Reviewer's report

Title: Up-regulation on Cytochromes P450 in Rat Mediated by Total Alkaloid Extract from Corydalis yanhusuo

Version: 4
Date: 10 July 2014
Reviewer: LIK VOON KIEW

Reviewer's report:

1. Is the question posed by the authors well defined?
   Yes. In the current study, the authors have attempted to assess the potential of total alkaloid extract (TAE) from YHS to effect the activity and mRNA levels of five cytochromes, namely CYP2E1, CYP3A1, CYP1A2, CYP2C11 and CYP2D1 in liver, lung, kidney and intestine, using rat as a model.

2. Are the methods appropriate and well described?
   The description on the method was found to be significantly improved in the latest edition. The authors are commended for their careful attention to the reviewers' comments.

3. Are the data sound?
   The data was generated from tissues collected at the end of a 2 weeks treatment period. The analysis and interpretation on the data generated were acceptable. Nevertheless, as there is no tissue collection performed along the 2 weeks TAE treatment period, the tissue CYP activities and related mRNA expressions of rats along the treatment period was not known. This has added uncertainty to the results reported, i.e. inability to tell if the elevated / suppressed CYP mRNA expression at the end of the study were due to the consistent TAE treatment, or any event that took place prior to tissue collection. This is the main limitation of the current study. Comments/justification from the authors on the absence of such data would be preferred.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes. The authors are commended for their careful attention in addressing the reviewers' comments in improving the data reporting of the manuscript.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   In the discussion, the author has described the potential induction of the CYP2E1 and CYP3A1 enzymes by TAE and indicate the risks of drug-herb interactions following co-administration of Corydalis yanhusuo and drugs. The write-up in the discussion was found to be improved in the current edition of the manuscript.

6. Are limitations of the work clearly stated?
The limitation in the use of rat CYP3A1 in representing human CYP3A4, as well as the absence of the data on tissue CYP activities and related mRNA expressions of rats along the treatment period were not discussed.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes

8. Do the title and abstract accurately convey what has been found? Yes.

9. Is the writing acceptable?
The grammar of the writing was acceptable.

Major Compulsory Revisions
The authors are commended for their careful attention to the reviewer’s previous comments. The reviewer has no additional comments/suggestion on major compulsory revisions.

Minor Essential Revisions:
Discussion: CYP2E1 induction associated with TAE toxicity
Paragraph 3 line 6:
“CYP2E1-mediated metabolism generates reactive oxygen species, such as oxygen and hydroxyl radicals, when these exceed the cellular detoxification systems, it results in oxidative stress with its various pathologic consequences.” Please provide reference for this statement.

Discretionary Revisions
Abstract: Results: line 3: an increase in liver CYP2E1 and CYP3A1 enzyme activity…
Methods: the comment of the reviewer Dr Shingen Misaka on the statistics methods (i.e. using one way ANOVA eth post-hoc test instead if t-test) should be taken into consideration.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests