Author's response to reviews

Title: Jacarehyperol A induced apoptosis in leukaemia cancer cell through inhibition the activity of BCL2 Proteins

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Author's response to reviews: see over
Authors’ Response

The authors are grateful to the reviewers and editors for their comments, which helped us to greatly improve our manuscript. This paper is revised exactly according to their comments.

For Editors:
Dr. Jöhrer remarked that repetition of same phrases in different sections of the manuscript should be avoided. In addition, she mentioned that some typing errors still have to be corrected. Therefore, I would invite the authors to revise their manuscript with respect to these minor issues before the ms proceeds to the production process.

Response: Thanks for your suggestion. We have revised these repetitions and typing errors.

For Referee 1:

Major Compulsory Revisions
1) Lane 65-68 in "Background" is also exactly found in the Discussion section (lane 369-372)
Response: Thanks for your suggestion. We have rewritten this section.

2) Lane 276-283 in the "Results" section shows the same wording as lane 356-363 in the Discussion section.
Response: Thanks for your suggestion. We have rewritten this section.

3) There are still some minor spelling mistakes, please proof-read!
Response: Thanks for your suggestion. We have checked and revised the typing errors.

For referee 2:

Major Compulsory Revisions
1. The authors claim “Jac-A possesses a broad antitumor effect for all tested cancer cells and remarkably inhibited the proliferation of leukaemia cells”. However, for the solid tumor cell lines, only inhibition of proliferation by Jac-A is shown, but no data regarding an antitumor effect is presented. As already mentioned in the first review process, to conclude on a broad and general role of Jac-A as a potential inducer of apoptosis and to identify Jac-A as potent anti-cancer drug the authors should at least need to perform Annexin/PI staining with the solid tumor cell lines. Especially LOVO cells are of interest as they are resistant to a variety of stimuli due to loss of Bax expression. It would be interesting to know if Jac-A can induce apoptosis in these cells or if Jac-A can sensitize LOVO cells to drug induced apoptosis. If the solid tumor cell lines were conserved too long to be used for test (as mentioned by the authors) they can easily obtained from commercial or academic sources.
Response: Thanks for your suggestion. We have performed Annexin/PI staining with the LOVO cell lines. Jac-A can induce apoptosis of LOVO cell lines, however, the
activity was weaker than leukaemia cells. 10 uM Jac-A induced about 24% LOVO cells apoptosis, which align with the MTT results for LOVO cell lines. These results have been added into the supplementary material.

Minor Essential Revisions

2. Figure S1: scattergrams of the controls are missing
   Response: Thanks for your suggestion. Controls have been added
3. Figure 3F: partitioning for the quadrants differs compared to figure 3A-E.
   Response: Thanks for your suggestion. We have repeated this experiment and replaced previous results.
4. A number of times: Bcl-XL instead of Bcl-xL
   Response: Thanks for your reminding. We have revised these errors.
5. As there is no figure S2 figure S3 should be renamed S2.
   Response: Thanks for your reminding. We have revised these errors.
6. Line 274: “...leukemia cells HL-60 and THP-1 (Figure S1_C, Figure S1_D);” regarding the legend of the figure, data for HL-60 and THP-1 are shown in Figure S1_A and Figure S1_B.
   Response: Thanks for your reminding. We have revised these errors.
7. Gossypol data in figure S1 is not mentioned in the main text.
   Response: Thanks for your suggestion. We have added this section in the main text.
8. Reference 13: a comment instead of the original paper was cited.
   Response: Thanks for your suggestion. We have added instead this reference.