Title: A double-blind, randomized clinical trial of dietary supplementation on cognitive and immune functioning in healthy older adults

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Author’s response to reviews: see over
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Tom Rowles, PhD
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Dear Dr. Rowles:

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. For those comments that could be directly included in the manuscript, we have marked the changes by highlighting them in yellow. All other comments have been answered below. We have addressed the following reviewers’ comments:

Reviewer Liz Isenring:

1) Abstract: hard to read as a stand alone. ie describe the key cognitive tests in abstract or list more general tests (just hard to read in the results when not described in the methods)

To provide clarity, we have added the names of our cognitive tests to the Abstract, i.e., the Stroop Color and Word Test, Trail Making Test A and B, Controlled Oral Word Association, Hopkins Verbal Learning, Mini-Mental State Exam, and Digit Symbol.

2) define whole foods

We have removed “whole foods” from the title and in reference to it throughout the manuscript, as after consulting with the manufacturer it was determined that the use of this term would be confusing. Also, we made a few corrections and additions to the section describing the content of each dietary supplement formula on page 6.
I would like more detail re N calculation and these cognitive tests ie what is the clinical importance of these differences. Can you provide some practical examples of what this might mean in performing tasks/activities

Sample Calculation: Because we assessed two combinations of whole food supplements that included ginkgo biloba and other nutrients specifically targeted to enhance cognition in synergy, we expected the effect of these regimens of supplements on cognitive outcome measures to be larger than that found by Mix and Crews (2000), who tested ginkgo biloba individually in their study. Our a priori calculation assumed a sample of 90 subjects (30 in each group) and α = .05, and thus we estimated power at about 0.82 (c.f., Cohen, 1988) to document an approximate medium effect. We added this information on page 9.


Improvement on the Trail Making Test-B: We showed an improvement in time on the Trail Making Test-B with the Ginkgo Synergy® plus Choline arm. Both parts of the test reveal information on visual search, scanning, speed of processing, mental flexibility, and executive functioning (Tombaugh, 2004). Part B is more closely associated with increased visual/nonverbal intelligence and motor speed (Gaudino et al., 1995). Larrabee & Curtiss (1995) found that Part B of the Trail Making Test was more closely associated with visual, nonverbal intelligence than with attention and information processing. Thus, Part B shows one’s ability to differentiate between numbers and letters, combine two independent series, serial retention and integration, and preparation.


Improvement on the Controlled Oral Word Association Trial-S: We showed significant increases for the Ginkgo Synergy® plus Choline arm and for the OPC Synergy® plus Catalyn® arm. The Controlled Oral Word Association Test (COWAT) is a measure of a person’s ability to make verbal associations to specified letters (i.e., a phonemic test). This measure is a useful component of a neuropsychological battery as it is able to detect changes in word association fluency often found with various disorders (Sumerall et al., 1997). The test appears to rely on both language and executive function domains (Malek-Ahmadi et al., 2012). Thus, our results showed that our subjects demonstrated slightly improved ability to recall a set of related words.


4) **provide more details re what sups re cognitive function were recommended not to take. How was this checked?**

As noted in the “Intervention Protocol” paragraph on page 8, we instructed participants not to consume other dietary supplements containing Ginkgo biloba, vitamin B complex nutrients, vitamin E, or any other cognitive-enhancing nutritional supplement beginning at the baseline assessment and for the entire 6 months of the study. For further clarification in this paragraph, we added, “Subjects listed all dietary supplements taken on the health history form, and products were reviewed to ensure none of these nutrients was consumed during the course of the trial.”

5) **Discussion- provide further details re the previous gingko studies. N, primary outcomes, actual results etc.**

We have provided additional details on pages 13-14 of the Discussion section regarding the Mix and Crews (2000), Napryeyenko et al. (2009), and Solomon et al. (2002) articles. Those additions are highlighted.

6) **why was the other supplement investigated as well as gingko, this could be better described**

The other formula was used primarily because of the grape seed extract with support of the other nutrients. We have added a statement to support its use in the Background section at the bottom of page 3.

7) **any plans to perform this study in those with declining cognitive fn?**

A next study in mild cognitive impairment or dementia would be wonderful. Pending additional funding, we would love to conduct such a study.

8) **Perform another editorial review to pick up typos e.g. Vitamin E rather than Vitamins E in abstract**

We have performed another editorial review of the paper and hopefully all typos have been eliminated.

**Reviewer Kylie A. O'Brien:**
You have indicated that you asked participants to maintain diet/exercise/medication regimes during the period of the study. Did you monitor this in any way and analyse their diets/exercise regime before and after? Any changes in these could be confounders. If you didn't, and you only have anecdotal evidence that participants didn’t alter these factors, I suggest that you state this in the limitations section of the article.

We concur that these variables could have been important to the results of our study. We have noted on page 15 that we did not assess dietary intake or physical activity level, so we have no way of knowing how these additional variables might have affected our results.

Also wondering if you followed up patient c) who dropped out of the trial with joint pains to see if these went away after they stopped taking the medication? It would be difficult to pin a causal link on joint pains and the study medication, of course, but might be worth reporting (it's up to you).

We have no additional information to report on this subject. We were not able to track her once she withdrew from the study.

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

Best regards,

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Associate Professor
Associate Director of the Medical Wellness Center