Dear Ruiz:

Please find the revised version of our manuscript ID: ijerph-434373 entitled “Combined Effect of Diosgenin Along with Ezetimibe or Atorvastatin on the Fate of Labelled Bile Acid and Cholesterol in Hypercholesterolemic Rats” by Alejandro Marín-Medina, Gonzalo Ruiz-Hidalgo, Jorge L. Blé-Castillo, Alma M. Zetina-Esquivel, Rodrigo Miranda-Zamora, Isela E. Juárez-Rojop *, Juan C. Díaz-Zagoya *, which we are re-submitting to be considered for possible publication in Int. J. Environ. Res. Public Health; section: Health Behavior, Chronic Disease and Health Promotion.

We have carefully considered the reviewers comments and Editor’s remarks as follows:

Reviewer 1

Comments and Suggestions for Authors: Accept with minor revision.

Dear authors,

I have reviewed the manuscript entitled "Combined Effect of Diosgenin Along with Ezetimibe or Atorvastatin on the Fate of Labeled Bile Acid and Cholesterol in Hypercholesterolemic Rats". Your study is very valuable and important as it alert people and health care system about this kind of material. I appreciate the scientific quality of the experiment, data treatment and interpretation. In addition, the manuscript is well written, fluent and well addressed to the hypothesis the authors wanted to test. After some minor revisions which are proposed below, the manuscript is suitable for publication in this journal. I only have few minor comments; please find them listed below:

1. Dose selection criteria of tested drug must be included in material and method section. Moreover, drugs (ATV, EZT and DG) used in the study are tablets, hence preparation of dosage and vehicle medium for administration in rats should be included and clarify the method of separation of excipients. If possible batch no. of drugs should also be included. This observation was included in the material and methods section (pag. 2, line 83-85)
2. It is not clear that whether labeled substance given on 30th day as a single dose or given for 10 consecutive days. We have included this point in the material and methods section (pag. 2, line 85 and 86).

3. Although HD+DG and HD+AVT alone and in combination show excellent results yet combination of HD+EZT are also good. Addition of another group HD+AVT+DG+EZT may be more promising in this study. We agree. We have included this point in the revised version of this manuscript.

4. Since cholesterol metabolism is complex process and study have multiple targets. It is suggested to add either working hypothesis chart or include a mechanistic pathway showing targets of study in discussion section. It was included in the first paragraph of the discussion (pag. 9. Line: 196-198). The particular objectives of the study were: a) to analyze the effect of DG, ATV and EZ in monotherapy or combined on the serum levels of cholesterol, glucose and triglycerides, as well as the hepatic cholesterol and triglyceride concentration; b) to analyze describe the concentration of cholesterol labeled in the liver, spinal cord, kidney, testis, epididymis and serum in the different groups; c) analyze the enterohepatic cycle of bile acids by marking with taurocolic acid; d) know the effect of these substances on the dynamics of fecal excretion of acidic and neutral steroids.

5. Probable mechanism of combined effect of HD+AVT+DG should be included in discussion. Discussion on this point has been included in the revised version (pag. 6, line: 218-223).

6. Page 4 line 141, small bowl should be replaced with intestine. Corrected

7. Page 5 line 154, “HD showed lower activity than ND-How it is possible?

   Apparently in the HD group, the kidney was the only organ with a lower activity respect to ND, it seems than in situations where the concentration of cholesterol increases, this is distributed mainly to the liver. It is also known that the concentrations of cholesterol in the organs vary according to the metabolic needs, however this dynamic is not well known. On the other hand, in the group with EZT there was a noticeable increase in activity in the kidney, and it was observed that a decrease in the neutral sterols excretion was present suggesting that EZT seems to redistribute cholesterol to the kidney.

    8. A small description about neutral steroids and acidic steroids should be included in discussion section. Discussion on this point has been included in the revised version (Section 4.3. Taurocholic acid in the liver, intestine and serum and Fecal elimination of neutral and acidic steroids)
9. There are many small typological errors were noticed like-page 4 line 238; page 4 line 141, 143 and 144. Corrected

10. Page 6 last para- discussion should be correlate with the results. We have included in the discussion section (page 7; line: 228-229)

11. Several references were found written in Upper case like reference no. 23, 31, 32 etc. We have modified this part.

12. Correct reference no. 1- Davis, K. Done

Best regards

Juan C. Diaz-Zagoya