

The effects of twenty-one nutrients and phytonutrients on cognitive function: A narrative review

John E. Lewis*, Jillian Poles, Delaney P. Shaw, Elisa Karhu, Sher Ali Khan, Annabel E. Lyons, Susana Barreiro Sacco, H. Reginald McDaniel

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Handling editor:

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1st Editorial decision
15-Apr-2021

Ref.: Ms. No. JCTRes-D-21-00015

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

Dear Dr. Lewis,

Reviewers have now commented on your paper. One reviewer has recommended a major revision and another reviewer has recommended a reject verdict. We would like to give you a chance to improve your manuscript in line with their suggestions.

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.

Please accept our apologies for the tardy decision. We were in fact waiting on a third reviewer who had the best intentions, but who was held back due to circumstances and could in the end not provide a timely review. Because of the recommendation from the other two reviewers, we wanted to wait on the third reviewer who would act as an independent arbiter, allowing the editorial board to recuse itself from the decision. On the other hand, we could not wait longer to stay fair to the authors.

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 May 15, 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: Manuscript Number: JCTRes-D-21-00015
The Effects of Nutrients, Phytonutrients, and Dietary Compounds on Cognitive Function: A Narrative Review.

The topic is certainly important and interesting; however, I still have major reservations about the manuscript.

Here some general points, which authors need to consider:

- As with all reviews the authors need to provide a critical assessment of the phytochemical, pharmacological and clinical data.
- Make sure that you do not simply provide a long list of (certainly interesting) facts (many copy paste duplicates from abstracts can be identified throughout the text) but provide a critical analysis.
- Please remember that the conclusion needs to be precise and needs to highlight the achievements and scientific gaps in our knowledge.
- If pharmacological studies are reviewed, we expect some information on the dose range tested, the minimal active concentration, the model used (including information whether it is an in vitro or in vivo study), if and what controls (including positive and negative) were used, duration, type of extract used as well as other basic pharmacological data. Maybe you could have one more table with this information and then to shorten the text accordingly by making appropriate reference to the table.
- The available toxicological information on the species needs to be reviewed, too.
- Plant species need to be validated taxonomically (e.g. www.theplantlist.org) and the full name including authorities and family needs to be included.

Below are some other comments.

Title: Dietary compound is not a functional term, which should be replaced for FDA approved term dietary supplement - a product taken orally that contains one or more ingredients (such as vitamins or amino acids) that are intended to supplement one's diet and are not considered food. Dietary supplements include:

* nutrients - substances that promotes growth, provides energy, and maintains life

* phytonutrients - plant-derived compound (such as resveratrol) associated with positive health effects

As a matter of fact, all substances under review are plant-derived natural compounds except Vitamin D. There is no sense for such differentiation of dietary supplements in the title

Abstract

In introduction the authors critically characterize "The current FDA-approved pharmacotherapeutics for dementia, which neither cure nor halt cognitive decline they just delay the worsening cognitive impairment".

This introduction suggests that dietary supplements might be different of FDA-approved pharmacotherapeutics in terms of halting cognitive decline and possibly cure dementia.

However, no aim task to reveal, confirm or deny that hypothesis was specified in the review.

Hypothesis was not defined and aim to summarize "the effects of nutrients, phytonutrients, and dietary compounds on cognitive function" does not suggest any scientific novelty of this narrative review.

Therefore, it is not surprising that nothing new was concluded compared to original publications. Words like dietary compounds may be promising says nothing. The section Relevance for Patients should be merged with conclusions.

This review is not systematized by:

- * the type of disease
- * key molecular mechanisms or modes of action
- * key type of active compounds

in order to find or disclose common features and make conclusions.

Instead, we see standard phrases like:

* "Phytonutrients, and dietary compounds showing promise in improving cognitive function certainly warrant continued study."

* "As additional research is necessary to make robust recommendations for any nutrient, phytonutrient, or dietary compound, some of those that were reviewed may offer an avenue for improving cognitive function in illnesses currently lacking effective conventional treatment

* Due to these limitations, additional larger studies are needed to investigate the safety and efficacy of dietary compounds in treating and preventing various neurocognitive disorders, while determining if any drug-supplement interactions occur in those taking medications, particularly those with serious side effects.

* As additional research is necessary to make robust recommendations for any nutrient, phytonutrient, or dietary compound, some of those that were reviewed may offer an avenue for improving cognitive function in illnesses currently lacking effective conventional treatment.

