Reviewer’s report

Title: Critical Pharmacokinetic and Pharmacodynamic Drug-Herb Interactions in rats between Warfarin and Pomegranate Peel or Guava Leaves Extracts

Version: 1 Date: 25 Sep 2018

Reviewer: Xiao Zheng

Reviewer's report:

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The manuscript by Maisa et al reports the interaction between warfarin and pomegranate peel/guava leave extracts based on the result of in vivo (rats) and in vitro (hepatocytes) study. Overall, the generally background and rationale for conducting this study are not clear. Moreover, the paper suffers from a lack of clarity and some methodological shortcomings.

Major points:
1) The information in the ABSTRACT should be made clearer about what the combination is. The "remaining combinations" are not appropriate.

2) The information in the INTRODUCTION tells too much about the pharmacological interactions, but little about the knowledge about CYP-mediated DDIs especially concerning the major active components such as flavonoids. Also, it is still unclear why the work focused on pomegranate peel and guava leaves extracts.

3) In the preparation of plasma samples, test plasma samples (100 μl) were mixed with 150 μl metronidazole benzoate (I.S.,1.5 μg/ml) and centrifuged at 14000 RPM for 10 min. It is confusing to the reviewer how this ratio could efficiently separate the target molecules and make ready-to-analysis supernatants? Has the method been previously validated in terms of recovery, precision and liner range?

4) The results are poorly organized, lacking sufficient description of the details.

Minor points:
1) The authors should carefully improve the language throughout the paper to make it more clear about the background and major findgins. For example, P3,ling 34-36 In addition, further polishing of the language is desirable.
2) The title should indicate that the results are based on study in rats and what the interactions are (PD, PK)

3) In the pharmacokinetic study, it is not clear how warfarin was administered?

4) How the dose of compounds in cell treatment was determined? Are they relevant to in vivo conditions?

5) In Fig.1, the validation results rather than the calibration curve are necessary in this place

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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