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Manuscript NO: 54470

Title: Potential of the ellagic acid-derived gut microbiota metabolite - Urolithin A in gastrointestinal protection

Dear Editors,

We would like to thank Reviewers for their comments that helped us to improve our manuscript. Our detailed responses to their comments are provided below. All changes have been highlighted in yellow. The line numbers refer to the new version.

Additionally, we have updated our manuscript with two new references, *i.g.*, Giménez-Bastida *et al.* 2020 and Norden *et al*. 2019.

Responses to the comments of Reviewer 03478404

SPECIFIC COMMENTS TO AUTHORS

The manuscript titled „Potential of the ellagic acid-derived gut microbiota metabolite - Urolithin A in gastrointestinal protection" represents a review of the all available to date studies in vitro, in animal models, as well as in humans. Accuracy of the data is much appreciated. The review is written in an elegant manner, easily to be followed. English language is of high quality. The authors highlight the chemopreventive and anti-inflammatory effects of Urolithin A (UA), with health benefits. The structure of the manuscript is well chosen, starting with the Introduction and then analyzing effects on colorectal cancer and inflammatory diseases, as well as on liver and pancreatic cancer and Barrett esophagus. 1. "Introduction" explains correctly the process of producing urolithins, and contains description of metabotypes and gut bacteria involved in urolithin A production (the type of urolithins associated with health benefits). Purpose is well stated: presenting the evidence of in vitro, in vivo and clinical studies showing the potential of Urolithin A in gastrointestinal protection, as well as of suggested mechanisms by which Urolithin A can protect against cancer and inflammatory diseases of the digestive tract. 2. The paragraph "Intestine" describes the effects against

inflammatory bowel disease and colorectal cancer. A. Colorectal cancer: most chemopreventive effects are shown in „in vitro" research. Although there are numerous in vitro studies supporting UA as a CRC chemopreventive agent, there is a lack of clinical evidence in this area. Results of these studies are nicely summarized in Table 1. There is only one clinical study, showing inhibition of expression of several CRC-related genes in cancerous colon tissues, after consumption of an ET-containing pomegranate extract, but this effect is not associated with the Urolithin A level in the tissue. B. Inflammatory bowel disease: UA at a concentration that is achieved in the colon through the diet, may possess anti-inflammatory effects, including through modulating gut microbiota, activities against pathogens (like Yersinia enterocolitica) and enhancing gut barrier functions. Existing studies are performed "in vitro" and on animal models. Anti-inflammatory effects are synthesized in Table 2, of very good quality. 3. Chemopreventive effects on liver cancer are demonstrated only a few studies and one study on pancreas cancer; studies were performed in vitro and on animal models. There has been only 1 study (phase I) in humans with Barrett esophagus. Results of all these studies are presented clearly in Table 3. All data in this review are supported by correct references, including the most recent ones. Conclusion is adequate. Since Ellagitannins (precursors of Urolithin A) are found mainly in pomegranate, berries, and nuts, supplementation with these foods seems promising, although more research is required, especially in humans.

RESPONSE: We sincerely appreciate the thorough analysis of our manuscript and its favorable assessment.

COMMENT: Only two minor deficiencies: 1. Short (running) title is missing. 2. Copyright License Agreement is missing.

RESPONSE: We provided running title "Urolithin A in gastrointestinal protection" on the first page in line 6. We also attached a scan of the signed Copyright License Agreement.

Responses to the comments of Reviewer 01434943

SPECIFIC COMMENTS TO AUTHORS

This is a timely review concerning bioactive compounds, specifically Urolithin A, sourced from certain plants including pomegranates and berries. The overall structure, logical progression and scientific content are very good.

RESPONSE: We thank the Reviewer for the comments and for the assessment of our manuscript as very good.

COMMENT: English grammar requires attention throughout, especially the use of singulars vs plurals.

RESPONSE: According to the reviewer's recommendation, our manuscript was corrected by a qualified native speaker.

COMMENT: The review is also a little verbose and would benefit from a more concise writing style.

RESPONSE: In line with this recommendation, we have shortened some paragraphs or rephrase some sentences (please refer to the highlighted in yellow text).

The Discussion would further benefit from a broader discussion of plant-sourced tannins and anthocyanidins in the sections on IBD and colorectal cancer (see studies on grape seed extract by Cheah et al).

RESPONSE: According to the Reviewer's comment, the discussion sections on IBD and CRC have been broadened by studies on procyanidins based on three new references Cheah *et al*. 2014; Cheah *et al*. 2013 and Toden *et al*. 2018 (please refer to lines 150-156 and 206-209).