ABDULLAH GÜL UNIVERSITY

RESPONSE TO REVIEWERS

Name of journal: World Journal of Clinical Cases

Manuscript NO: 53911

Title: The prophylactic and therapeutic roles of oleanolic acid its derivatives in several diseases

REVIEWERS #1 [Reviewer's code: 02809917]

SPECIFIC COMMENTS TO AUTHORS

GENERAL COMMENT

This is an extensive review on oleanolic acid, with 349 references and 127 pages. The 9 Tables and 5 Figures are nicely organized and presented, offering a lot of information on this triterpenoid. However, the information included is too diversified to make a focus. Listed below are specific comments:

GENERAL RESPONSE

We express our sincere appreciation to Reviewer #1 for his/her careful reading of the manuscript and constructive remarks. The reviewers' comments have been carefully considered and alterations have been made as listed below.

COMMENT #1

1. "The good story is simple and to the point". This review covers too much information to be focused. Their recent publication in the Journal focused on P450 in ulcerative colitis is a good review with 165 references (World J Gastroenterol. 2019 Jun 21;25(23):2846-2862.), and this style should be followed in this review, not covering every aspects, including plant biogenesis.

RESPONSE #1

We totally do agree with the Reviewer. However, let us to say that the story for oleanolic acid is very broad and could not be compared with our previous review on P450 in ulcerative colitis. Almost all of the reports were used and cited in that review while only

10-15% of the reports were cited in current review. Nonetheless, in order to make the story is good, we have reduced the content of the manuscript by reducing the number of references used from 349 to 204. In addition, some aspects like plant biogenesis were omitted along others, as explained in following comments.

COMMENT #2

2. Like their recent review on ulcerative colitis, human relevance and clinical applications are utmost important, followed by intact animal studies, and cell culture studies. However, in 9 Tables presented, there is no or little human studies, and in vitro studies predominate. Caution should be taken not to exaggerate these in vitro studies.

RESPONSE #2

We have omitted all of the in vitro studies from the manuscript (both from the text and the tables) so that only in vivo works are included in the review. We believe that the presented in vivo studies are important for human relevance. Additionally, we have combined section 2.8 and 2.9 as one section, i.e., section 2.8 in a way to lessen the coverage.

COMMENT #3

3. In this review, it seems that OA is a "cure-all" drug candidate. In traditional medicines, dietary supplements with low doses of OA, this could be true. However, higher dose and longer-time use of OA and its derivatives, toxicity occurred. This is the major reason for CDDO-Me (or similar OA derivatives) withdrawal from Phase-3 clinical trials. The adverse effects and toxicity should be discussed.

RESPONSE #3

Of course, OA is not a "cure-all" drug or drug candidate but a multifaceted prophylactic agent at right dose regime. This was emphasized in the manuscript. Moreover, the information about the withdrawal of the CDDO-me from trials was also given in the manuscript. The possible adverse effects were discussed in section 2.9.

COMMENT #4

4. Fig. 3 and Fig. 4 are missing or other figure numbers should be changed.

RESPONSE #4

Figure and the Table numbers are corrected accordingly.

REVIEWERS #2 [Reviewer's code: 03408355]

SPECIFIC COMMENTS TO AUTHORS

GENERAL COMMENT

Minor revisions were needed.

GENERAL RESPONSE

Thanks to the Reviewer #2 for reading our manuscript and accepting with minor revisions. We appreciate and express our sincere gratitude for these encouraging and supporting evaluations