Author's response to reviews

Title: Effects of Green Tea Catechin and Theanine on Preventing Influenza Infection among Healthcare Workers: A Randomized Controlled Trial

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Author's response to reviews: see over
Miss Iratxe Puebla  
The BioMed Central Editorial Team  
*BMC Complementary and Alternative Medicine*  

MS: 2014234646465336  

Dear Miss Iratxe Puebla  
The BioMed Central Editorial Team:  

Thank you very much for your e-mail of November 26th concerning our manuscript (MS # 2014234646465336 - Effects of Green Tea Catechins and Theanine on Preventing Influenza Infection among Healthcare Workers: A Randomized Controlled Trial) consideration as a "Research Article" to the *BMC Complementary and Alternative Medicine*. We are happy that the manuscript might be acceptable with some revisions and we are grateful to you and the referees who have made valuable comments.  

With regard to your comments, we would like to respond as the following comments, highlighting with yellow markers in the revised manuscript.  

We have done our best to take advantage of all of the valuable comments of the referees, for whose guidance we are most grateful. We hope that we have succeeded in offering you an acceptable paper.  

Very truly yours,  

Hiroshi Yamada, MD, PhD, FACP  

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Response to the Editorial Requests:

With regard to your comments, we would like to make the corrections as follows, highlighting with yellow markers in the revised manuscript. The manuscript has been also corrected by the native English.

1. We ensure that the reporting of the trial in the revised manuscript adheres to the CONSORT guidelines and have uploaded the file of the checklist.

2. We have added the suggested change in the Competing interests section between the Conclusions and Authors contributions as follows:

   This work was supported by a grant from the Japanese Ministry of Health, Labor, and Welfare, and a grant from ITO EN Ltd. ITO EN Ltd played a role in providing the experimental supplements.

3. We have added the suggested change in the Authors' contributions section after the Competing interest as follows:

   KM had complete access to all the data in the study, and he is responsible for the integrity of the data and the accuracy of the data analysis. HY designed the study protocol and participated in its coordination. NT participated in the study coordination. HN and YMS participated in the design of the study and provided the experimental supplements. All authors read and approved the final manuscript.

4. To describe the statistical aspects of the analyses in as much detail as possible, we have added the results of univariate analyses in the Results section as follows:

   In the univariate comparison between the incidence of clinically defined influenza infections and baseline characteristics, age was the only significant variable ($P = 0.027$). Significant associations were not found among other variables such as sex, vaccination, preventive measures for maintaining hygiene (i.e., hand washing, facemask application, and gargling), smoking, and alcohol and tea consumption.

5. We have formatted the manuscript and ensure that the revised manuscript conforms to the journal style.
Response to the reviewer 1:

With regard to your comments, we would like to make the corrections as follows, highlighting with yellow markers in the revised manuscript:

- We have also done the subgroup analysis (e.g. male/female; vaccination; smoking; alcohol consumption), but there were no significant differences found except for age. Therefore we have added the suggested change and explanation in the Results section as follows:

  In the univariate comparison between the incidence of clinically defined influenza infections and baseline characteristics, age was the only significant variable ($P = 0.027$). Significant associations were not found among other variables such as sex, vaccination, preventive measures for maintaining hygiene (i.e., hand washing, facemask application, and gargling), smoking, and alcohol and tea consumption.

- We did not keep track of the incidence common cold episodes, therefore did not mention them in the manuscript.

- Statistically Review:
  To describe the statistical aspects of the analyses in as much detail as possible, we have added the results of univariate analyses in the Results section as the above reply highlighted with yellow markers.
Response to the reviewer 2:

With regard to your comments, we would like to make the corrections as follows, highlighting with yellow markers in the revised manuscript.

1. As your suggestion, tea intake is an important factor of contamination in randomized controlled trial, but less than 250 mL tea intake is fuzzy. Therefore, we have added the suggested change and clearly identified it in the Study Design of Method section as follows:

   Their tea consumption habits before intervention were also determined, and any tea beverage such as black, green, oolong or herbal tea intake was restricted to less than 250 mL per day over the entire course of the study.

2. As your suggestion, it would be better to exclude the participants with vaccination for influenza virus. However, it would be impossible in the study period at the 2009/H1N1 pandemic season, because almost all healthcare workers in Japan were recommended to be vaccinated. Therefore we studied in that situation, as discussed in the third paragraph of the Discussion section.

3. We have added the suggested change in the Outcomes section as follows, and explained the definition of clinically defined influenza infection in details and also added the paper in the Reference section.

   The doctor diagnosed clinically defined influenza on the basis of fever (temperature, ≥37.8°C) and any 2 of the following clinical symptoms: cough, sore throat, headache, or myalgia.12

4. We have added the suggested change in the Abstract and Outcomes section as follows, and attempted to explain clearly the definition of the time free influenza infection. We consider the outcome measure is reasonable on the aspect of indicating the effect on prophylaxis of influenza infection.

   The secondary outcomes were (1) the incidence of laboratory-confirmed influenza infection with viral antigen measured by immunochromatographic assay (RapidTesta FLUII, Sekisui Medical Co, Ltd, Tokyo, Japan) and (2) the time for which the patient was free from clinically defined influenza infection, i.e., the period between the start of the intervention and the first diagnosis of influenza infection.

5. The sensitivity of the antigen test used in our manuscript depends on the sampling timing and examiner’s skill. In Japan, the test has relatively high sensitivity compared to other countries, probably because the test is performed by a trained doctor with the appropriated timing. We have added the Japanese paper confirming it in the Reference section. Also at the 2009/H1N1 pandemic season in Japan, it was really in a difficult situation to test the specimen examined by the local centre for disease control, and the antigen test was recommended as a best test in public.

6. We calculated the sample size according to our previous study. We have added the suggested change in the Statistical Analyses section as follows,

   In consideration of our previous study in the aged-group participants,
we estimated that the primary outcome would occur in 1% of participants in the catechin/theanine group and 11% of those in the placebo group.¹⁰

7. We have added the suggested change in the Results section as follows, and provided the conditional status which is important for influenza infection.

In the univariate comparison between the incidence of clinically defined influenza infections and baseline characteristics, age was the only significant variable (P = 0.027). Significant associations were not found among other variables such as sex, vaccination, preventive measures for maintaining hygiene (i.e., hand washing, facemask application, and gargling), smoking, and alcohol and tea consumption.

8. We have added the explanation of OR and HR in the Abbreviations section. Also we have asked a statistician and identify them suitable.

9. We have added the suggested change and added the paragraph to infer mechanism in the Discussion section as follows:

Experimental studies have shown some mechanisms of the action of green tea catechins and theanine on the prevention of influenza infection. These studies have shown that green tea catechins bind to the hemagglutinin molecule of influenza virus, thereby inhibiting the virus adsorption to the host cells and blocking virus assembly or maturation cleavage.¹⁴⁻¹⁶ Theanine enhances the systemic immunity (γδ T-cell function) for influenza infection.¹¹ Our results seem to provide clinical evidence to confirm these biological activities.

10. We have provided the detailed list of update CONSORT 2010 checklist for this RCT with attached file.

Quality of written English:
The manuscript has been corrected by the native English.

Statistically Review:
To describe the statistical aspects of the analyses in as much detail as possible, we have added the results of univariate analyses in the Results section as above No. 7’s reply highlighted with yellow markers.