Author's response to reviews

Title: Interactions of commonly used dietary supplements with cardiovascular drugs: A systematic review

Authors:

  Salmaan Kanji (skanji@ottawahospital.on.ca)
  Dugald Seely (Dseely@ccnm.edu)
  Fatemeh Yazdi (fayazdi@ohri.ca)
  Jennifer Tetzlaff (jtetzlaff@ohri.ca)
  Kavita Singh (kasingh@ohri.ca)
  Alexander Tsertsvadze (atsertsvadze@ohri.ca)
  Andrea C. Tricco (andreatricco@me.com)
  Margaret E. Sears (megsears@ncf.ca)
  Teik C. Ooi (tcooi@toh.on.ca)
  Michele A. Turek (mturek@toh.on.ca)
  Becky Skidmore (bskidmore@rogers.com)
  Mohammed T. Ansari (moansari@ohri.ca)

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Author's response to reviews: see over
Dear Editors,

Please find attached below a list of all of the peer review comments and author responses for the submitted manuscript: Interactions of commonly used dietary supplements with cardiovascular drugs: A systematic review.

Please note that we are submitting both a version with tracked changes (as per your request) as well as a clean version due to the magnitude of changes that took place.

Regards,

Mohammed Toseef Ansari, M.B.B.S., M.Med.Sc., M. Phil
moansari@ohri.ca

**Associate Editor Comments:**
"This is a methodologically well done review, as one would expect from an Evidence Based Practice Center, but I fear that readers won't benefit as much as they should because:

1. as currently written it is very dense and difficult to follow the story and pick out the conclusions of interest. This is one of those situations where "less is more", and by not attempting to report everything they looked at and did the authors will be able to craft an article which will have more impact by making it possible for readers to follow their story and then be able to judge their conclusions. This is essentially the same comment as Reviewer #2, comment #4, which says that the results section lacks a clear structure and it is difficult to follow.

Authors’ response: To address this comment, we restructured the Results section of the manuscript and made it easier for a reader to follow the text. Specifically, the section now is organized by a dietary supplement within which the reviewed evidence is further broken down by a CV drug. The results for each dietary supplement are presented with respect to the following outcome categories: a) clinical efficacy (e.g., mortality, stroke, quality of life, myocardial infarction, restenosis), b) intermediate efficacy (e.g., LDL-C, HDL-C), c) harms (e.g., AST/ALT levels, serious adverse events), and d) pharmacokinetic. The cluttered and dense text in the Results section has been cleaned by removing results for non-gradable outcomes. Thus only results of gradable outcomes are presented throughout. Agreeing with comments from other peer-reviewers, we further curtailed this section by removing evidence on selected dietary supplements crossing boundaries between dietary supplement and pharmaceutical effects (e.g., vitamin K, niacin, minerals). Similar results showing benefits/harms (statistically significant and conclusive results; low grade or higher), no benefits/harms (statistically non-significant and conclusive results; low grade or higher), or inconclusive
benefits/harms (insufficient grade) for a dietary supplement across different CV drugs were integrated using overarching statements.

2. But rather than try and better organize all that you have, my suggestion to the authors is to decide what take-home messages they feel are most important for readers. Suggestions:
   2.1. Organize the results section around these alone, and strip everything else out. For example, right now in the conclusion there are list 3 bullet points - one each about omega-3 fatty acids, one about vitamin K (and I'll come back to that in a moment) and one about garlic.
   2.2. For two of these (omega-3 fatty acids, and garlic), the main point in the bullet seems to be that the agents don't interfere with pharmaceuticals and may provide additional benefit in terms of lab test results. The authors might consider building the paper around these outcomes. They would need to provide an overarching organization that would accommodate this, but it would then mean - after stating this is part of a broad review - telling the reader that the manuscript is going to focus on only a sub-section of the evidence overall.
   2.3. And I would definitely suggest NOT focusing on Vitamin K and warfarin - warfarin is a Vitamin K antagonist and Vitamin K is the treatment for inadvertant warfarin overdose. There is a known physiology about how these work, and Vitamin K is a purified compound which bears much more in common with pharmaceuticals than does, say, garlic, hawthorn, ginger, and echinacea. I'd suggest avoiding all such "supplements" like vitamins, minerals, amino acids, niacin (another vitamin that has known pharmaceutical properties in this context), etc. etc. I don't think that's what clinicians will want to read in a paper about "dietary supplements". They will want to read about the other things - garlic, ginger, etc. Even omega 3 fatty acids are in the process of crossing the line between 'dietary supplement' and 'pharmaceutical treatment', and I suppose you can continue keeping them in here, but then I'd focus only on the potential for harmful interactions, since the benefit side of this was reviewed in exhaustive detail by the EPCs just a few years ago.
   2.4. And then what clinicians will be most interested in is about evidence for drug-supplement interactions.

