Reviewer’s report

Title: Anti-hyperalgesic properties of a flavanone derivative Poncirin in acute and chronic inflammatory pain models in mice

Version: 3 Date: 11 Jan 2019

Reviewer: Reviewer 2

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Not sure - key details are missing from the manuscript

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Not sure - key details are missing from the manuscript

Statistics - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable
OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS:

1. The Authors have provided a thorough in vivo examinations of four types of inflammation mice pain model. What are the differences between these four inflammation models and/or how this strengthens Author's conclusion should be clearly stated (e.g. mimics the acute or chronic state of inflammatory pain). For example, Carrageenan induced two phases of edema with the first phase been the low-intensity edema.

Ref: Mouse paw edema. A new model for inflammation? (PMID:3690058)

2. Preventive protocols have been used for the test item poncirin. For better mimics that in the clinical setting, the intervention protocol will be more appropriate. What is the reason that the prevention protocol was used rather than intervention?

3. Method section, animals: What strain of mice? Also, typical body weight for mice at the age of 3-4 weeks should be ~20-25g. Please double check. If available xy fig for the animal body weights should be included as part of the result.

4. Dose volume of the vehicle control should be stated

5. Major concern: The behavioural readings (e.g. mechanical hyperalgesia and allodynia baselines) are much higher compared to other published data using mice. For example, Authors cited Cho H et al 2012 (ref #22), their von Frey and Randall Selitto baseline readings (Supplementary Fig6) are similar to this manuscript (~300g cf ~400g). However, Cho H et al use SD rats (SFig6) not mice. Based on my knowledge and experience the behavioural baselines between rats and mice are distinctly different.

6. ".....cardiac puncture following anesthesia with xylazine + ketamine (16 mg+ 60 mg)". I will assume this should be 16mg/kg + 60mg/kg. Please double check.

7. At what time point/s Authors collected the serum samples for the renal and liver toxicity test?

8. Under Method section, Statistical analysis. Did Authors use SPSS for the statistical analysis or SPSS and Sigma Plot?

9. Table 2: Should include dexamethasone result in Table 2 if available.
Future direction: a positive control that alters (mild/moderate) the liver/kidney functions should be included.

REQUESTED REVISIONS:

Refer to Research Quality Review Commentary, especially comment #5 (major concern).

Note: This reviewer report can be downloaded - see attached pdf file.

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.

No

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:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

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