanthin decreased the number of mature osteoclasts in culture, an action that was inhibited by inhibitors of caspase-3, suggesting that β -cryptoxanthin was inducing apoptotic cell death.¹³³ Zinc appeared to have synergistic effects with β -cryptoxanthin, stimulating bone formation and inhibiting bone resorption.^{129,135,136}

Animal studies provided some corroboration of the cell culture results. Rats fed moderately high doses of β -cryptoxanthin (50–100 μ g/kg body weight) in combination with zinc sulfate (zinc, 1–5 mg/kg body weight) for 1 week showed increases of alkaline phosphatase activity and calcium concentrations in diaphyseal tissues.¹³⁵ Additionally, young male or older female rats fed high doses of β -cryptoxanthin (100–500 μ g/kg body weight) for 1 week also showed increased alkaline phosphatase and calcium in diaphyseal and metaphyseal tissues.^{131,138} Furthermore, several laboratories found that feeding moderate doses of β -cryptoxanthin to ovariectomized rats inhibited bone loss^{134,139,141} and periodontal bone resorption.¹⁴⁰

There have been few human studies on the effects of β -cryptoxanthin or β -cryptoxanthin-rich foods on osteoporosis, most of which have been small, and results have been inconclusive. No significant associations were found in a prospective cohort study of carotenoid intakes and risk of hip fracture or other indices of bone health in the

Framingham Osteoporosis Study.^{143,144} In another study conducted in the United States, β -cryptoxanthin intakes were higher in postmenopausal women with osteoporosis than in postmenopausal women without osteoporosis.¹⁴⁵ On the other hand, epidemiological studies in Japan showed that high β -cryptoxanthin intake or the intake of Satsuma mandarins was associated with high bone mineral density in postmenopausal women.^{146–148} Furthermore, comparison of the highest and lowest tertiles of dietary intakes of vitamin C and β -cryptoxanthin in menopausal female subjects from Mikkabi, Japan, showed that these antioxidants were associated with higher bone mineral density (odds ratio of 0.40; 95% confidence interval [CI], 0.17–0.92).¹⁴⁹ In a 4-year follow-up of the Mikkabi study, 15 postmenopausal women developed osteoporosis. After adjustments for confounders, the odds ratio for osteoporosis in the highest tertiles of serum β -cryptoxanthin was 0.07 (95%CI, 0.01–0.88). Serum β -cryptoxanthin was also inversely associated with osteopenia/osteoporosis ($P=0.037$).¹⁵⁰ There are many differences between these studies that could explain the varying results, including study design, study population, and diets. One factor that may be important is that the Japanese have one of the highest intakes of β -cryptoxanthin, coupled with relatively low intakes of preformed vitamin A. β -Cryptoxanthin is not a large part of the American diet, so intakes may have been too low to have had an effect.

EMERGING AREAS OF RESEARCH

Similar to findings for other phytonutrients, new research suggests that β -cryptoxanthin might have other functions that can impact human health. For example, β -cryptoxanthin may influence some aspects of immune function (such as CD4⁺ lymphocytes and immunoglobulin [Ig] G, IgA, and IgM levels).¹⁵¹ β -Cryptoxanthin might also influence cholesterol homeostasis by inducing mitochondrial sterol 27-hydroxylase (CYP27A1).¹⁵² Finally, β -cryptoxanthin has been associated with decreased risk of insulin resistance and liver dysfunction, possibly helping to prevent nonalcoholic fatty liver disease.¹⁵³ Further research in these areas is necessary to determine whether, when, and how β -cryptoxanthin could impact these functions.

Similarly, further research on the role of β -cryptoxanthin on eye health would be useful. There is considerable evidence suggesting that lutein and zeaxanthin have important roles in eye health.^{154–157} Lutein and zeaxanthin are xanthophylls with structures similar to that of β -cryptoxanthin, but no recent research has focused on β -cryptoxanthin in the eye, and little is known about β -cryptoxanthin transport in the

eye or about potential interactions with lutein and zeaxanthin.

A few studies have assessed β -cryptoxanthin (as well as many other antioxidants) as a risk factor for ocular diseases, with mixed results. A cross-sectional study of the concentrations of antioxidant nutrients (including β -cryptoxanthin) in Indian patients with low antioxidant status showed an inverse correlation of cataract risk with β -cryptoxanthin (and other antioxidant) intake.¹⁵⁸ A case-control study that measured β -cryptoxanthin concentrations in glaucoma found no significant correlation between risk and concentration.¹⁵⁹ A few studies have measured β -cryptoxanthin (as well as other antioxidant nutrients) in patients with macular degeneration.^{160–163} An early study showed a trend toward greater risk with lower β -cryptoxanthin concentrations,¹⁶⁰ but more recent studies showed no relationship between intake and risk.^{161–163} It should be noted, however, that β -cryptoxanthin intakes in these populations were generally much lower than intakes of β -carotene, lutein, vitamin E, or most other antioxidants measured. Thus, more research on the metabolism and potential effects of β -cryptoxanthin in the eye would be useful.

CONCLUSION

There is good evidence from in vitro, animal, and human studies that β -cryptoxanthin is well absorbed from its major food sources. Like other carotenoids, β -cryptoxanthin appears to be an antioxidant under most physiological conditions. Recent research indicates it may have anticarcinogenic effects, particularly with regard to lung cancer. There is also mounting evidence that β -cryptoxanthin-rich foods can provide substantial amounts of vitamin A. Due to its high bioavailability from foods, β -cryptoxanthin may have a greater potential to improve vitamin A status than previously assumed. Finally, there is intriguing evidence suggesting that β -cryptoxanthin might have an anabolic effect on bone, thereby offering some protection against osteoporosis.

Thus far, however, there are not enough data on the absorption, metabolism, or function of β -cryptoxanthin to accurately estimate its effects on health at this time. There are little data on (1) the dose-response and reaction kinetics of physiological concentrations of β -cryptoxanthin, (2) the normal variability of these reactions, or (3) the effects of genetic and host factors such as deficiencies of other nutrients or the nutrient interactions that might influence absorption, metabolism, or potential toxicity. There is also almost no information on the effects of the food matrix, cooking and food processing, or food storage on β -cryptoxanthin concentrations or bioavailability in foods. This is a promising area of research, but more work is necessary.

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