

The effects of twenty-four nutrients and phytonutrients on immune system function and inflammation: A narrative review

Jillian Poles, Elisa Karhu, Megan McGill, H. Reginald McDaniel, John E. Lewis

Corresponding author

John E. Lewis

*University of Miami Miller School of Medicine, Department of Psychiatry & Behavioral
Sciences, 1120 NW 14th Street, Suite #1482A (D28), Miami, FL 33136*

Handling editor:

Michal Heger

Department of Pharmaceutics, Utrecht University, the Netherlands

Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

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Ref.: Ms. No. JCTRes-D-21-00004

The Effects of Nutrients, Phytonutrients, and Dietary Compounds on Immune System
Function and Inflammation: A Narrative Review
Journal of Clinical and Translational Research

Dear Dr. Lewis,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Apr 10, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author.

You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: - The title and abstract are extremely generic. Referring to "nutrients, phytonutrients and dietary compounds", when the review included 24 specific compounds may mislead the reader. Were the authors at the time of designing the literature review planning to include ALL compounds in the review and as part of the results only found 24 of more relevance? As a suggestion, the title and abstract should indicate that a specific number of compounds were reviewed.

- Methods section does not describe the reason to disregard 1507 publications out of the 1684 initially found. Were the articles limited to US publications?

- Authors did a good job providing information on the database accessed, inclusion and exclusion criteria, and time limit. However, to comprehensively cover scientific information and to overcome limitations of separate online libraries, it is recommended to search at least 2-3 credible databases. Was the Cochrane Library reviewed to verify clinical trials included on the review matched their data?

- Table 1 clearly synthesis the review. It could be improved if the sample size of the studies reviewed is included. Was the sample size a reason to disregard a significant number of publications? Were the studies include to the review selected for having clearly defined sample sizes?

- There is a good description on limitations of the studies included in the review, but authors did not mention limitations inherent to their review and their impact on the validity of the main messages.

The article is based in a clearly important research question and scientific need. However, the length of the paper, dissimilarity of the compounds, and inclusion of different diseases, makes the paper challenging to read and follow. It is suggested to explore the idea of splitting the review by diseases category.

Reviewer #2: A huge and comprehensive document - how did you ever choose which supplements to include? The authors need to discuss inflammation a little differently - inflammation is important part of immunity - immunity wouldn't function without inflammation. Not all inflammation is bad. Acute inflammation is necessary and important. In a healthy subject - you wouldn't expect anything to happened to inflammatory markers because inflammation doesn't exist and there is nothing to reduce. If chronic disease, then inflammation is likely chronic and contributes to the progression of the disease. Chronic

inflammation is not good while acute inflammation is very important.

Reviewer #4: This is a very thorough and relatively extensive narrative of the subject matter.

Authors' response

UNIVERSITY
OF MIAMI



Department of Psychiatry & Behavioral Sciences
Clinical Research Building
1120 NW 14th Street, Suite 1482A (D28)
Miami, FL 33136

Office: 305-243-6227
Cell: 305-962-5286
Fax: 305-243-1619
E-mail: jelewis@miami.edu

April 10, 2021

Michal Heger, Ph.D.
Editor-in-Chief
Journal of Clinical and Translational Research

Dear Dr. Heger:

We thank the Reviewers for their thorough evaluation of our manuscript. As per the requests of the Reviewers, we have endeavored to modify our paper to improve its quality and suitability for publication. We have addressed the following Reviewers' comments:

Reviewer #1

The title and abstract are extremely generic. Referring to "nutrients, phytonutrients and dietary compounds", when the review included 24 specific compounds may mislead the reader. Were the authors at the time of designing the literature review planning to include ALL compounds in the review and as part of the results only found 24 of more relevance? As a suggestion, the title and abstract should indicate that a specific number of compounds were reviewed.

The Title and Abstract now specifically state that 24 nutrients and phytonutrients were reviewed from 87 articles on clinical trials. The term "dietary compounds" was eliminated in the title and throughout all the rest of the manuscript to be clearer. We were not planning to include the entire universe of dietary compounds in this review. We included these 24 nutrients and phytonutrients based on much of our previous work. We had studied some of these in our lab, and we were familiar with others that had showed interesting effects on immune function and inflammation. We also subdivided the nutrients by those classified as primarily antioxidant versus those that are not. While this is not necessarily an important distinction, we carefully reviewed every nutrient and phytonutrient included in this reviewed to determine the most meaningful strata. Thus, we also moved around many sections of the paper to include them in the following order: antioxidant nutrients, not primarily antioxidant nutrients, and phytonutrients and alphabetized within each group for convenience.

Methods section does not describe the reason to disregard 1507 publications out of the 1684 initially found. Were the articles limited to US publications?

We have updated the Methods section to list all exclusion criteria. Articles were limited to those written in English, not necessarily in “US publications.”

Authors did a good job providing information on the database accessed, inclusion and exclusion criteria, and time limit. However, to comprehensively cover scientific information and to overcome limitations of separate online libraries, it is recommended to search at least 2-3 credible databases. Was the Cochrane Library reviewed to verify clinical trials included on the review matched their data?

We chose to limit ourselves to PubMed because this is the gold standard repository for peer-reviewed scientific journals, and our search was already very thorough and comprehensive based on the number of articles our searches uncovered. Thus, we did not need to search other databases, given the scope of PubMed as it covers thousands of journals. We did not search the Cochrane Library specifically.

Table 1 clearly synthesis the review. It could be improved if the sample size of the studies reviewed is included. Was the sample size a reason to disregard a significant number of publications? Were the studies include to the review selected for having clearly defined sample sizes?

We have added sample size for each article, and it is displayed in Table 1 as suggested. We did not exclude an article based on the sample size of its study. All studies had a clearly defined sample size.

There is a good description on limitations of the studies included in the review, but authors did not mention limitations inherent to their review and their impact on the validity of the main messages.

We have expanded the limitations in the Discussion to include those inherent to a narrative review.

The article is based in a clearly important research question and scientific need. However, the length of the paper, dissimilarity of the compounds, and inclusion of different diseases, makes the paper challenging to read and follow. It is suggested to explore the idea of splitting the review by diseases category.

While we realize that the paper may be difficult to completely digest because of the reasons stated, we also wanted to provide the reader with a current compilation of the findings on these nutrients and phytonutrients in one paper. No paper of this type has been previously written to our knowledge, and we wanted to provide a global picture of how these nutrients and phytonutrients affect immune function and inflammation. We did not split the paper by disease because it would significantly reduce the usefulness of the paper. Our topic of interest is what the nutrient or phytonutrient does to immune function or inflammation regardless of the population under study. We did remove the articles that were based only on healthy subjects to have the paper more focused on diseases and disorders.

Reviewer #2

A huge and comprehensive document - how did you ever choose which supplements to include?

We included these 24 nutrients and phytonutrients based on much of our previous work. We had studied some of these in our lab, and we were familiar with others that had showed interesting effects on immune function and inflammation.

The authors need to discuss inflammation a little differently - inflammation is important part of immunity - immunity wouldn't function without inflammation. Not all inflammation is bad. Acute inflammation is necessary and important. In a healthy subject - you wouldn't expect anything to happen to inflammatory markers because inflammation doesn't exist and there is nothing to reduce. If chronic disease, then inflammation is likely chronic and contributes to the progression of the disease. Chronic inflammation is not good while acute inflammation is very important.

We agree that inflammation can be very different depending on the circumstances (necessary versus detrimental), and we provided minor adjustments to the Introduction to reflect that. We also eliminated all the articles from this review on healthy subjects only, so that the effects on immune function and inflammatory markers would be discussed in the context of a disease or disorder.

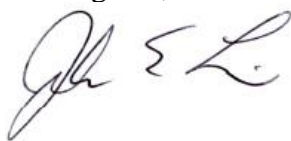
Reviewer #4

This is a very thorough and relatively extensive narrative of the subject matter.