Ultimately, it is for the authors to decide what they think their most important messages are, and so my comments above where to focus are merely suggestions for them to consider. But focus they must, because as it currently stands even people interested in this topic will not be able to gain the benefit they deserve from all this work because of the way it is presented."

Authors' response: please see our response above

Reviewer 2: Evangelia Ntzani
Kanji S et al report a systematic review on the effect of combination therapies of dietary supplements with cardiovascular drugs. They assess issues of efficacy, harms and pharmacokinetics in this diverse category of interventions and claim that evidence of low validity supports a possible favorable effect of omega-3 fatty acids, vitamin K, coenzyme Q10, and garlic co-administration, for specific intermediate outcomes and they raise concerns about safety due to paucity of relevant information. The question posed by the authors is very interesting and well defined, the methods appropriate but the reported results are not sound and well controlled.

The authors did not succeed at various points through the manuscript in systematically organizing the evidence they retrieved. As far as the comparisons with a quantitative synthesis are concerned, the authors do not provide the detailed data of the performed meta-analyses and thus render the manuscript problematic to review.

**Major Compulsory Revisions**

1. **Methods:**
   1.1. Paragraph 2: The search strategy should be provided in a supplementary file.
   Authors’ response: Thanks, we will put search strategies in an appendix

   1.2. Paragraph 3: The selection of the group of supplements under study is reported to be based on reported surveys and an independent expert panel. The authors should briefly comment on the underlying rationale thereof.
   Authors’ response: We added information on the rationale for selecting specific supplements in Methods - study selection sub-section

   1.3. Paragraphs 6 & 8: The authors state that meta-analysis was performed when there was clinical and methodological homogeneity or unexplained statistical heterogeneity. The term homogeneity, as opposed to the term heterogeneity, is quite confusing here; the authors should elaborate on the definitions and criteria used for homogeneity (outcome, intervention, design, etc) and support their decision on a case-by-case basis.
   Authors’ response: We revised the paragraph accordingly to clarify the peer-reviewer’s comment (see Methods – Data synthesis and Analysis sub-section).

   1.4. A random-effects model meta-analysis is reported throughout the manuscript. Although, in the absence of heterogeneity, random-effects and fixed-effects estimates are interchangeable, varying degrees of heterogeneity would yield varying degrees of confidence for the effect estimates and the universal adoption of a random-effects model precludes an over-conservative approach. The authors should justify their choice of model.
   Authors’ response: We added more details regarding the decision for pooling studies and choice of statistical model for a meta-analysis (see Methods – Data synthesis and Analysis sub-section).
1.5. Finally, the authors state that meta-regression or subgroup analysis were planned for pre-defined subgroups, but fail to report which.
Authors’ response: We added information regarding pre-selected subgroups divided by clinical (e.g., age, sex, race/ethnicity) and methodological aspects (e.g., parallel vs. crossover design, risk of bias, type of analysis, baseline health status). See Methods – Data synthesis and Analysis sub-section.

2. Results:
2.1. The reporting of the Results section lacks a clear structure and it is rather difficult for the reader to follow through the various interventions, outcomes, reports of amount of evidence and individual study results.
Authors’ response: please see our response above to associate editor’s # 1 comment.

2.2. The reported evidence should be organized per outcome or per supplement in order to enhance comprehension and systematic appraisal of the provided evidence.
Authors’ response: please see our response above to associate editor’s # 1 comment.

2.3. Information provided in the text regarding N studies, N participants, summary effect estimates (95% CI) and heterogeneity should be incorporated in systematically constructed Tables.
Authors’ response: we tried to strike a reasonable balance in reporting numerical data between text vs. table. We removed some of less important numerical data from the text to make it less dense but left only important numerical data such as pooled estimates from meta-analyses.

2.4. Current Tables 1 & 2 could be moved to the supplementary material and be replaced by tables summarizing the published data.
Authors’ response: Thanks, we will put the Tables 1-2 in an appendix.