* In summary, this narrative review highlights the current evidence of specific nutrients, phytonutrients, and dietary compounds that may improve aspects of cognitive function, with potential benefit in the prevention and adjunct treatment of cognitive dysfunction.

Well self-characterised - just highlights of known observations, nothing else.

I would also argue with the statements like:

- * The heterogeneity of study design and methodological quality also pose a limitation to generalizing the results. - The authors can use Cochrane risk of bias graphs and Jadad's Quality scales for inclusion of studies in the review and draw rigid, justified conclusions.
- * While many of the studies were randomized, double-blind, placebo controlled trials, others were limited by small samples and lack of blinding or placebo or control group. - The authors can exclude open label studies, which small sample size have no impact on the results when the deference between pancebo and verum is significant.
- * Treatment amount and type and follow-up time across studies also ranged significantly, making it difficult to predict any long-term risks for certain nutrients and perhaps preventing the detection of benefits that may only manifest with chronic ingestion of a compound. Predict long-term risks is not possible without pharmacovigilance Phase IV studies for many years. However, the safety of many herbal medicines used in traditional medicinal systems for more that 30 years was formally accepted by European Medical Agency.

Several concluding statements are not based on actual content of the review:

- * treatment regimens should be individualized as much as possible with ongoing evaluation of benefits and risks for adjustment.
- * Dietary supplements may interact with some prescription and over-the-counter medications through direct interaction or modulation of key enzymes implicated in drug metabolism.
- * Plant compounds also display immensely complex multiphysiological activity and often act synergistically, making the function of isolated extracts less predictable.
- * Thus, careful review of current medication and dietary supplement intake should precede the addition of new compounds, especially among the elderly who are more vulnerable to adverse interactions through polypharmacy and changes in drug metabolism.

Methods: Inclusion and exclusion criteria were not validated for accuracy. As a result, 19 dietary supplements (herbal extracts and individual compounds which author call "categories") were selected for reviewing. As a result, at least three plant extracts, namely, *Rhodiola rosea*, *Withania somnifera* and *Andrographis paniculata*, which are effectively improve cognitive functions and mental health in clinical studies are out of scope of this review.

Regretfully, I would not recommend this article for publication in present form, major revision is required, where the authors will adequately address reviewers' comments and suggestions.

Reviewer #2: This paper provides a narrative review of the effects of nutrients, phytonutrients, and dietary compounds on cognitive function. This is a huge area and while the authors cover many topics there are several important areas missing, such as the effects of caffeine. The review only uses one search engine which may miss articles, especially the "grey literature". The main problem is that this is not really a review but a list of studies. One would expect more detailed critical evaluation of the research. This should take the form of consideration of whether reported results could be chance effects, or whether the absence of effects could be due to design features such as sample size. The focus on statistical significance may also be problematic as one needs to know whether the effect sizes are going

to lead to clinically significant improvements.
My suggestion would be to focus on specific topics and provide a systematic review or meta-analysis rather than a list of studies.

Authors' response

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June 17, 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 topic is certainly important and interesting; however, I still have major reservations about the manuscript.

Here some general points, which authors need to consider:

- As with all reviews the authors need to provide a critical assessment of the phytochemical, pharmacological and clinical data.

While we understand the need to be critical of others' work when it is appropriate, this was not the purpose of our narrative review. We chose to write a narrative review because the literature needs to have an article of recent research that summarizes the findings about certain nutrients and phytonutrients on cognitive function. We limited our review to only clinical data, as we were not interested in pre-clinical data or observational/epidemiological studies. We also were not attempting to document all of the phytochemical and pharmacological data, which are separate topics in and of themselves.

- Make sure that you do not simply provide a long list of (certainly interesting) facts (many copy paste duplicates from abstracts can be identified throughout the text) but provide a critical analysis.

Once again, the point of our narrative review was not to criticize the work of others. We have mentioned issues in the limitations of the Discussion related to research in nutrition and dietary supplements and related to narrative reviews in general, but it was not the purpose of our narrative review to point out research design and/or statistical problems and flaws. Our position is that every study has flaws and nutritional science is also hindered by limits on generalizability in almost every study and situation. We also did not copy and paste any findings from any article. That is a serious charge of plagiarism, which we absolutely did not do!

