Author's response to reviews

Title: Beneficial immunostimulatory effect of short-term Chlorella supplementation: enhancement of Natural Killer cell activity and early inflammatory response

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Version: 2 Date: 8 July 2012

Author's response to reviews: see over
Dear Editor-in-Chief,

We are happy to submit the revise version of manuscript (Manuscript ID 1052292330731789) to *Nutrition Journal*. We sincerely appreciate the time spent in reviewing this manuscript and editors’ and reviewers’ advices to improve it. Please, see the attached files (revised manuscript, point-by point answers to reviewers’ queries and comments). We marked the correction 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 manuscript 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.

**Beneficial immunostimulatory effect of short-term Chlorella supplementation: enhancement of Natural Killer cell activity and early inflammatory response (Randomized, double-blinded, placebo-controlled trial)**

* Tables: 2 & Figures: 3

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Thank you very much for your time.

Sincerely yours,

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Answers for Reviewers’ comments

Manuscript ID 1052292330731789
Title: Beneficial immunostimulatory effect of short-term Chlorella supplementation: enhancement of Natural Killer cell activity and early inflammatory response

Dear Reviewer Ju Yeon Park

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.

<General comments>

In this paper, Kwak et al reported the beneficial immunostimulatory effect of Chlorella supplementation in humans. The concept and the objective of this study are interesting and meaningful in aspect of being performed in non-disease, healthy people. It is well written. Study design (randomized, double-blinded, placebo-controlled trial) is good, the methods are adequate, and data presentations are elegant, but there are some minor points to be corrected.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

Minor points:
- The reviewer recommends the authors to add brief explanation the reason why 7 in the placebo group and 2 in test group were dropped-out. Answer) Following the reviewer’s comment, we briefly explained in the text the reason why 7 in the placebo group and 2 in test group were dropped-out.
  “ …. Among the 9 drop-outs, 7 were in the placebo group (2 for personal problems, 5 for no good-compliance on tablets consumption) and 2 (for personal problem) were in Chlorella supplement group.”

- The reviewer recommends the authors to clarify some sentences explaining ‘net change (s)’. For example, ‘The net changes of these cytokines before and after the intervention were significantly higher in the Chlorella group than the placebo group.’ should be revised to ‘The increments of these cytokines in the Chlorella group after the intervention were significantly bigger than those in the placebo group’.
  Answer) As you advised, we revised those sentences to clarify the meaning of it.
Answers for Reviewers’ comments

Manuscript ID 1052292330731789
Title: Beneficial immunostimulatory effect of short-term Chlorella supplementation: enhancement of Natural Killer cell activity and early inflammatory response

Dear Reviewer Yonshiji Yamada

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.

<General comments>
Kwak et al. examined the effect of Chlorella on the NK cell activity and serum concentrations of interferon-gamma, interleukin-1beta, and interleukin-12 in 51 Korean healthy individuals. The authors observed that serum concentrations of interferon-gamma, interleukin-1beta, and interleukin-12 as well as the NK cell activity were increased in individuals having Chlorella compared to those having placebo after eight weeks. The authors concluded that short-term Chlorella supplementation enhanced the NK cell activity and the production of interferon-gamma, interleukin-1beta, and interleukin-12 in healthy individuals. Although the manuscript has interest observations, the reviewer has a few comments on the manuscript.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

1. In Figure 1, serum concentrations of interferon-gamma and interleukin-12 were significantly decreased in the placebo group after eight weeks, and these components seemed to be substantial portions in the significant changes of these parameters shown in upper parts of the graphs. It is not clear why serum concentrations of interferon-gamma and interleukin-12 were significantly decreased in the placebo group. As commented, the authors had tried to search the factors which might affect the decrease of these parameters in the placebo group, but it is not easy to address in a word why these phenomenon occurred. First, we thought the possibility of lactose, the contents in the placebo affecting cytokine levels, but it seemed not influence the cytokine levels. Second, there were no significant difference in the baseline value between the two groups, and the net change values were generally much greater in the Chlorella group than those in the placebo group, even though the direction for increment or decrement were not the same between the two groups. However, the correlation pattern among NK cell activity and cytokines were consistently in the positive direction, which may indicate that the measurements and the results are reliable. However, to make it sure, we thought that we may need further study with increased number of study subjects and for longer period in the future. We briefly mentioned it as a study limitation in the discussion section.
2. In Figure 2, the NK cell activity was also decreased in the placebo group, although it was not significant. It was not clear why.

Answer) As you commented, NK cell activities were significantly increased in the Chlorella group, and the activity seemed slightly decreased in the placebo group, but it is not statistically significant. However, the increments were much greater in the Chlorella group than the Placebo group. Furthermore, the correlation pattern among NK cell activity and cytokines were consistently in the positive direction. In addition, there were no significant difference in the baseline value between the Chlorella group and Placebo group. Therefore, the authors thought the results for NK cell activities would be ok. To clarify the result, we shortly added some explanation on it in the text.

3. Given that the authors described P < 0.05 was considered statistically significant, P < 0.1 was not required to show.
Answer) Following your advice, we deleted the mark for p-value <0.1.