2.5. All reported results to the quantitative synthesis are not supported by supplementary material (the authors cite a link that is not valid). As a result, it is not possible to properly review the meta-analysis part.
Authors’ response: the links have been updated

3. Minor Essential Revisions

3.1. Methods, Par Paragraph 4: The rationale behind the need for and implementation of AMSTAR is unclear here and needs to be supplemented by the comment provided in the Results about obviating the need for a de novo evidence synthesis.
Authors’ response: this was specified in the review protocol, but we identified only one potentially relevant systematic review which was outdated and therefore it did not contribute to the review. Since it is less relevant for this manuscript, we removed the sentence mentioning AMSTAR.
3.2. Methods: Lines 129-130 should be moved right after line 124 in the part referring to methodological homogeneity.

Authors’ response: this section has been extensively revised

Reviewer 1

Minor Essential Revisions (please note: The review was drafted in Word, and comments 3-5 originally contained revision marks; if the suggested revisions are unclear, please let me know, and I'll submit a Word file):

Abstract:
1. Line 52: Space-permitting, it would be helpful to specify what pharmaceutical(s) the omega-3 fatty acids and garlic were combined with, or at least to say, e.g., “with use of X and omega-3 fatty acids…” Otherwise, it appears some of the findings pertain to supplements themselves, rather than combinations of a supplement with a pharmaceutical. It’s a bit confusing, as reams of studies exist on the efficacy and safety of omega-3s alone.
Authors’ response: Changed as suggested

Background:
3. It would be helpful to define or specify the classes of CV drugs.
Authors’ response: This is described in detail in Table 1.

The clarity of the text could be improved with some editing, for example:

3. Line 62: “front line therapies treatment for prevention and tx of CVD are is primarily pharmaceutical…”
Authors’ response: Thank you. Changed as suggested

4. Line 63: Start new paragraph with: “However billions of dollars are spent annually…”
Authors’ response: Thank you. Changed as suggested

5. Line 65: “…this expenditure is spent directly on …” Also, run line 66 back into line 65 to combine with that sentence.
Authors’ response: Thank you. Changed as suggested

6. Line 70: “have”# “has”
Authors’ response: Thank you. Changed as suggested

7. Line 76: “and” before “pharmacokinetic”
[I won’t continue listing suggested edits but if you would like, I can provide a marked up version of the draft, if you’d like. I consider these minor but necessary revisions.]
Authors’ response: Thank you. Changed as suggested

8. Line 88: Why only English and German? You address this point in the Discussion but it would make more sense to address here, I believe.
  Authors’ response: We feel that this fits better within our discussion of limitations. If this reviewer feels strongly that it needs to be in the methods section as well we would be happy to reconsider.

9. Line 92: I suggest citing the source of the definition of dietary supplement, which is probably something like the US DSHEA definition.
  Authors’ response: Citation added as suggested.

10. Line 104: and Canada?
  Authors’ response: Yes. We added as suggested.

Results:

11. In the subsection entitled, “Clinical Outcomes of Effectiveness,” it would be extremely helpful to use leading sentences to distinguish paragraphs discussing studies with no evidence of an effect, studies of adherence, and studies with some evidence of an effect.
  Authors’ response: Thank you. Changed as suggested

12. Also, I’d discuss adherence at the end of the subsection or in a separate subsection.
  Authors’ response: Thank you. Changed as suggested

13. Line 167: are you referring to the strict inclusion criteria of your review or the studies themselves?

  Authors’ response: Thank you. Changed as suggested

15. Line 247: please specify that nifedipine is a Ca-channel blocker.
  Authors’ response: Thank you. Changed as suggested

16. Lines 264 and 265: please use “participants” or “subjects” consistently. I think “participants” is more appropriate for human studies.
  Authors’ response: Thank you. Changed as suggested

17. Line 290: Please specify what a clinically significant change in warfarin pharmacokinetics would be, since the findings are apparently at least statistically significant.
  Authors’ response: Thank you. Changed as suggested
18. Line 333: I would conjecture that another factor introducing error to study findings is the almost certain failure to assess baseline use of supplements, dietary intake (of dark fish and vitamin K, for example), and nutrient status. I suggest mentioning, space-permitting.

Authors’ response: Thank you. Changed as suggested

List of References:

19. Reference 17 seems to have an odd phrase added at the end

Discretionary Revisions:

Conclusion:

Authors’ response: Thank you. Changed as suggested

20. Line 427: I’m really not sure that seeking even well-conducted prospective observational studies, however tempting, is likely to be terribly productive, given the differences in supplement content from brand to brand and even batch to batch.

Authors’ response: Thank you. Agreed

21. Line 430: Would it be possible to identify some combinations of supplements and pharmaceutical that, based on known mechanisms of action, might have the strongest potential for interactions? Doing so might help spur researchers to focus on the studies most likely to produce worthwhile results.

Authors’ response: Thank you. This is a good suggestion for future research efforts