Editorial

β-cryptoxanthin and fatty liver disease: new insights

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Comment on: Liu C, Rafacho BPM, Wang XD. Xanthophyll β-cryptoxanthin treatment inhibits hepatic steatosis without altering vitamin A status in β-carotene 9',10'-oxygenase knockout mice. Hepatobiliary Surg Nutr 2022;11:188-98.

Keywords: Liver; non-alcoholic fatty liver disease; β-cryptoxanthin

Submitted Apr 18, 2023. Accepted for publication Apr 28, 2023. Published online May 06, 2023.
doi: 10.21037/hbsn-23-201
View this article at: https://dx.doi.org/10.21037/hbsn-23-201

β-cryptoxanthin is a nutritionally important xanthophyll found in orange-fleshed tropical and citrus fruits, including papaya, oranges, and tangerines (1). It is also one of the most commonly detected carotenoids in human tissues (1). Uniquely, β-cryptoxanthin is the only regularly consumed dietary xanthophyll to have an intact β-ionone ring, thus in addition to functioning as an antioxidant it can also be metabolized to vitamin A. A limited number of past studies have shown a beneficial effect of β-cryptoxanthin supplementation in animal models of hepatic steatosis (2). As discussed below, the recent publication by Liu *et al.* from the group led by Dr. Xiang-Dong Wang has provided new insight into the benefits of β-cryptoxanthin supplementation in the context of fatty liver disease (3).

Epidemiological data and animal studies have suggested that high dietary carotenoid intake, including β-cryptoxanthin, may have beneficial health effects on hepatic fat accumulation (2,3). As discussed elsewhere, there are multiple possible mechanisms through which β-cryptoxanthin exerts its beneficial effect, this includes the molecule acting as an antioxidant, or undergoing oxidative cleavage to produce vitamin A or bioactive apocarotenoids (2). Regarding its cleavage, the two major carotenoid cleavage enzymes that can metabolize β-cryptoxanthin are BCO1 (β-carotene-15,15'-oxygenase), which generates vitamin A, and BCO2 (β-carotene-9',10'-oxygenase), which generates apocarotenoids (2,3). In this context, there is a gap in our knowledge regarding the mechanism underlying β-cryptoxanthin's beneficial effects, and whether cleavage by BCO1 and/or BCO2 is required to mediate these effects. Indeed, past studies in rodent models of non-alcoholic fatty liver disease have demonstrated a protective effect of β-cryptoxanthin supplementation on markers of hepatic fat accumulation and inflammation (4-6). Despite their positive results, these studies did not shed light on whether these effects were dependent on β-cryptoxanthin metabolism by BCO1/2. In two separate studies, also from the group of Dr. Wang, the effect of β-cryptoxanthin supplementation was studied in a mouse model consuming a diet high in refined carbohydrates (7,8). The importance of β-cryptoxanthin cleavage was genetically dissected in these studies through the use of *Bco1*$^{-/-}$/*Bco2*$^{-/-}$ double knockout mice. Both studies showed that β-cryptoxanthin supplementation inhibited hepatic lipid accumulation, inflammation and hepatocellular carcinoma progression. Moreover, this effect was independent of *Bco1/Bco2* genotype, suggesting that these positive effects were mediated by intact β-cryptoxanthin and occurred independently of its cleavage by BCO1/2 (7,8). As

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expanded upon below, the current study by Liu *et al.* extends these studies further by focusing on the contribution of BCO2 in β-cryptoxanthin metabolism in the prevention of hepatic steatosis (3).

The goal of the study by Liu *et al.*, was to assess the beneficial effects of β-cryptoxanthin supplementation on hepatic steatosis and liver inflammation, with an emphasis on the contribution of BCO2 in mediating these effects (3). The work's experimental design included 3 months of β-cryptoxanthin supplementation (10 mg/kg diet) in male *Bco2*$^{-/-}$ mice ending at 4 or 8 months of age. A strong phenotype was not observed in 4-month-old mice, thus this discussion will focus on the groups of mice aged 8 months. Most strikingly, *Bco2*$^{-/-}$ mice supplemented with β-cryptoxanthin had significantly lower hepatic triglyceride levels, which was also reflected in a lower grade of steatosis determined by histological scoring. While there was evidence of decreased hepatic inflammation in mice receiving the β-cryptoxanthin supplement, this did not reach statistical significance. As mentioned above, β-cryptoxanthin can be metabolized to generate retinoids; however, hepatic retinyl palmitate levels were not different in *Bco2*$^{-/-}$ mice supplemented with β-cryptoxanthin, versus those consuming the control diet, suggesting that the beneficial effect of β-cryptoxanthin occurred independently of changes in hepatic retinoid stores. Mechanistically, the beneficial effects of β-cryptoxanthin supplementation were associated with increased SIRT1 deacetylase activity, as evidenced by decreased acetylation of FOXO1, with downstream effects on multiple aspects of hepatic lipid metabolism. For example, it was speculated that increased SIRT1 activity could suppress hepatic *de novo* lipogenesis via decreased SREBP-1c expression, as supported by decreased mRNA levels of the lipogenic genes *Fasn* and *Scd1*. Conversely, the deacetylation and activation of PGC1α was linked with increased protein expression levels of PPARα and its target gene *Mcad*, suggesting increased β-oxidation. Taken together, evidence was provided that suggests β-cryptoxanthin treatment, through SIRT1, decreased hepatic steatosis by inhibiting hepatic *de novo* lipogenesis and stimulating hepatic fatty acid oxidation. As such, the authors concluded that β-cryptoxanthin protects against hepatic steatosis by modulating SIRT1 activity, which occurred independently of BCO2.

In summary, the study by Liu *et al.* adds to the existing literature that supports a beneficial effect of β-cryptoxanthin supplementation in the context of non-alcoholic fatty liver disease (3-8). A limitation of this study is that it did not include control groups of wild-type mice fed β-cryptoxanthin. This did not allow a comparison of β-cryptoxanthin's effect in wild-type and *Bco2*$^{-/-}$ mice, nevertheless it is clear that in the absence of BCO2 the liver is protected, thus the cleavage of β-cryptoxanthin by BCO2 is not required for it to mediate its beneficial effects. The study also raises several unanswered questions that require further study. It is suggested that β-cryptoxanthin exerts its beneficial effects by activating SIRT1, although the mechanism for this activation remains unclear. A beneficial effect of β-cryptoxanthin supplementation was only seen in 8-month old mice, and not 4-month old mice, thus the role of age requires further exploration. As is common in the literature (2), Liu *et al.* only included male mice in their study, thus the potential beneficial effects of β-cryptoxanthin supplementation still need to be explored in females. One of the most interesting areas for future consideration is the dose of β-cryptoxanthin required to protect the liver. Liu *et al.* saw beneficial effects of β-cryptoxanthin at a dose of 10 mg/kg, which is consistent with the literature and claimed to be physiologic; however, the question remains what is the optimal dose, and does excess β-cryptoxanthin damage the liver? Indeed, it has been shown that at a dose of 50 mg/kg, lutein or zeaxanthin supplementation in *Bco2*$^{-/-}$ mice causes severe hepatic steatosis, which was attributed to mitochondrial dysfunction secondary to the accumulation of carotenoid metabolites within the mitochondria (9). Thus, while the study supports the benefits of β-cryptoxanthin supplementation in the liver, future studies should explore the safe limits of supplementation.

In closing, there is growing evidence to support a role for β-cryptoxanthin supplementation to improve non-alcoholic fatty liver disease. The study by Liu *et al.* reinforces this idea, provides important mechanistic insight into how β-cryptoxanthin acts in the liver, and suggests important areas for future study (3).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE

uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-201/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Clugston RD. β-cryptoxanthin and fatty liver disease: new insights. HepatoBiliary Surg Nutr 2023;12(3):450-452. doi: 10.21037/hbsn-23-201