- Please remember that the conclusion needs to be precise and needs to highlight the achievements and scientific gaps in our knowledge.

We have provided specific conclusions about the findings. Scientific gaps are not as easily addressed when writing a narrative review about many different nutrients and phytonutrients. Our conclusion was not to just restate the previously reviewed content, but rather to discuss the reason why someone should thoughtfully determine if a nutrient or phytonutrient should be included in a daily regimen. Our conclusions serve as a discussion that is relevant to the subject of dietary supplementation in general, which adds more to the paper than just restating previously reviewed information.

- If pharmacological studies are reviewed, we expect some information on the dose range tested, the minimal active concentration, the model used (including information whether it is an in vitro or in vivo study), if and what controls (including positive and negative) were used, duration, type of extract used as well as other basic pharmacological data. Maybe you could have one more table with this information and then to shorten the text accordingly by making appropriate reference to the table.

As noted previously, our narrative review consisted only of clinical trials with cognitive function outcome assessments, so the pharmacological data were irrelevant to our purpose. We did not review the articles for pharmacological data, as that was not the point of our narrative review. We have listed the dose of each active ingredient for each study both in the table and in the text.

- The available toxicological information on the species needs to be reviewed, too.

Toxicological data are not germane to our narrative review. All of the nutrients and phytonutrients listed are readily available and sold as dietary supplements in the United States.

- Plant species need to be validated taxonomically (e.g. www.theplantlist.org) and the full name including authorities and family needs to be included.

Each plant species was updated to include the taxonomic name.

Below are some other comments.

Title: Dietary compound is not a functional term, which should be replaced for FDA approved term dietary supplement - a product taken orally that contains one or more ingredients (such as vitamins or amino acids) that are intended to supplement one's diet and are not considered food. Dietary supplements include:

** nutrients - substances that promotes growth, provides energy, and maintains life*

** phytonutrients - plant-derived compound (such as resveratrol) associated with positive health effects*

As a matter of fact, all substances under review are plant-derived natural compounds except Vitamin D. There is no sense for such differentiation of dietary supplements in the title

We have changed the title of the paper to, “The Effects of Twenty-one Nutrients and Phytonutrients on Cognitive Function: A Narrative Review.” Dietary compound has been eliminated from the title and the text. We have grouped the review by: (1) primarily antioxidant nutrients, (2) not primarily antioxidant nutrients, and (3) phytonutrients. For ease of reference, we have sorted the table and text by group and then alphabetically within each group.

Abstract

In introduction the authors critically characterize "The current FDA-approved pharmacotherapeutics for dementia, which neither cure nor halt cognitive decline they just delay the worsening cognitive impairment".

This introduction suggests that dietary supplements might be different of FDA-approved pharmacotherapeutics in terms of halting cognitive decline and possibly cure dementia.

However, no aim task to reveal, confirm or deny that hypothesis was specified in the review.

Hypothesis was not defined and aim to summarize "the effects of nutrients, phytonutrients, and dietary compounds on cognitive function" does not suggest any scientific novelty of this narrative review.

We do not agree that a hypothesis is necessary for a narrative review. We are summarizing a voluminous amount of data on the effects of nutrients and phytonutrients on cognitive function. Our criticism of the FDA-approved drugs for dementia and their lack of much efficacy is factual, and we did not imply anywhere in our narrative review that nutrients or phytonutrients may cure dementia. Again, we were interested in summarizing how nutrients and phytonutrients impact cognitive function in healthy adults and those with health challenges, like dementia. Having dementia is not a requirement to test one’s cognitive function.

Therefore, it is not surprising that nothing new was concluded compared to original publications. Words like dietary compounds may be promising says nothing. The section Relevance for Patients should be merged with conclusions.

The point of a narrative review is to summarize the articles reviewed, not to introduce new findings to the world. The latter is the point of original research, not our review. Our review is to provide a resource for someone who is interested in one reference summarizing recent findings that includes these nutrients and phytonutrients.

This review is not systematized by:

** the type of disease*

** key molecular mechanisms or modes of action*

** key type of active compounds*

in order to find or disclose common features and make conclusions.

Yes, the point of our narrative review is to summarize the findings of certain nutrients and phytonutrients, regardless of the patient population studied or if the study was conducted in healthy adults. Cognitive function is the assessment (outcome) of interest, not biochemical or physiological modes of action. We have classified all of the active ingredients, so I am unsure what is different from naming the nutrients and phytonutrients versus referring to “active compounds.”