Thank you for the compliment! This paper has been a lot of work!

Please let us know if you have any additional questions or clarifications, and we look forward to the next review of our paper.

Best regards,



John E. Lewis, Ph.D.
Associate Professor

2nd Editorial decision
11-Apr-2021

Ref.: Ms. No. JCTRes-D-21-00004R1
The Effects of Twenty-Four Nutrients and Phytonutrients on Immune System Function and Inflammation: A Narrative Review
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are

appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by May 11, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for submitting your revised draft to JCTR.

The manuscript has passed through peer review. However, before the journal can publish your paper, we kindly ask you to peruse over the paper one more time and eliminate residual grammatical/spelling/syntax errors.

For example (manuscript page/line), please consider this non-exhaustive list of items to address:

- 2/41 (and throughout document): please note that beta glucans are are class of substances, and not a single molecule. It should therefore appear as plural unless you are referring to a specific beta glucan (e.g., lentinan in the shiitake mushroom section). Moreover, the active principles in shiitake mushrooms are beta glucans, so why are these mentioned distinctly?
- 2/53: NF-kB, TNF-a, etc. are not effects but mediators of the effects you are alluding to.
- 2/55: CD4+ should read CD4+ T cells.
- 4/46-48: "the incidence of colds, viruses, and bacteria..." should read "...the incidence of colds, viral infections, and bacterial infections..."
- 4/53: "This review will summarize..." should read "This review summarizes..."
- throughout document: please eliminate 2 spaces after a period

We are counting on your team to address the rest of errors/omissions.

Thank you and kindest regards,

Michal Heger
Editor

Authors' response

UNIVERSITY
OF MIAMI



Department of Psychiatry & Behavioral Sciences
Clinical Research Building
1120 NW 14th Street, Suite 1482A (D28)
Miami, FL 33136

Office: 305-243-6227
Cell: 305-962-5286
Fax: 305-243-1619
E-mail: jelewis@miami.edu

April 24, 2021

Michal Heger, Ph.D.
Editor-in-Chief
Journal of Clinical and Translational Research

Dear Dr. Heger:

We thank you for the evaluation of our manuscript and your conditional acceptance. As per your requests, we have endeavored to modify our paper to improve its quality and suitability for publication. We have addressed your comments, among others:

- 2/41 (and throughout document): *please note that beta glucans are are class of substances, and not a single molecule. It should therefore appear as plural unless you are referring to a specific beta glucan (e.g., lentinan in the shiitake mushroom section). Moreover, the active principles in shiitake mushrooms are beta glucans, so why are these mentioned distinctly?*

We have made beta-glucans plural throughout the manuscript. We kept shiitake mushrooms separate because it has two distinct compounds, lentinan and AHCC, that come from shiitake mushrooms, whereas other beta-glucans come from different sources.

- 2/53: *NF-kB, TNF-a, etc. are not effects but mediators of the effects you are alluding to.*

We changed the structure of the sentence you questioned and ensured that no similar statements were repeated throughout the manuscript.

- 2/55: *CD4+ should read CD4+ T cells.*

We noted "T cells" in this instance and throughout the rest of the manuscript for the appropriate CD molecules.

- 4/46-48: *"the incidence of colds, viruses, and bacteria..." should read "...the incidence of colds, viral infections, and bacterial infections..."*

This was changed as noted.

- 4/53: *"This review will summarize..." should read "This review summarizes..."*

This was changed as noted.

- *throughout document: please eliminate 2 spaces after a period*

We changed the spacing after each sentence throughout the document.

Please let us know if you have any additional questions or clarifications, and we look forward to the acceptance of our paper.

Best regards,



John E. Lewis, Ph.D.
Associate Professor

3rd Editorial decision
27-Apr-2021

Ref.: Ms. No. JCTRes-D-21-00004R2
The Effects of Twenty-Four Nutrients and Phytonutrients on Immune System Function and Inflammation: A Narrative Review
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: