Author’s response to reviews

Title: Beneficial effects of Korean red ginseng on lymphocyte DNA damage, antioxidant enzyme activity, and LDL oxidation in healthy participants: A randomized, double-blind, placebo-controlled trial

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Author’s response to reviews: see over
COVER LETTER

Nehme Gabriel, Editor-in-Chief
Nutrition Journal

Dear Nehme Gabriel

We are very happy to resubmit our revised version. We sincerely appreciate the time spent in reviewing this manuscript and your advice to improve it. Please, see below our answers to your queries and comments. We also marked the corrected and revised parts of the text in red. We hope that you find them satisfactory. The principle author and all co-authors have read, and approved the submission of the revised version of manuscript; the material is an original research, has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract. And there will not be any potential conflict of interest.

Full title: Beneficial effects of Korean red ginseng on lymphocyte DNA damage, antioxidant enzyme activity, and LDL oxidation in healthy participants

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Thank you very much for your time.

Best regards,

Jong Ho Lee, Ph.D., R.D.
Full professor,
Dept. of Food and Nutrition,
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Response to Reviewers

MS: 6821581306442202

Title: Beneficial effects of Korean red ginseng on lymphocyte DNA damage, antioxidant enzyme activity, and LDL oxidation in healthy participants : A randomized, double-blind, placebo-controlled trial

Dear Reviewer

In accordance with your advices, we made answers.
We hope that they would be appropriated.

Sincerely yours,

Jong Ho Lee, Ph.D., R.D.
Full professor,
Dept. of Food & Nutrition, College of Ecology
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Reviewer 3

Reviewer’s comments

1. While the rationale for comet assay and antioxidant enzymes is sound, it still does not answer the concern with multiple outcome measures and does not provide rationales for them (ie Blood pressure, BMI, cholesterol etc). Secondly, the power analysis should be transparently described in the manuscript, as well as have primary and secondary outcomes clearly outlined.

*Answer:* The authors are sorry for making the reviewer confused due to unclear explanation. As described, the main outcome markers are DNA damage (comet assay) and antioxidant enzymes. Other outcome markers such as blood pressure, BMI, cholesterol etc. were measured to examine if basic biochemical characteristics were not different among the groups (placebo, test groups), because these markers might influence antioxidant status. Therefore, as presented in the text, main outcome markers (at baseline, after the intervention and net changes) among the groups were tested by ANCOVA using a general linear model (GLM) with adjustments for age, sex, BMI, smoking, drinking, systolic BP, diastolic BP, and baseline values (for net change). We also described the power analysis in the subjects section like ‘The study subjects number calculation assumed a two-tailed alpha=0.05 and 1-β=90% to detect a 10% difference with a standard error of 0.28 in the comet assay which is primary outcome and an attrition rate (20%). Biomarkers for testing antioxidant/oxidative effects and the number of subjects were determined by following the criteria recommended by the Korea Food and Drug Administration.’ In addition, we clarified the parameters for example, as primary or secondary outcomes in each of measurement section.

2. While the background now provides citations for clinical and preclinical studies, the effects (i.e. antioxidant, antitumor, antimutagenic, and immunomodulatory) are still not differentiated between preclinical and clinical evidence. It should read: “Although a number of pre-clinical studies have reported medicinal benefits of KRG including antioxidant, antitumor, antimutagenic (10-12) and and a clinical study has reported immunomodulatory actions (13),…”

*Answer:* As you pointed out, we corrected it.
3. Lines 124-134 greatly resemble previously published journal article on Korean red ginseng. Please revise in your own words.

**Answer:** Following your advice, we revised this part like below:

**Test capsule and study design**

Identical-looking capsules contained red ginseng (low dose, 300mg; high dose, 600mg) or placebo (300mg of KRG-flavored capsule containing corn starch). Red ginseng and placebo capsules were provided by the Korea Ginseng Cooperation (KGC, Daejeon, Korea). The red ginseng contained 16.58 mg/g total ginsenosides, and the ratio of protopanaxadiol ginsenosides (Rb1, Rb2, Rc, Rd, and Rg3) to protopanaxatriol ginsenosides (Rg1, Re, and Rf) was 1.65. Analyses of common ginsenosides were performed in quadruplicate using standard HPLC-UV techniques (14) at the Korean Ginseng Research Institute in Daejeon, Korea.

This study design was the randomized double-blind, placebo-controlled intervention trial for 8 week and was approved by the Institutional Review Board of Yonsei University (#RA-2009-650). After written informed consent was obtained, subjects were randomly assigned to placebo (n=23) or KRG (low-dose [n=24] or high-dose [n=22]) groups. All subjects were asked to take 10 capsules in total per day immediately after any main meals. For example, three capsules after breakfast, three capsules after lunch, and four capsules after dinner. Compliance of KRG consumption was assessed at the end of the study by counting capsules remaining and self-recording. If compliance was beneath 75%, the subject dropped out. All participants were encouraged to maintain their usual lifestyle and dietary habits.

4. Lines 311-312: This information is not fully correct, based on up to date sources. I.e. there are reports that >60 ginsenosides have been isolated from Panax quinquefolius.

(Lian-Wen Qi, et al. Ginsenosides from American ginseng: Chemical and pharmacological diversity Phytochemistry. 2011 June; 72(8))

**Answer:** In accordance with your advice, we revised this part.

It has been reported that about 200 substances, such as ginsenosides, polysaccharides, polyacetylenes, peptides, and amino acids etc, have been isolated from Korean ginseng, and more than 100 substances have also been isolated from American ginseng and Notoginseng (1, 2). Among the substances isolated from ginseng, ginsenosides are the primary active
components of ginseng (3). According the recent report, more than 60 ginsenosides have been found in the American ginseng (4). These ginsenosides have been discovered continuously in the Korean ginseng, and it has been assumed that Korean ginseng contains over 60 ginsenosides (2).


Quality of written English: Not suitable for publication unless extensively edited

Answer: As you pointed out, we edited the manuscript by native speaker (Sonia Morgan-Linnell in BioScience Writers #12594)