

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risks and benefits of antioxidant dietary supplement use during cancer treatment: Protocol for a scoping review
AUTHORS	Wieland, L. Susan; Moffet, Ilana; Shade, Sydney; Emadi, Ashkan; Knott, Cheryl; Gorman, Emily; D'Adamo, Christopher

VERSION 1 – REVIEW

REVIEWER	Yu-Chiang Hung Kaohsiung Chang Gung Memorial Hospital , Chinese medicine
REVIEW RETURNED	08-Dec-2020

GENERAL COMMENTS	1. Statistics are not appropriate and described fully? 2. The references the authors are looking for should have IRB certification.
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REVIEWER	Nadja Klafke University Hospital Heidelberg, Department of General Practice and Health Services Research
REVIEW RETURNED	23-Dec-2020

GENERAL COMMENTS	<p>This is an interesting study protocol on a very relevant topic for cancer treatment and care. Many cancer patients are interested in complementing their treatment and care with dietary supplements, but they find it difficult to differentiate between risky and beneficial intake, and need professional counselling about this. Healthcare professionals often would like to counsel patients on complementary therapies, but they often feel unsure about making recommendations, as they are not familiar with the evidence-base or do not have enough experience with this.</p> <p>Therefore, it is important to bring more clarity on this topic with the planned scoping review on the “risks and benefits of antioxidant dietary supplement use during cancer treatment.”</p> <p>Overall, the protocol is very systematic and includes all relevant details which are important to consider when conducting systematic reviews/scoping reviews. I would just like to mention a few aspects for improving the study protocol:</p> <p>1) Do you only want to include systematic reviews in this scoping review? I was just wondering if you might like to include some individual RCTs or case reports, which are perhaps not yet included in the existing systematic reviews.</p> <p>If you include other study types as well – which is actually recommended and a huge advantage when following a scoping review – you need to change this statement (under Article</p>
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	<p>Summary):</p> <p>“The review will use the AMSTAR-2 tool to distinguish between systematic reviews providing different levels of certainty for results and emphasize reviews at overall high or moderate certainty.”</p> <p>2) Please provide more arguments why you decided to conduct a scoping review (and not just a systematic review or evidence map of systematic reviews). This topic has briefly been raised at the end of the introduction, but needs to be extended.</p> <p>3) You decided to apply the AMSTAR-2 tool (and not CASP or Revman) for the critical appraisal of the studies included in your review. Please provide more information on how you plan to use this tool and how you will interpret the results of this tool. For example, how will you decide for high, medium, or low risk of bias of the studies of your review? Do you calculate a score or do you count the category options...?</p> <p>4) A comprehensive discussion is currently missing. This section directly starts with the implications, but before this, a short summary of the manuscript needs to be reported with one or two aspects picked for discussion. For example, you might want to discuss on specific antioxidants (where there exists conflicting evidence at the moment) or the potential difficulties of assessing the risk of bias of the selected studies/reviews.</p> <p>5) How is the time plan of this review? You did report on the initial search strategy for Embase. Have you conducted the other searches as well? When do you plan to finish the review (this is important for other authors to know, as they might want to inform you on potential publications)?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Yu-Chiang Hung, Kaohsiung Chang Gung Memorial Hospital

Comments to the Author:

1.Statistics are not appropriate and described fully?

The intention of a scoping review is only to identify what studies exist, and therefore formal narrative or quantitative synthesis is not part of the scoping review methodology (see Chapter 11 of the JBI Handbook (<https://doi.org/10.46658/JBIMES-20-12>), which details methodological guidance for the conduct of scoping reviews). Scoping reviews generally extract information into tables or charts and do not carry out statistical summaries or syntheses. We have stated that we will describe the elements of the relevant systematic reviews and calculate some frequencies for specific data elements extracted from those reviews when appropriate.

2.The references the authors are looking for should have IRB certification.

The unit of analysis for this scoping review is systematic reviews. IRB approval is needed for research involving human participants, to ensure that the research is ethical and scientifically valid and to protect the autonomy and well-being of participants. Therefore, all of the RCTs examined as part of a systematic review should have received IRB certification. However, systematic reviews themselves

evaluate the RCT literature. They may not have collected information from the RCTs on IRB approval and they do not themselves require IRB approval, as they are literature-based rather than experimental.

Reviewer: 2

Dr. Nadja Klafke, University Hospital Heidelberg

Comments to the Author:

This is an interesting study protocol on a very relevant topic for cancer treatment and care. Many cancer patients are interested in complementing their treatment and care with dietary supplements, but they find it difficult to differentiate between risky and beneficial intake, and need professional counselling about this. Healthcare professionals often would like to counsel patients on complementary therapies, but they often feel unsure about making recommendations, as they are not familiar with the evidence-base or do not have enough experience with this.

Therefore, it is important to bring more clarity on this topic with the planned scoping review on the “risks and benefits of antioxidant dietary supplement use during cancer treatment.”

