

COMMENTS TO AUTHORS and Rebuttal

Reviewer #1:

Comment: You have prepared an article devoted to the actually problem of experimental medicine. The material is presented logically and correctly.

Reviewer #2:

Comment:The introduction section was too long. To me, it should be shortened.

Answer: Introduction section has been shortened.

Comment:The article is written very irregularly. The sequence in the methodology section of the article must be changed. Because I tried to read ten times, but I had difficulty concentrating.

Answer: Methodology section has been simplified

Comment: Eight groups are specified, but it should be clearly stated how many rats are used in each group.

Answer:The number of animals was already stated in methodology section under biological evaluation

Comment: Anova is never suitable for experimental work. A nonparametric method should be used in studies where the number of subjects is low or the results are not normally distributed.

Answer: One way ANOVA method was used because we found our data to be normally distributed and referring to all the previous reports related to this work, we found that one-way ANOVA method was widely used by researchers [1-5].

References

1. **Rana SV, Attri S, Vaiphei K, Pal R, Attri A, Singh K.** Role of N-acetylcysteine in rifampicin-induced hepatic injury of young rats. *World J Gastroenterol* 2006; **12**(2):287-291[PMID:16482631 DOI: 10.3748/wjg.v12.i2.287]
2. **Singh C, Jodave L, Bhatt T, Gill MS, Suresh S.** Hepatoprotective agent tethered isoniazid for the treatment of drug-induced hepatotoxicity: Synthesis, biochemical and

histopathological evaluation. *Toxicol Rep* 2014; **1**: 885–893 [PMID: 28962300 DOI: 10.1016/j.toxrep.2014.10.001]

3. **Wang C**, Fan RQ, Zhang YX, Nie H, Li K. Naringenin protects against isoniazid- and rifampicin-induced apoptosis in hepatic injury. *World J Gastroenterol* 2016; **22**(44): 9775-9783 [DOI: 10.3748/wjg.v22.i44.9775]

4. **Chanchal SK**, Mahajan UB, Siddharth S, Reddy N, Goyal SN, Patil PH, Basavaraj P, Bommanahalli BP, Kundu CN, Patil CR, Ojha S. In vivo and in vitro protective effects of omeprazole against neuropathic pain. *Sci Rep* 2016;**6**:30007[PMID:27435304 DOI: 10.1111/j.1432-1033.1974.tb03714.x]

5. **Bais B**, Saiju P. Ameliorative effect of Leucas cephalotes extract on isoniazid and rifampicin induced hepatotoxicity. *Asian Pacific Journal of Tropical Biomedicine* 2014; **31**;4:S633-S638.[DOI:10.12980/APJTB.4.2014APJTB-2014-0236]

Comment: This study have a few problems in terms of statistical analysis methods. As a result, the world journal of gastroenterology is often read by clinicians. The articles written by pharmacologists should be written with the logic that can be understood by the clinicians. Because the clinician who reads this article will get out of this article?

Answer: The reason for selection of given statistical method has already been stated above.

Reviewer #2: This manuscript is a basic paper showing that a prodrug made as a mix of isoniazide and n-acetylcysteine may be a good approach to reduce the isoniazide hepatotoxicity frequently observed in anti-tuberculosis treatment. Manuscript is well written and results are interesting. Several points should be clarified by authors to ameliorate the reading of the paper: 1 -

Comment: Throughout the introduction and result sections, several abbreviations are used that have not been previously defined in the text (they can be defined later) as TEA, DCM, OPA, MGI, CMC. It would be good to have a list of abbreviations at the beginning of the article to facilitate reading.

Answer: List of abbreviation has been included after keywords in the manuscript

Comment: Was the histopathological analysis blind? How the authors guarantee that the histopathological analysis was unbiased?

Answer: The standard experimental method for histopathological analysis was employed with help of pharmacologists in CPCSEA- approved animal facility of Poona College of Pharmacy, Pune, India. Liver samples of all six rats from each group were outsourced for histopathological analysis. The histopathologist was unaware of the protocols or nature of induced diseased state. The histopathologist was not directly involved in the study, but we have mentioned the histopathology laboratory details in the manuscript to whom the work was outsourced. Statement to this effect has been included now in the protocol section.

The slides were labeled using codes and results obtained were provided by the histopathologist for those codes only. This guaranteed the unbiasedness of the analysis. One representative image from each group has been included in manuscript.

Comment: Authors describe results as mean and SD and analyze differences among groups using ANOVA test. Was data normality ascertained before the analysis? How were analyzed values who didn't follow a normal distribution?

Answer: Before proceeding for one-way ANOVA test for analysing data, normality was ascertained with the help of Kolmogorov-Smirnov method (with Dallal-Wilkinson-Lilliefors P value) using GraphPad PRISM 7 software. All the values that were obtained followed normal distribution.

Comment: A very great part of the text in the discussion section is about results or procedures. Discussion should be shorter and easy to read and centered in discuss the meaning of findings. Results description must appeared in result section and methodology descriptions should be remove from this section of the text.

Answer: All the corrections have been made, result description is placed in result section and discussion is made shorter.
