

Reviewer(s)' Comments to Author:

Reviewer: 1

I would like to express my gratitude to the Reviewer and Scientific Editor for providing insightful comments and for their efforts towards improving the manuscript. I have addressed and provided detailed responses to the feedback received below:

Comments to the Author

1. Page #5 and line 7, acid is missing for ascorbic acid.

**AUTHOR RESPONSE:** The reviewer's feedback has been duly noted and the abbreviated form AA has been used throughout in the manuscript for consistency.

2. Reference # 12 is not an appropriate reference for citing about Vitamin C transporters in page #5..

**AUTHOR RESPONSE:** We have taken on board the reviewer's feedback and the citation has been amended to

Tsukaguchi H, Tokui T, Mackenzie B, et al. A family of mammalian Na<sup>+</sup>-dependent L-ascorbic acid transporters. *Nature* 1999;399:70-5.

3. Since this review mainly focusing on the intestinal absorption, the author should consider to cite more intestinal vitamin C transport related references.

**AUTHOR RESPONSE:** We thank and agree with the reviewer, and have now expanded both the text and references to include:

Lykkesfeldt J, Tveden-Nyborg P. The pharmacokinetics of vitamin C. *Nutrients* 2019;11:2412.

Subramanian VS, Srinivasan P, Wildman AJ, et al. Molecular mechanism(s) involved in differential expression of vitamin C transporters along the intestinal tract. *Am J Physiol Gastrointest Liver Physiol* 2017;312:G340-G347.

Malo C, Wilson JX. Glucose modulates vitamin C transport in adult human small intestinal brush border membrane vesicles. *J Nutr* 2000;130:63-9.

Vera JC, Rivas CI, Fischbarg J, et al. Mammalian facilitative hexose transporters mediate the transport of dehydroascorbic acid. *Nature* 1993;364:79-82.

Corpe CP, Eck P, Wang J, et al. Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. *J Biol Chem* 2013;288:9092-101.

Schmitt CC, Aranas T, Viel T, et al. Intestinal invalidation of the glucose transporter GLUT2 delays tissue distribution of glucose and reveals an unexpected role in gut homeostasis. *Molecular Metabolism* 2017;6:61-72.

Science Editors Comments to Author:

- (1) Minor comments: 1. Page #5 and line 7, acid is missing for ascorbic acid. 2. Reference # 12 is not an appropriate reference for citing about Vitamin C transporters in page #5. 3. Since this review mainly focusing on the intestinal absorption, the author should consider to cite more intestinal vitamin C transport related references.

**AUTHOR RESPONSE:** Comments raised by the Reviewer have been addressed as follows:

- the abbreviated form AA has been used throughout in the manuscript for consistency.
- Reference has been amended to Tsukaguchi H, Tokui T, Mackenzie B, et al. A family of mammalian Na<sup>+</sup>-dependent L-ascorbic acid transporters. *Nature* 1999;399:70-5.
- As the review mainly focusing on the intestinal absorption - the text (highlighted) and the references have been expanded to include:

*Lykkesfeldt J, Tveden-Nyborg P. The pharmacokinetics of vitamin C. Nutrients 2019;11:2412.*

*Subramanian VS, Srinivasan P, Wildman AJ, et al. Molecular mechanism(s) involved in differential expression of vitamin C transporters along the intestinal tract. Am J Physiol Gastrointest Liver Physiol 2017;312:G340-G347.*

*Malo C, Wilson JX. Glucose modulates vitamin C transport in adult human small intestinal brush border membrane vesicles. J Nutr 2000;130:63-9.*

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*Corpe CP, Eck P, Wang J, et al. Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. J Biol Chem 2013;288:9092-101.*

*Schmitt CC, Arantias T, Viel T, et al. Intestinal invalidation of the glucose transporter GLUT2 delays tissue distribution of glucose and reveals an unexpected role in gut homeostasis. Molecular Metabolism 2017;6:61-72.*

- (2) Issues raised: The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text

**AUTHOR RESPONSE:** We than the Editor for their valuable feedback. I was unable to add the Highlights to the online revised version of the Manuscript but have added it here were the section to be required for an Opinion Review.

“Mechanism to facilitate the transport or bioavailability of poorly absorbed molecules across the intestinal mucosa may be enhanced via co-transport. Of particular interest is Vitamin C or ascorbic acid, an essential nutrient that is key for various biological function. Altered or increased small intestinal permeability resulting from the absorption of Vitamin C can be potentially explored as a safe and novel application for the delivery of molecules via the paracellular pathway.”