Overall, the protocol is very systematic and includes all relevant details which are important to consider when conducting systematic reviews/scoping reviews. I would just like to mention a few aspects for improving the study protocol:

1) Do you only want to include systematic reviews in this scoping review? I was just wondering if you might like to include some individual RCTs or case reports, which are perhaps not yet included in the existing systematic reviews.

If you include other study types as well – which is actually recommended and a huge advantage when following a scoping review – you need to change this statement (under Article Summary):

“The review will use the AMSTAR-2 tool to distinguish between systematic reviews providing different levels of certainty for results and emphasize reviews at overall high or moderate certainty.”

Thank you for this comment. We agree that there are multiple sources of information on the potential consequences of antioxidant supplementation for cancer treatment. RCTs are generally considered the highest level of evidence on an intervention, and systematic reviews of RCTs are assessments and summaries of this evidence. Our motivation for including only systematic reviews in this initial scoping of the literature was to begin with the summaries of the evidence, instead of searching, selecting, assessing, and summarizing individual RCTs ourselves. We will evaluate whether the effects of antioxidants upon chemotherapy have been addressed as part of the research questions in systematic reviews of RCTs. Our additional step of identifying reviews with the best methodological quality is to focus the most extensive examination on the summaries that would be likely to provide the most valid answers to those questions, and to determine whether there is a sufficient number of adequate quality and relevant systematic reviews for an overview, a need to scope the literature further, or a need to conduct further systematic reviews or RCTs. We recognize that the scoping review of systematic reviews is a first step and have indicated this in Step 2/Types of evidence sources.

2) Please provide more arguments why you decided to conduct a scoping review (and not just a systematic review or evidence map of systematic reviews). This topic has briefly been raised at the end of the introduction, but needs to be extended.

Thank you for the opportunity to clarify our approach. We are carrying out a scoping review to explore the research questions of the reviews themselves as a first step towards further research. We think it is possible that for some antioxidants this question may have already been answered, so we are using the scoping approach to see what has already been asked, what has been answered, and what remains to be investigated. If we were to carry out an evidence map of systematic reviews, we would likely be focusing on the findings of the reviews, but we are carrying out a more fundamental inquiry into the research questions. After this scoping review, we will have perspective on both the questions that remain to be addressed by new studies (primary studies or reviews), and the findings that already exist in the literature and can be mapped and disseminated.

We have now added text to the Introduction and the Discussion to clarify our approach and our focus on the research questions within systematic reviews.

3) You decided to apply the AMSTAR-2 tool (and not CASP or Revman) for the critical appraisal of the studies included in your review. Please provide more information on how you plan to use this tool and how you will interpret the results of this tool. For example, how will you decide for high, medium, or low risk of bias of the studies of your review? Do you calculate a score or do you count the category options...?

We have added more description about AMSTAR-2 in the text to the current detailed information in Appendix 3 about how the tool is used and how the results are interpreted. It is now specified in the text that tool contains 16 yes/no questions about review conduct, of which 4 are of critical importance, and that the overall assessment of the review depends upon the number and importance of apparent flaws in review conduct.

The quality of review conduct is not related to the risk of bias of the studies included in the review. If a review is of good quality, it will have adequately assessed the risk of bias of included studies and incorporated this information into the review results. A good-quality review may find that the evidence on a topic is of poor quality and will reflect this appropriately in the review conclusions, which then provide useful information to the reader. For that reason, we focused on assessment of the systematic review and did not consider using a tool such as the Cochrane Risk of Bias tool from Revman, which reflects the risk of bias of included studies.

The Critical Assessment Skills Program (CASP) systematic review checklist guides readers through an assessment of the methods, results, and applicability of a systematic review. Our goal in the scoping review is to identify whether there are systematic reviews of good methodological quality that address the research question of interest. The CASP assessment of adequate methods is based on five fairly general questions, the checklist is intended to be a pedagogic tool, and the checklist does not include a scoring system (https://casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-2018_fillable-form.pdf). We chose to use AMSTAR-2 because it is a detailed examination of the methods of a systematic review and provides an overall assessment of confidence in the review.

4) A comprehensive discussion is currently missing. This section directly starts with the implications,

but before this, a short summary of the manuscript needs to be reported with one or two aspects picked for discussion. For example, you might want to discuss on specific antioxidants (where there exists conflicting evidence at the moment) or the potential difficulties of assessing the risk of bias of the selected studies/reviews.

We have now added more information to the Discussion section. We now summarize the rationale for the scoping review and explain further why we are using the scoping review process and how we plan to use it in moving forward to inform future research.

5) How is the time plan of this review? You did report on the initial search strategy for Embase. Have you conducted the other searches as well? When do you plan to finish the review (this is important for other authors to know, as they might want to inform you on potential publications)?

We have now added information about the timing of the review. Since submitting the protocol manuscript, we have completed all of the searches and we are carrying out the title and abstract screening. We now describe in the manuscript that our target date for completion is the second half of 2021.