

Peer Review File

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Reviewer A

Comments:

Although I do not disagree with the intend of the article, I struggle with its hypothetical nature, reliance of limited datasources, and with a primary referred source being both critiqued, doubted and praised in the same section.

I'd strongly suggest to go back to the drawing board, pull more substantive datasources that are far less hypothetical to build up towards a conclusion that is far less speculative.

Reply 1: Thanks for the comment. Due to this manuscript is an editorial comment, we consider that evaluating the results with a critical and constructive spirit could include the three aspects mentioned (critiqued, doubted and praised). Likewise, the in silico studies developed in the original work are predictive ones with great speculative potential to raise hypotheses and generate validation projects. However, in response to the reviewers' comments, we modified the text and added some bibliographical references as suggested. It was not possible to incorporate a larger quantity of references due to the limitation on the number allowed.

Changes in the text: The Outcome analysis section was modified (highlighted in yellow) and the following references were added to build up towards a conclusion less speculative:

12. Gao X, Cai Y, Wang Z, He W, Cao S, Xu R, et al. Estrogen receptors promote NSCLC progression by modulating the membrane receptor signaling network: a systems biology perspective. *J Transl Med.* 2019;17:1–15.
13. Shalaby NMM, Abd-Alla HI, Ahmed HH, Basoudan N. Protective effect of *Citrus sinensis* and *Citrus aurantifolia* against osteoporosis and their phytochemical constituents. *J Med Plants Res.* 2011;5(4):579–88.
14. El-Kersh DM, Ezzat SM, Salama MM, Mahrous EA, Attia YM, Ahmed MS, et al. Anti-estrogenic and anti-aromatase activities of citrus peels major compounds in breast cancer. *Sci Rep.* 2021;11(1):7121.
15. Song S, Huang W, Lu X, Liu J, Zhou J, Li Y, et al. A network pharmacology study based on the mechanism of *Citri reticulatae pericarpium-pinelliae rhizoma* in the treatment of gastric cancer. *Evidence-Based Complement Altern Med.* 2021;2021:1–17.

Reviewer B

Comments:

Comment 1: The inhibitory effect of apigenin on Mcl-1 expression had been demonstrated by the authors. Therefore, it is predictable enough. although the cell line used in this study is different. (Please refer to references: Polier G et al. *Cell Death Dis* 2011;2:e182 (Fig. 4b) and Polier G et al. *Int J Cancer.*136(3):688-98 (Fig. 6C)).

Reply 1: Thank you very much for the contribution

Changes in the text: The second paragraph of the Outcome analysis section were modified (highlighted in yellow) and the references were added.

Comment 2: In outcome analysis section, it is hard to follow what authors suggest. It should be reorganized so that the main points are clearly conveyed.

Reply 2: Thanks for your suggestion

Changes in the text: Outcome analysis section was reorganized with the aim of clarifying the concepts. The modified text was highlighted in yellow throughout the manuscript.

Comment 3: Many references are missing (line 23, 55, 59, etc) or incorrectly indicated (little relevance). And there are fewer references compared to the description.

Reply 3: Thank you for the observations. The references were checked and references were added according to a maximum limit of 25 allowed for the editorial comment text.

Comment 4: It is necessary to change the title of manuscript to make it simple and clear what the authors suggest.

Reply 4: Thank you for the contribution. However, the great length of the title is because in the editorial comment we should keep the subject of the original title.

Comment 5: In many cases, abbreviations appear first without mentioning the full form of the term.

Reply 5: Thank you for the observations

Changes in the text: The abbreviations were now correctly mentioned throughout the manuscript (highlighted in yellow)

Comment 6: English should be improved.

Reply 6: Thank you for the observations.

Changes in the text: The English was improved with María José Martínez contribution (Public Sworn Translator of English)

Reviewer C

Comments:

Comment 1: The editorial sent by Hereñú and Crespo is well-written and cites relevant references that support the authors' statements. The topic is within the scope of Translational Cancer Research and will certainly contribute to future investigations and advances in this field of study.

Reply 1: Thank you very much for the kind comments.
