Reviewer's report

Title: Investigating the biological properties of carbohydrate derived fulvic acid (CHD-FA) as a potential novel therapy for the management of oral biofilm infections

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Reviewer: Riina Richardson

Reviewer's report:

This is a well-designed, sound study and the text reads well. There are some minor but essential points, discretionary revisions and clarifications that need to be addressed.

1. There should be at least a brief introduction to all aspects of the study in the Introduction section. For example, what do we know about the tissue toxicity of or inflammatory responses provoked by mouth rinses presently in use? Some introduction to why these aspects were studied in this work is needed. There is literature on this.

2. The tissue toxicity of CHD-FA was analysed in the absence of biofilms whereas the inflammatory responses were analysed in the presence of biofilms. Why? Should not both have been tested in both conditions?

3. Did the authors consider using ex-vivo mixed species biofilms instead of a four-species model?

4. Did the authors look at the proportion of species before and after mouth rinse exposure in the multispecies biofilms? What changes could be seen?

5. In Figure 3 the authors present results for two pHs (7 and 2) and it appears that pH has a radical impact on the efficacy of CHD-FA. What pH of CHD-FA was used for the other experiments? What is the pH of the commercially available mouth rinse? This should be clarified in the Materials and Methods and discussed (beyond brief mention) in the Discussion.

5. The Discussion lacks discussion of the method and the limitations of the study. For example, the authors should be aware, and point this out to the readers, that immune responses to any stimulus involves both cellular and humoral innate and adaptive immune responses which act in concert and regulate each other. Looking at few selected immune mediators in the absence of all cellular and number of humoral components capable of up- and/or down-regulating those mediators measured in this study has major limitations. The authors are appropriately careful in interpreting their results regarding this but as this is a clear limitation of the study it needs to be discussed. Similarly, a four-species biofilm hardly represents mixed oral biofilms.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I have no competing interests to declare.