Instead, we see standard phrases like:

** "Phytonutrients, and dietary compounds showing promise in improving cognitive function certainly warrant continued study."*

** "As additional research is necessary to make robust recommendations for any nutrient, phytonutrient, or dietary compound, some of those that were reviewed may offer an avenue for improving cognitive function in illnesses currently lacking effective conventional treatment"*

** Due to these limitations, additional larger studies are needed to investigate the safety and efficacy of dietary compounds in treating and preventing various neurocognitive disorders, while determining if any drug-supplement interactions occur in those taking medications, particularly those with serious side effects.*

** As additional research is necessary to make robust recommendations for any nutrient, phytonutrient, or dietary compound, some of those that were reviewed may offer an avenue for improving cognitive function in illnesses currently lacking effective conventional treatment.*

** In summary, this narrative review highlights the current evidence of specific nutrients, phytonutrients, and dietary compounds that may improve aspects of cognitive function, with potential benefit in the prevention and adjunct treatment of cognitive dysfunction.*

We have rewritten the conclusions and summary on pages 94-96 to be as specific as we can to this narrative review, including the statements specifically mentioned by the Reviewer. In addition to modifying some of the general limitations, we have included other limitations germane to a narrative review. As noted above, our conclusion was not to just restate the previously reviewed content, but rather to discuss the reason why someone should thoughtfully determine if a nutrient or phytonutrient should be included in a daily regimen. Our conclusions serve as a discussion that is relevant to the subject of dietary supplementation in general, which adds more to the paper than just restating previously reviewed information.

Well self-characterised - just highlights of known observations, nothing else.

I would also argue with the statements like:

** The heterogeneity of study design and methodological quality also pose a limitation to generalizing the results. - The authors can use Cochrane risk of bias graphs and Jadad's Quality scales for inclusion of studies in the review and draw rigid, justified conclusions.*

Many nutrients and phytonutrients have very few clinical trials actually conducted on them. We are not trying to eliminate what little information exists. We are providing a summary of the existing data.

** While many of the studies were randomized, double-blind, placebo controlled trials, others were limited by small samples and lack of blinding or placebo or control group. - The authors can exclude open label studies, which small sample size have no impact on the results when the deference between pancebo and verum is significant.*

We do not want to exclude open label studies because once again some of these nutrients and phytonutrients have few clinical trials performed with them. Thus, being too rigid in our threshold for including studies in this narrative review was not of interest.

** Treatment amount and type and follow-up time across studies also ranged significantly, making it difficult to predict any long-term risks for certain nutrients and perhaps preventing the detection of benefits that may only manifest with chronic ingestion of a compound. Predict long-term risks is not possible without pharmacovigilance Phase IV studies for many years. However, the safety of many herbal medicines used in traditional medicinal systems for more than 30 years was formally accepted by European Medical Agency.*

Yes, studies have evaluated different doses of the treatment over different time periods. Table 1 provides a quick reference for the reader to be able to read those differences in patient populations (or healthy adults) under study.

Several concluding statements are not based on actual content of the review:

** treatment regimens should be individualized as much as possible with ongoing evaluation of benefits and risks for adjustment.*

** Dietary supplements may interact with some prescription and over-the-counter medications through direct interaction or modulation of key enzymes implicated in drug metabolism.*

** Plant compounds also display immensely complex multiphysiological activity and often act synergistically, making the function of isolated extracts less predictable.*

** Thus, careful review of current medication and dietary supplement intake should precede the addition of new compounds, especially among the elderly who are more vulnerable to adverse interactions through polypharmacy and changes in drug metabolism.*

These statements can be important to include because they are based on what is needed for furthering the research and also to provide information to consumers who may be using this review as a point of reference for including some of these nutrients and phytonutrients in their daily regimen. This narrative review is not just a summary of the literature, but a practical resource that professionals and laypeople can use to make decisions about using these nutrients and phytonutrients in their own lives. For example, it is ethically responsible to let people know that further research is always warranted to either discover interactions that may exist between nutrients and phytonutrients and other compounds or to provide evidence that those interactions do not exist. Since it will be impossible to determine the whole realm of possible interactions, it is at least ethically warranted to make a general observation about such a possibility. These types of summary statements do not detract from the overall quality of our paper.

Methods: Inclusion and exclusion criteria were not validated for accuracy. As a result, 19 dietary supplements (herbal extracts and individual compounds which author call "categories") were selected for reviewing. As a result, at least three plant extracts, namely, Rhodiola rosea, Withania somnifera and Andrographis paniculata, which are effectively improve cognitive functions and mental health in clinical studies are out of scope of this review.

Thank you for these suggestions. We have updated the review to include *Rhodiola rosea* and *Withania somnifera*. However, *Andrographis paniculata* did not have any articles on cognition that fit our inclusion criteria for the review (i.e., a clinical trial published after 2000

in English). All of the clinical trials that we found for it were irrelevant to cognition and were investigating its effects on respiratory infections, pain management, diabetes, and arthritis, among others.

Regretfully, I would not recommend this article for publication in present form, major revision is required, where the authors will adequately address reviewers' comments and suggestions.

Reviewer #2

This paper provides a narrative review of the effects of nutrients, phytonutrients, and dietary compounds on cognitive function. This is a huge area and while the authors cover many topics there are several important areas missing, such as the effects of caffeine. The review only uses one search engine which may miss articles, especially the "grey literature". The main problem is that this is not really a review but a list of studies. One would expect more detailed critical evaluation of the research. This should take the form of consideration of whether reported results could be chance effects, or whether the absence of effects could be due to design features such as sample size. The focus on statistical significance may also be problematic as one needs to know whether the effect sizes are going to lead to clinically significant improvements.

My suggestion would be to focus on specific topics and provide a systematic review or meta-analysis rather than a list of studies.

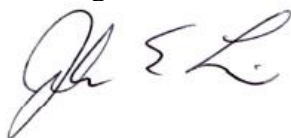
Please refer to the section on xanthines, which includes caffeine! We covered it.

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.

While we understand the need to be critical of others' work when it is appropriate, this was not the purpose of our narrative review. We chose to write a narrative review because the literature needs to have an article of recent research that summarizes the findings about certain nutrients and phytonutrients on cognitive function. We limited our review to only clinical data, as we were not interested in pre-clinical data or observational/epidemiological studies. We also were not attempting to statistically summarize all the data, which is the point of a systematic review or meta-analysis. We do understand the need to point out statistical significance as opposed to clinical significance, and we have included that in the Discussion section.

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
19-Jun-2021

Ref.: Ms. No. JCTRes-D-21-00015R1
The Effects of Twenty-one Nutrients and Phytonutrients on Cognitive Function: 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 Jul 19, 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 a revision and rebuttal letter. The editorial board has deemed your manuscript suitable for publication pending minor revision.

The minor revision pertains to mainly grammar and spelling errors as text formatting issues (e.g., p 88, line 14: FDA approved should read FDA-approved).

Kindly go through the manuscript and eliminate all registered trademark symbols, capital letters where no capitalization is exacted (e.g., section headers), and syntax mistakes (e.g., p. 31, lines 43-48: Nonetheless, related to mechanistic aspects of brain function, it has been shown that vitamin D increases acetylcholine level [140] and hippocampal neuron densities [141] and augments amyloid-B clearance [142] -> level and densities; why singular and plural? Both should be plural because they are measurable and occur at multiple quanta).

For clarity, please number the sections and sub(sub)sections.

Thank you,

Michal Heger
Editor

Authors' response

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July 8, 2021

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

Dear Dr. Heger:

We thank the Editorial Board for its evaluation and acceptance of our manuscript. As per the requests of the Board, we have thoroughly reviewed our paper to improve its quality and suitability for publication. We have addressed all minor revisions pertaining to grammar and spelling errors as text formatting issues (e.g., FDA-approved is consistent throughout the paper). We have eliminated all registered trademark symbols, capital letters where no capitalization is needed (e.g., section headers), and other syntax issues. We have numbered the sections and subsections in the same style as our previous review paper.

Please let us know if you have any additional questions or clarifications, and we look forward to getting the paper published soon.

Best regards,



John E. Lewis, Ph.D.
Voluntary Associate Professor

3rd Editorial decision
08-Jul-2021

Ref.: Ms. No. JCTRes-D-21-00015R2
The Effects of Twenty-one Nutrients and Phytonutrients on Cognitive
Function: 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: