Reviewer's report

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

Version: 2 Date: 12 Nov 2018

Reviewer: Joseph Stephan

Reviewer's report:

The manuscript titled "Anti-hyperalgesic properties of a flavanone derivative Poncirin in acute and chronic inflammatory pain models in mice" is an interesting and comprehensive assessment of the effect of Poncirin in several models of inflammatory pain in mice. The paper is of potential interest and the results are clear. A few minor points below should be addressed:

Minor comments:

- Formalin model: the methods state that mice were observed for 60 minutes, divided into the first 10 minutes (early phase) and a late phase (10-30 min), which gives a total of 40 min total max: correct numbers; also, related figure divides 1st phase into 0-5 minutes rather than 0-10; correct

- Legend of figure 3 conflicts with text as to what figure 3c represents, make clearer please

- "There was no tolerance effect of poncirin on mechanical hyperalgesia and allodynia during interruption of dose on day 5, which was reestablished when the drug was administered on day 6 (Fig.4C & D).": the difference is very hard to see in the presented graphs, and doesn't seem very clear cut. The authors should temper their conclusion or its language.

- The reference provided in the discussion for the use of poncirin in ancient times (ref 14) is inaccurate; cite original reference

- Figure 11: an effort to show larger fields should be made by the authors; also, was any attempt at quantification of the data conducted? It is unclear what the statistical analysis referred to in the figure 11 legend refers to, and where it is shown!
In general, the materials section is very large, and I feel this has been done a bit at the expense of the results, which occupy a significantly smaller portion of the paper. Authors should attempt to compensate for this imbalance.

Typos and other textual corrections:

Page 3 line 13: should be heme oxygenase
Page line 45: remove "while" from beginning of sentence
Page 9, line 45: renal and liver toxicity; "renal and hepatotoxicity" is incorrect
Page 12 line 12 and 15: should read poncirin doesn't
Page 12 line 23: in plasma
Page 13 line 36: with unbearable side effects
Page 13 line 40: and these medicinal plants have been used

**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.

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:

Needs some language corrections before being published

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