

Peer Review File

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Review Comments A:

Comment 1: I've read with attention the paper of Ishiwata et al. that is potentially of interest. The background and aim of the study have been clearly defined. The methodology applied is overall correct, the results are reliable and adequately discussed. Considering the small amount of new data reported and the small patient sample, I'd suggest the author to strongly reduce the length of the paper.

Reply 1: Thank you for your thoughtful comments. We have reduced the length of the manuscript, as suggested.

Changes in the text: Please see the changes made throughout the manuscript.

Comment 2: Moreover, I'd suggest the authors to consider the citation of the following papers: Mar Drugs. 2019 Aug 29;17(9):508. doi: 10.3390/md17090508. Nutraceutical support in heart failure: a position paper of the International Lipid Expert Panel (ILEP). Cicero AFG, Colletti A, von Haehling S, Vinereanu D, Bielecka-Dabrowa A, Sahebkar A, Toth PP, Reiner Ž, Wong ND, Mikhailidis DP, Ferri C, Banach M. Nutr Res Rev. 2020 Mar 16:1-25. doi: 10.1017/S0954422420000049.

Reply 2: We have cited the suggested references with brief comments and have added them to the reference list.

Changes in the text: Pages 17 and 19, References 20 and 25

Review Comments B:

This is an interesting paper on the effects of astaxanthin in a human pilot study.

The methods used are very clever and the results have important human relevance but there is not enough new data in the manuscript.

Major points:

Comment 1: The Authors stated that the present study is a sub-study of their previous pilot study published recently in Nutrients (2020 Jun 26;12(6):1896.). However, this is no excuse for more than 50% of the data presented here is included in the previous manuscript. Extending the subject's group with one patient will not create new dataset for a completely new publication. The new data presented in the current manuscript is based on self-reported physical activity and health-related quality of life test. They are very subjective, not measurable parameters and as it stated in the Conclusion as limitation of the study by the Authors, the placebo effect could not be excluded. Without control group the changes presented in this study could not be considered as the effects of astaxanthin treatment.

Reply 1: Thank you for your comments. We have removed several parts with data that may potentially overlap with our previous publication. We agree with the comment on subjective parameters. However, we believe that self-reported physical activity and health-related quality of life, as used in our study, are established and measurable. We completely agree with the comment on potential placebo effects and the lack of a control group. Considering your comments, we have changed the title (and the running title) as well as expressions throughout the manuscript to avoid stating the causality of astaxanthin supplementation for these improvements, and to highlight that the improvements in these parameters were just an observation following the supplementation.

Changes in the text: Please see the changes made throughout the manuscript.

Minor points:

Comment 2: Abstract: What do the numbers in parenthesis mean after the SAS values? A relationship could not be significant. It can be weak, strong, follows a linear, exponential, or some other functions, but not significant.

Reply 2: The numbers indicate the “median (interquartile range)”, which are now

specified in the Abstract. In addition, we have revised the results section of the abstract to avoid the use of “significant” when referring to the relationships.

Changes in the text: Pages 4-5

Comment 3: Methods: The cohort group would be more consistent if the patient who is in the NYHA class III would be excluded.

Reply 5: Thank you for your smart suggestion. We have reanalyzed the data entirely after excluding the patient with NYHA class III. However, the findings obtained were the same as those obtained when this patient was included. Considering this and the small sample size, we decided to retain the patient with NYHA class III.

Comment 3: Results: Relation between %Delta values: It is mathematically provable that if a parameter increases or decreases in average after a treatment then the %Delta values follows similar relationship as the original values comparing to the basal values.

Reply 6: We have removed the results and descriptions showing the relationships between baseline values and their changes (i.e., %delta).

Changes in the text: Please see the changes made throughout the manuscript.

Comment 4: What does the SAS (Mets) axis legend mean in Figure 1?

Reply 4: We have added both SAS and Mets to the abbreviation list. In addition, we have added Mets as the unit of SAS in the Abstract.

Changes in the text: Please see the legend to Figure 1 and the Abstract.

Comment 5: BAP and 8-OHdG is not defined in Table 2.

Reply 5: We have added the definitions to the abbreviation list.

Changes in the text: Please see Table 2.

Comment 6: HRQoL and SAS is not presented in Table 2.

Reply 6: We have removed them from the abbreviation list.

Changes in the text: Please see Table 2.