Reviewer's report

Title: Postprandial effects of encapsulated polyphenolic grape extract (PGE) on appetite and food intake: a randomised dose-comparison trial

Version: 2 Date: 18 May 2015

Reviewer: Julien Cases

Reviewer's report:

The work by Shin et al., Postprandial effects of encapsulated polyphenolic grape extract (PGE) on appetite and food intake: a randomized dose-comparison trial, deals with a key feature of prevention strategy in nutrition and nutraceutical industry to manage the body weight through a targeted effect reducing calorie assimilation. The topic is particularly interesting since only few researches have been performed on this topic with polyphenols and none of them have been performed with Humans.

The rationale of the research is well described, with many references and it can easily, a priori, be understood what kind of clinical demonstration should be involved to support the hypothesis.

The involved population is accurate according inclusion and non-inclusion criteria, nevertheless it is not clear, despite volunteers are described as healthy, if psychological disorders have been checked for non-inclusion criteria of volunteers, as those troubles generally often the time interfere with appetite.

The primary outcome of the study is not clearly set, even if we understand that it is supposed to be appetite rating. Consequently the level of performance expected for the study cannot be set and there are no possibilities before the start to ensure that it will be possible to verify if the result of such a study can be a success or not. In addition, and probably because the primary outcome is not so clear, there is no description of the statistical power used to calculate the amount of population to be involved in the investigation. So and because there is no primary outcome clearly set and no performance clearly aimed, with no statistical power determined, the study rather looks like a pilot one and should be therefore clearly described as such from the title of the paper. The clinical model used, the cross-over, is gold standard for such a study and clearly improves the statistical power but the latter is still unknown.

The product used for the study is poorly described in Table 1 and no one knows which method for dosage of polyphenols have been used; there are so many methodologies and depending on the choice of the methodology the amount of polyphenol can vary within a ratio from a 1 to more than 10 depending on the method of dosage and on the polyphenol reference used. In addition, there is a huge gap between references cited within the rationale with most of them describing until the name of individual polyphenols inside tested products whereas in the present paper authors only used a product called PGE which
seems to have been analyzed in bulk at 353 mg polyphenols per 500 mg extract. In addition, it is not known from where does the extract comes (supplier) and what is the process of production of the extract; red grape? White grape? Only seed extract? Skin extract? The both? Whole grape extract? Water or solvent process? Polyphenol purification on resins or else? A clear description of the extract should have been done with a HPLC fingerprint highlighting main polyphenol species and an evaluation of amount of total polyphenols should have been performed according a validated method: HPLC to identify individual species and Folin Ciocalteu for global quantification at least.

There is another gap between the title and the supplement description when authors speak about encapsulation; indeed, someone having skills on polyphenol formulation for nutraceutical industry should expect that a process of encapsulation is at a microscopic level (encapsulation of individual polyphenols inside nano or/and microcapsules) to try increase bioavailability of the product, but here this is just only to describe that the product has been put in a capsule; this should not be put in the title, this is not relevant for a supplement; additionally authors should rather speak of supplementation instead of treatment as the latter is generally used for drugs study.

Besides, because the diet generally provides various amounts of polyphenols with fruits, vegetables and beverages, it is unfortunate that authors did not instructed volunteers not to ingest such foods at least 24h before the start of the study and preferentially 72h before the study in order to avoid to introduce a bias in a study on effects of polyphenols.

Many authors which have studied the effect of polyphenols on amylase and glucosidase inhibition but also on lipase inhibition, generally gave the supplement 30-60 min before meal to let enough time for polyphenols to play their inhibiting action during the digestion without interacting with other nutrients within the bolus. This alternative is not proposed in the design neither discussed in the paper; authors should have try to compare both, before and during meal; at least they should have discuss the possibility to compare and explained why not introduced.

Based on the rationale, if the mechanism of inhibition of CHO digestion highlighted by authors would have been involved, at least partially during appetite management, it would have been interesting to monitor postprandial glycaemia during 2h in order to verify that the supposed mechanism of glucosidase and amylase inhibition was or was not involved; comparison of glycaemia area under curve would have given interesting response to this question.

In the last part of the study, authors discuss the possibility of a too low dosage compared to rodent trials and they set an equivalence of 70-100 mg/kg for rodent with 5-7 g for humans. The reviewer recommends to authors the Guidance for Industry and Reviewers Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers and a divided factor (Km) should be applied to respect the weight to surface ratio between rodents and humans edited by US FDA where the km factor is 12.3 for mouse, 7.4 for hamsters, 6.2 for rats…demonstrating that once an animal dose is established, the conversion toward Humans is very easy. It is generally considered a body weight of 60 kg for
both sex; it can be considered less for women only and more for men only. Here for a human 60 kg the 70-100 mk/kg animal dose corresponds to 341-488 mg polyphenols if the animal model was mice and to 677-968 mg if the animal model was rats; the dosage set at 353-1059 mg polyphenols by authors was within the accurate range until the methodology of polyphenol quantification is the “good one”.

The perspective of authors to go furthers with supplementation at different time intervals, including pre-supplementation, demonstrate they have a critical analysis of their work.

All together, these remarks, comments and pending questions cannot allow publication of the paper in its current form. Reviewer recommends that authors take consideration of this report and that they rewrite the manuscript to such an extent that additional data are available, before submitting a new version of the paper.

PS: as general remark, it is recommended to use standard deviation in order to standard error to the mean as the latter can be considered as a "manipulation" of standard deviation. This can be as well confusing when readers need to export data for variance calculation in order to determine a statistical power.

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

As Director of Innovation and R&D of a company involved in development of polyphenol extracts for nutraceutical industries, I declare that it can be considered that there is a possible conflict of interest to review a paper on effects of polyphenols in Nutrition. Nevertheless I declare that my company has no links with the team and the company that wrote the paper neither is a known competitor of this team and this company. I declare that my company is not directly involved on appetite and food intake management, the main topic of this paper, and that my review of the paper is a true and faithful representation of the ethic that can be expected from a honourable researcher.