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: 16 Aug 2018

Reviewer: Xia Chunhua

Reviewer's report:

The present study have investigated the impact of co-administration of pomegranate peel and guava leaves extracts, including their quality markers namely; ellagic acid and quercetin, respectively, on warfarin's in vivo dynamic activity and pharmacokinetic actions, in addition to potential in vitro inhibition in cytochrome P450 enzymes (CYP). However, there have been many literatures about the interactions between the above natural products and warfarin. Additionally, there are some major issues in the paper as follow:

1. The results showed a significant effect on CYPs, but had no impact on t1/2 and MRT which can better represent the elimination process, and the elimination ration was often correlated to the activities of CYPs. How to explain this phenomenon?

2. HPLC method: the linear range for the determination of warfarin was from 100 to 4000 ng/ml, but the measured concentrations of warfarin in rat plasma partly exceed the upper limit (4000ng/ml), which can be seen from figure 2. How to quantify for these samples? Dilution effect assessment performed?

3. The CYP isoforms (CYP3A4, CYP2C9, CYP2C8) in human were not expressed in rats.

4. The content of quercetin and ellagic acid in Guava leaves extract and pomegranate peel extract should be provided in the Materials Section. Can the dosing of quercetin (12.75 mg/kg) and ellagic acid ((40 mg/kg) be comparable that in Guava leaves extract (250 mg/kg) and pomegranate peel extract (100 mg/kg)?

5. The data should be represented as mean±SD, not mean±SEM, in tab3 and figure 2, etc.

6. All the figures were very vague and should be redrawn.

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

Yes
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.

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