

Author's response to reviews

Title: Mangosteen juice blend for the reduction of inflammation (C-reactive protein) in obese subjects: a randomized, double-blind, placebo-controlled, dose finding study.

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Version: 3 **Date:** 25 May 2009

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MS: 1675415107248352

Mangosteen juice blend for the reduction of inflammation in obese subjects: a randomized, double-blind, placebo-controlled, dose finding study.

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Dear Editors for the Nutrition Journal,

We thank you for the reviewer's comments on our manuscript. We would now like to resubmit our manuscript that has been revised in accordance to those comments. Below is a compilation of the comments from the reviewers along with our responses.

Thank you for your consideration of our revised manuscript.

Minor Essential Revisions

1) Do non obese patients have elevated CRP levels? Could the study have just looked at effect of Mangosteen on elevated CRP levels? Why control for weight?

Response: There are many causes of elevated CRP levels including injury, cancer and some forms of heart disease. We were specifically interested in looking at increases in CRP associated with increased central adipose tissue.

2) The reason for excluding certain patients is not very clear. Please elucidate.

Response: Exclusion criteria are specified in the Methods section.

3) There is not a mechanism to ensure that the patients took the product.

Response: There was a mechanism (subjects returned all unused investigational product at each visit) and the Results section has been altered to reflect this.

4) Why are most subjects female in the study?

Response: It just happened that females responded to the recruitment ads. They were not specifically selected.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. One-way repeated measures ANOVA is the appropriate between group data analysis to be used. Without performing this analysis, between group t-test comparisons should not be reported, as they are misleading. Despite this being a pilot study, ANOVA should be performed and reported.
2. Significance threshold should be corrected for multiple comparisons.

Response: The use of an ANOVA or ANCOVA would have been much more appropriate if we had a robust enough population to run repeated measures. This was a pilot study and the purpose was to determine whether or not there was enough of an effect to run a subsequent study with a larger population. Thus the decision was to use a simpler statistical analysis in order to better maximize our exploration of the product. Also, with repeated measures you would expect something to vary in addition to the product effect, and with a small number of people it would be difficult for us to have found a reliable covariant. We certainly could have tried any of the possible covariants, but they were likely to be unreliable due to the sample size.

3. Resolve discrepancy between average baseline hsCRP values reported in Table 1 vs. Table 2. The axis on Figure 1 appears to correspond to the values reported in Table 2. These hsCRP values are very high, much higher than those reported in Table 1. Explain & resolve.

Response: Thank you for pointing this out. The data in Table 1 was in error and has been removed. The data in Table 2 and Figure 1 are in agreement.

4. Were statin medication users excluded? If not, how was the proportion of statin users in randomization groups balanced? Statins clearly lower CRP and, if not excluded, confound these results.

Response: The use of statins during the study was not allowed and the manuscript has been altered to reflected this.

5. Manuscript title suggests positive effect and attributes this effects to Mangosteen juice, when neither is supported by the results. See below. Title needs to be more conservatively written and refer to the juice as a “blend” at minimum.

Response: The title has been changed to “Mangosteen juice blend for the reduction of inflammation (C-reactive protein) in obese subjects: a randomized, double-blind, placebo-controlled, dose finding study”.

6. Major issues are apparent in the intervention and placebo descriptions reported in the Methods. “Mangosteen” juice appears to be a juice blend; for scientific reasons the proportion of each juice in the blend needs to be reported. Without direct measurement of constituents from Mangosteen, any effects can only be attributed to the blend.

Response: The information on the juice ingredients is proprietary. The description of the product in the manuscript has been changes to “proprietary Mangosteen juice blend”.

7. The placebo used in this study does not appear to be inert. The only significant results appear to results from comparisons between the placebo and the 18 oz

arm; this is likely a significant result only because CRP in placebo group increased, not due to robust reductions in the 18oz arm. The amount of sucrose in the “placebo” needs to be reported; refined sweeteners are known to elevate CRP in the short term following consumption due to endothelial dysfunction, and obese adults may be particularly vulnerable to this effect. Depending on the amount of sucrose, the “placebo” maybe increasing CRP and the juice may have no effect since there is no evidence of a dose response and the variability in response in the “juice” arm is so great.

Response: The placebo contained 3 g sucrose per 30 mls. The placebo juice was used to make up the volume for the lower test doses. This information has been added to the manuscript.

8. Were diabetics excluded? The methods state “were diabetic and taking diabetic medication”, which is vague and suggests only those taking medications were excluded. Were diabetics not taking medications excluded? If not, how many were included and what was the effect on blood sugar?

Response: Diabetics were excluded and the manuscript has been edited to be clearer in this regard.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Abbreviations like “CBC” and “CMP” need to be written out the first time they are used.

Response: Done

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. List of exclusion criteria is very long and unnecessarily detailed. A simple summary statement like “Subjects were excluded if they smoked, abused drugs or alcohol, had major systemic, inflammatory or chronic disease, or were using medications known to have anti-inflammatory or anti-coagulant activity.” is probably adequate.

Response: the list of exclusion criteria has been shortened.