Title: Immunomodulatory Effects of a Mycelium Extract of Cordyceps (Paecilomyces hepiali; CBG-CS-2): A Randomized and Double-Blind Clinical Trial

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Author’s response to reviews:

Reviewer reports:

1. Meysam Shirzad, M.D., Ph.D. (Reviewer 1): The subject is novel and the study is well designed. However, there are some mistakes should be corrected as following:

1) Exclusion criteria are the ones excluded during the study not to confound the results. Most of exclusion criteria mentioned in the article are in fact inclusion criteria because of which the case has not been included in the study; e.g. BMI less than 18.5 kg/m2 at the time of the screening test.

=>Response:

In our study, participants with BMI<18.5 kg/m2 were excluded as being underweight. The reason is that the underweight rate of Korean adults (2016) was investigated by 4.0±0.3(%) for adults over 19 years old and 4.2±0.4(%) for adults 19~64 years old in which about 4 % were underweight (1). They reported that underweight is highly correlated to physical health, especially in the elderly, the underweight increased mortality (2). This is because the criteria for selecting participants in our study were for males and females those aged 20 to 75 years. Also, the underweight was considered to be vulnerable to infection because of a lack of essential nutrients and nutritional deficiencies, either due to a weakened constitution or immune system.
For those over 65 years of age, the underweight (18.5 ≤ BMI < 25.0) or below the normal weight (18.5 ≤ BMI) was poorly recognised for their perceived health condition (2). In addition, based on the report that in those who are over 60 years of age and with the lowest weight, they showed the highest rate of experiencing severe depression (3,4), the underweight equivalent to BMI<18.5 was excluded.

# References list;


2). It is mentioned in page 4: "Participants who had a "gastroesophageal reflux disease", such as Crohn's disease, affecting the absorption of the test product...". It should be changed to gastrointestinal disease or any other relevant phrase.

=>Response:

As you suggested, we made following changes.

It was changed to "Those who have gastrointestinal diseases or histories of gastrointestinal surgery that may affect the absorption of products for the human body test."
3). In Table 3, where does "* p<0.058" in the bottom of the table refer to?

=>Response: It was corrected and presented from p<0.058 to p<0.05.

2. Marzieh Qaraaty, Assistant Professor (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Please specify the inclusion criteria.

1) Why BMI less than 18.5 kg/m2 is the is one of the exclusion criteria were?

=>Response:

In our study, participants with BMI<18.5 kg/m2 were excluded as being underweight. The reason is that the underweight rate of Korean adults (2016) was investigated by 4.0±0.3(%) for adults over 19 years old and 4.2±0.4(%) for adults 19~64 years old in which about 4 % were underweight (1). They reported that underweight is highly correlated to physical health, especially in the elderly, the underweight increased mortality (2). This is because the criteria for selecting participants in our study were for males and females those aged 20 to 75 years. Also, the underweight was considered to be vulnerable to infection because of a lack of essential nutrients and nutritional deficiencies, either due to a weakened constitution or immune system. For those over 65 years of age, the underweight (18.5 ≤ BMI < 25.0) or below the normal weight (18.5 ≤ BMI) was poorly recognised for their perceived health condition (2). In addition, based on the report that in those who are over 60 years of age and with the lowest weight, they showed the highest rate of experiencing severe depression (3,4), the underweight equivalent to BMI<18.5 was excluded.

# References list ;


2). What's the meaning of ae in Availability of data materials?

=>Response : As a result of this review, the information was deleted as it was entered incorrectly.

3). Please check the format of References.

=>Response : Revised as suggested.

4). In Figure 1 & placebo group, you wrote "excluded from primary analysis: 40". is it true?

=>Response:

The participants selected in our study participated in this human body test through random assignment and a double blind method. A total of 80 study subjects completed all procedures specified in our protocol. It was demonstrated that in our protocol, we will analyze the main unit of the evaluation of the primary validation using the Per Protocol Set. For this reason, we conducted a total of 79 analyses (Cordyceps Mycelium extract group, n=39; Placebo group, n=40) except for one person (Cordyceps Mycelium extract group) who was not compliant with (<70%) of taking the test products.

Actual number of products taken

Product Compliance (%) = -------------------------------- X 100

Number of products to be taken
3. Mojtaba Heydari (Reviewer 3):

Please overwrite this text when adding your comments to the authors.

1). Was the registration of trial done after termination of the study? Why? Mention in limitations if so.

=>Response:

We did not mention it to the limitation because we implemented an end report to IRB Committee after the end of the clinical trial.

2). Was any important change to methods after trial commencement (such as eligibility criteria)? If not please state in the methods.

=>Response:

There were no significant changes to the eligibility criteria during our human body tests.

However, there were some changes to the plan from the first approved one to the peripheral blood phagocytes item, which is an indicator of effectiveness. Although the change was a second endpoint, peripheral blood phagocytes, within the original plan, the evaluation item of the peripheral blood phagocytes was excluded because the analysis could not be performed due to a supply disruption of the PHAGOTEST test kit.

3). Was there any specific instruction on the time of taking the capsules (for example before or after meal).

=>Response:

We provided oral doses to the Cordyceps Mycelium extract group twice a day, two capsules a dose, and after breakfast and dinner (1.68 g/day, 1.43 g/day by the Cordyceps Mycelium extract). In the same way, the placebo group was also taken twice a day, two capsules a dose, and after breakfast and dinner (1.68 g/day).

4). "Peripheral blood phagocytes" is considered as an outcome in the methods but no information is provided about the results.

=>Response:
As explained earlier in Item 2, it failed to present the second endpoint evaluation indicator, the item of peripheral blood phagocytes. The reason was that we were unable to present the results as we could not obtain the data because of a supply disruption of the PHAGOTEST test kit even though the peripheral blood phagocytes were the second endpoint in the original plan.

5). How the random allocation list is generated?

=>Response:

Our study was performed by assigning test and control groups randomly as a parallel test method. The required number of the subjects for the human body test was 80, 40 for each group, considering the elimination rate (20%). For all participants who satisfy the selection and exclusion criteria in the first visit (Baseline Visit, Week 0), the human body test institution assigned subjects to each group according to the allocation code of the block randomization method.

The block randomization table was obtained on the creation of a permutation of the random numbers (random numbers of A and B) generated by the Randomization program of the SAS® system before the human body test in which the permutation was applied to the subjects from the number 1 successively. The client attached the label to the food for the human body test according to the block randomization table in the packaging of the food used to the human body test and then supplied it to the human body test institution before starting the human body test.

During the human body test, the random allocation code shall be kept by the client in principle for maintaining a double blind state. Also, all subjects in the study did not unlock the double blind state until they completed the human body test and the data was locked.