

Reviewer 1

Number ID:03647461

Conclusion: Minor revision

Classification: Grade B (Very good)

Language Evaluation: Grade B: minor language polishing

In the word version of the manuscript, the omega symbol is missing (e.g. ω 3 polyunsaturated fatty acids (ω 3 PUFA) **Response: It has been added in the revised version of the manuscript.** Also, other terms such as PPAR and PPAR are missing suffixes such as alpha and gamma Greek letters. **Response: These suffixes have been added in the revised version of the manuscript.** There are also multiple other places within the document where certain symbols are replaced with arbitrary squares. **Response: It has been corrected in the revised version of the manuscript.** It would have been better to have two histopathologists instead of one to score the histology grading as subjectivity measures vary. Nowhere in the document have GLP-1, GIP or PPAR α /gamma have been spelt out as Glucagon-like peptide-1, Gastric Inhibitory Polypeptide, and peroxisome proliferator-activated receptors α /gamma respectively. **Response: These names have been added in the revised version of the manuscript.** They should have been adequately defined at the first encounter. Chemiluminescence was misspelt in line 217. **Response: It has been corrected in the revised version of the manuscript.** Also, "As shown in Fig. 1A and 1B, all HFD-derived groups showed significant higher weight from the sixth week onwards" is better replaced with "As shown in Fig. 1A and 1B, all HFD-derived groups showed significant increase in weight from the sixth week onwards". **Response: It has been modified in the revised version of the manuscript.** There are many grammatical errors that should be corrected (eg. Line 314 "the main finding in HFD+DS group was the drastic decrease of in the number in of fat vesicles as well as minimal ballooning (Fig. 7A and 7B)" **Response: It has been corrected in the revised version of the manuscript.** The authors could expand the description of each histological micrograph in Figure 6 so that the figure can stand on its own. Section 3.8 in line 311 had the histological description. The legend in Fig. 6 should have a similar but concise description for each live tissue. **Response: It has been added in the revised version of the manuscript.** In the discussion section the sentence "Following with In the groups treated with omega-3 hydroxy-fatty acids, the unaltered weight level in these groups could be the result of no effect on energy intake and energy balance hormones by the fatty acids administrated" is not clear and should be rephrased **Response: It has been rephrased in the revised version of the manuscript.** The group of sentences starting in line 412-418 state "In contrast, a phase 2 trial failed to prove histologic amelioration on individuals with non-alcoholic steatohepatitis using ethyl-eicosapentanoic acid [37]. Explanation for the lack of efficacy seems to lie on the administered dose. It is important to remark that the dosage used in this study was greatly lower (In average: 950 nanograms per day) compared to previous studies in animals with similar objective using EPA and DHA". Although the dosage may have contributed to that trial outcome but there may be more important and distinct reasons for that failure including the purity and potency of the EPA and DHA used in the treatment. **Response: This part has been modified in the revised version of the manuscript.**

Reviewer 2

Number ID: 02860898

Conclusion: Major revision

Classification: Grade C (Good)

Language Evaluation: Grade A: priority publishing

In this paper, Rodriguez-Echeverria et al. studied the effect of two compounds belonging to the 3PUFA-derived family and diet-switch regimen on high fat diet induced obesity and liver injury. The administration of 18-HEPE and 17-HDHA to mice fed with high fat diet exert a differential but moderate hepatoprotective effect, mainly due to the upregulation of PPARs and adiponectin, as well as decrease of leptin and resistin. On a separate group of mice, the authors described that diet switch regimen exerted a marked effect on liver injury. Overall, the study is scientifically sound and is well designed. However, some concerns are raised: 1. The authors failed to mention in the text the results and conclusions regarding diet switch regimen, which are important **Response: Conclusions have been extended in the revised version of the manuscript.** 2. It will improve the manuscript if authors provide information about which type of cells are infiltrating the liver. Even though there is no change in global amount of infiltrating cells, it could be possible that a shift in the type of infiltrating cells is taking place after administration of metabolites or diet switch regimen. 3. Fibrosis is only addressed by histology quantification. The authors found no differences in overall collagen deposition. This doesn't come as a surprise due to the fact that mice were fed only 16 weeks. It has been previously shown the presence of fibrosis when mice are fed HFD for 24 weeks. However, in this early time point, it could be possible that the activation of stellate cells is starting to take place. Authors should explore the expression of fibrotic markers, such as α SMA, CTGF, TGF β , among others, which could indicate stellate cell activation that could led to collagen deposition in a late time point. **Response: We carried out an immunohistochemistry analysis to determine α SMA expression in liver tissue. (Figure 9).**