Reviewer's report

Title: Samsoeum, a traditional herbal medicine, elicits apoptotic and autophagic cell death by inhibiting Akt/mTOR and activating the JNK pathway in cancer cells

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Reviewer: shigeomi shimizu

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Minor Essential Revisions

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

Review “Samsoeum, a traditional herbal medicine, elicits apoptotic and autophagic cell death by inhibiting Akt/mTOR and activating the JNK pathway in cancer cells”

In this study, the authors discovered that Samsoeum (SSE), a traditional herbal medicine, induces cell death through apoptosis and autophagy in cancer cells but not in normal cells. More specifically, SSE was found to affect certain pathways to induce apoptosis and autophagy in a cooperative manner. Although several reports have already examined the effects of the components in SSE on cancer cell death, this study contains novel results that could provide useful information for cancer therapy. But there are some concerns with the experiments that would not be addressed.

Major comments;
The authors concluded that SSE was not cytotoxic to normal cells because hepatocytes were resistant to SSE. I think, however, more cell types should be studied before making such a general conclusion. Furthermore, hepatocytes are rather distinct from carcinomas and melanomas. The authors should use more appropriate cells as a control. In addition, more discussion on why normal cells are resistant to SSE should be provided.

Figure 5C
To demonstrate more clearly that both apoptosis and autophagy cause cancer cell death, examine if the treatment of 3-MA also partially inhibits cell death, and
whether simultaneous addition of 3-MA and z-VAD-fmk fully inhibits it.

Minor comments;
“Methods” section describes that the “S.E.” was used for the statistical analyses, whereas the “S.D.” was used in the figures.

p13, line2-line9
It would be better that this part explaining the behaviors of LC3 on autophagy is moved to the previous paragraph which refers to the images of RFP-LC3.

Figure 3B
It is difficult to judge chromatin condensation and nuclear fragmentation from the images.

Figure 3C
In B16F10 cells, the RFP-LC3 signal looks punctuated even without the treatment of SSE.

Figure 8 should be cited in the text and needs a legend that includes the meaning of the colors.