Reviewer’s report

Title: Grape-supplemented diet for colon cancer prevention: Effects on proliferation and Wnt signaling greatest for those over age 50 and with high arginine consumption

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Reviewer: Sifan Chen

Reviewer’s report:

Holcombe et al confirmed the beneficial effects of grape intervention for small-scale subjects in this pre-clinical trial, showing mechanistically the potential involvement of regulation of Wnt signaling pathway. This is an interesting study, implicating that the daily food consumption (with particular components) may give a novel strategy to improve human health. However, the current data are not sufficient to support the conclusion and some critical points remain to be addressed:

Major Compulsory Revisions

1. The authors claimed that 30 healthy volunteers were selected to participate this trial, however, Table 1 indicates the average BMI of the overall is 28.12, being considered as obesity. Thus, it would be greatly appreciated if the authors could provide the measurements, i.e., total cholesterol (TC) and triglycerides (TG) of the subjects in the “pre-grape” conditions, or at least, provide evidence to show these subjects are healthy without suffering hyperlipidemia or insulin resistance, etc. Moreover, the authors should take it into concern in the discussion that resveratrol is previously reported to be involved in the improvement of lipid and glucose metabolism.

2. In the second paragraph of the RESULTS, it was described that the participants snacked less because of feeling full after grape consumption. This raises an important question that all the beneficial effects which the participants got after the trial is due to the grape uptake per se or just because of changes of dietary style, i.e., taking less snack, etc. To address this, it would be very helpful to detect the effects which are caused by resveratrol intervention itself, i.e., by measuring SIRT1 and/or AMPK expression level and/or enzymatic activity.

3. Regarding the dosages of this trial, up to 1 pound of grapes was taken for consideration. Are these dosages referred to relevant published literature or it is designed by the authors? This has to be discussed because one of the disadvantages of resveratrol application is the potential toxic side effect.

4. In Fig. 1G, it is not clear what to compare with as “negative control”.

5. In Fig. 2C, what is the difference of cMYC expression levels between pre- and post-grape consumption in overall group?
Minor Essential Revisions

1. The title of this manuscript indicating “for colon cancer prevention” is not appropriate, since this study did not trace and monitor the possible incidence of cancer development in the future, therefore measurements of several markers hereby are not sufficient to support this claiming.

2. Please use kg or g instead of pound in the context of description of the dosages.

3. In the MATERIALS and METHODS, it is not clear why the participants were placed onto a low resveratrol diet for four weeks in advance. Please explain the rationality.

4. In the first paragraph of RESULTS, what and how did the authors monitor the toxicities during the intervention? This should be indicated.

5. In the third line of second paragraph of RESULTS, it is not proper to write “patients” since the authors claimed all participants are healthy.

6. In Table 1, for the Race/Ethnicity in the overall group, all the different races actually sum up to 36 but not 30.

7. In Table 2, the consumption of total sugars was shown to be greatly increased post grape intervention. Was this calculated including the sugar from grape supplementation?

8. In Fig. 1A, all the small dots representing individuals do not sum up to 30. Moreover, the distribution of the weights from this population seems to be quite diverse.

Discretionary Revisions

1. It would be appreciated if the authors could analyze the protein expression levels of the markers shown in this study in addition.

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests.