

# Review of: "Hepatoprotective Effect of the Ursolic Acid-Oleanolic Acid Mixture Administered Intragastrically in Mice with Liver Damage Induced by Anti-TB Drugs"

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Potential competing interests: No potential competing interests to declare.

## Comments for authors

Thank you for the opportunity to review your manuscript titled, "**Hepatoprotective Effect of the Ursolic Acid-Oleanolic Acid Mixture Administered Intragastrically in Mice with Liver Damage Induced by Anti-TB Drugs**". The topic is interesting and of great importance. There are certain issues that the authors need to address, and I hope to be useful for improving the manuscript.

## Title and subtitles

1. Please, titles and subtitles of the manuscript should follow the instructions of the journal.
2. The title includes liver damage only and a hepatoprotective role only for the Ursolic Acid-Oleanolic Acid Mixture while the manuscript studies the hepato- and nephroprotective effects of the UA/OA mixture against damage caused by the RIF/INH/PZA mixtures, as mentioned in the aim of the study at the end of the introduction.
3. Please avoid abbreviations in the title.

## Abstract

4. The authors mentioned in the abstract and introduction sections "over 60 days"; please unite that the trial was for 60 days.
5. The abstract should briefly contain all methods and results obtained in the manuscript.

## Materials and Methods

6. The authors mentioned in the method section "BWG was recorded every third day." Please clarify the meaning.
7. Please insert the total number of animals used at the beginning of the experiment and determine the number of deaths if present.
8. Please insert the age of the mice used in their *in vivo* assay.

9. Please determine the organ index beside the absolute organ weights.
10. The authors mentioned concerning the RIF/INH/PZA mixture dose, "The assay was performed following the methodology described earlier (7,8,21) ". Please revise the references used because these references do not match the doses used and are for other substances.
11. Please mention the reference for the used silymarin dose.
12. Please insert the acclimation period for the mice before starting the experiment.
13. Please determine where the authors performed the anesthesia of the animals before they were sacrificed by cervical dislocation; please mention the agents used with doses and insert the references.
14. Please mention in the method section the method of obtaining the serum and the observation of the serum until analysis.
15. The authors mentioned "ALT, AST, alkaline phosphatase (ALP), cholesterol (CHOL), triglycerides (TRIG), and High-density lipoproteins (HDL) were determined." Please insert references for their methods of measurement.
16. The authors mentioned" liver, kidney, and spleen were extracted to record weight and for histological analysis". Please check where the authors mentioned in oxidative stress measurement also "Levels of oxidized proteins (OxP) and oxidized lipids (LOx) were determined in the homogenate without centrifugation", and please determine which organs were used for oxidative stress biomarkers determination.

## Results

17. The authors mentioned" liver, kidney, and spleen were extracted to record weight and for histological analysis". Please check where the manuscript mentioned only liver histopathological findings (figure) without kidney and spleen.
18. The results for oxidative stress biomarkers are not found in the manuscript. Please check.
19. Please unite the abbreviation for standard error beneath the tables.
20. Please correct the abbreviation of its standard error (e.s.) in the figure legend of figure 1
21. Please, in figure one, insert the unit of measurement for body weight gain (g) on the vertical axis.
22. The authors mentioned "only the weight of the liver of group II (anti-TB) showed a slight increase (1.37 g) with regards to the weight of the other groups (<1.33 g)". Where are the significance letters in table 1?
23. Also, in table 2, where are the significance letters for liver enzymes (AST, ALT, ALP) where there are great differences between means? Please check.
24. Please insert the full names beside the abbreviations for lipid profile parameters in the footnotes of table 2.

25. In table 3, the authors mentioned "Histological analysis of the liver", and splenomegaly is mentioned in table 3. Please revise.

26. Please insert the arrows and letters in the histopathological figures and mention their expressions in the figure legends to clarify the differences between groups.

### **Discussion**

27. The discussion needs to be rewritten with more attributions for the obtained results; agreements with previous studies alone are not enough.

### **Conclusion**

28. The conclusion should briefly cover all the findings of the manuscript and the hepato-renal protective role of the Ursolic Acid-Oleanolic Acid Mixture, not just liver findings.

### **References**

29. References need to be updated and revised, either inside the text or in the references list, to follow the instructions of the journal and collect all references together.