Point by point (PeerJ)

Dear Editor …

The present study entitled **(In vivo assessment of pharmacokinetic interactions of empagliflozin and henagliflozin with sorafenib: an animal-based study)** presented an interesting subject highlighting the importance of a possible drug-drug interaction between sorafenib with either empagliflozin or henagliflozin focusing on a certain key metabolic pathway in the liver and the role of certain intestinal and hepatic transporters on the plasma bioavailability and clearance of these agents. The manuscript was well written with good grammar and scientific language phrasing. The information was well-connected and presented in a stepwise and sequential manner, which made the process of reading and understanding the work much easier. I commend the researchers for this interesting and remarkable work. The basic reporting, experimental design, and validity of findings were structured clearly with minor corrections to be made. For this research to be accepted, minor and few major revisions need to be looked over thoroughly as described:

Minor Revisions:

1- The "background" part needs to be shorter in the abstract. Remove lines 11 & 12 (starting with empagliflozin and ending with (T2DM)). Remove lines 14,15, & 16 (starting with previous studies and ending with SGLT2 inhibitors). Rephrase the aim (lines 16 & 17) to be (this study aimed to investigate the pharmacokinetic profiles of coadministration of sorafenib with novel SGLT2 inhibitors, either empagliflozin or henagliflozin and to explore their potential mechanisms)
2- Remove all unnecessary abbreviations in the abstract, since you've given their definition
3- Make sure all abbreviations used regularly are defined at their first appearance
4- In the "introduction" section, lines 117 – 119 starting with (pharmacokinetic parameters till the end of the paragraph) should be removed because they are unrelated to the objectives
5- In the "Animals" sub-section, rats age must be specified
6- Mention the route and frequency of administration of your test agents in the "pharmacokinetic study" sub-section
7- It is for better and easier understanding if you provide a study design flowchart highlighting the exact timeline of the study with the interventions
8- Line 149, "The doses were chosen by converting the clinically recommended doses for patients to animal doses". Add equation, conversion factor, and reference.
   Nair, A. B., & Jacob, S. (2016). A simple practice guide for dose conversion between animals and human. Journal of Basic and Clinical Pharmacy, 7(2), 27. https://doi.org/10.4103/0976-0105.177703
9- Line 197, I think you mean "henagliflozin" instead of "empagliflozin". Please check
10- In the "statistical analysis" section, why did you estimate the sample size for the experiment using the resource equation method and not using the statistical G*Power 3 analysis program for precise estimation?

Faul F, Erdfelder E, Lang AG et al (2007) G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 39:175–191. https://doi.org/10.3758/bf031 93146

11- Remove figure title (Data1) from Figure 5

Major Revisions:

1- The “results” section is written well, easily going, and understandable highlighting the most important outcomes. Figure 3 needs more explanation in the caption. Why are there 2 figures one inside the other in one image? If they represent different outcomes, mark each one with a letter and explain in the caption

2- All included figures need a caption highlighting the sample size, significance level, data presentation (e.g.: mean ± SEM), and statistical analysis method

3- I couldn’t find Figure 6 which you mentioned and cited in the text, the one representing the gene expression analysis. please make sure that all figures cited are included in the manuscript.

4- Please justify the relationship between UGT1A7 and UGT1A9 and the functional role of UGT1A7 on the metabolizing activity of UGT1A9 clearly since you explained the importance of UGT1A9 in the “Introduction” whereas you investigated the molecular expression of UGT1A7

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