Reviewer's report

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

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Reviewer: Evangelia Ntzani

Reviewer's report:

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, Paragraph 2: The search strategy should be provided in a supplementary file.

2. Methods, 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.

3. Methods, 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. 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. Finally, the authors state that meta-regression or subgroup analysis were planned for pre-defined subgroups, but fail to report which.

4. Results: 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. The reported evidence should be organized per outcome or per supplement in order to enhance comprehension and systematic appraisal of the provided evidence. Information provided in the text regarding N studies, N participants, summary effect estimates (95% CI) and heterogeneity should be incorporated in systematically constructed Tables. Current Tables 1 & 2 could be moved to the supplementary material and be replaced by tables summarizing the published data.

5. Results: 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.

• Minor Essential Revisions

1. Methods, 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.

2. Methods: Lines 129-130 should be moved right after line 124 in the part referring to methodological homogeneity.

• Discretionary Revisions

None at this point.

Level of interest: An article of importance 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.