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Bacopa monnieri supplementation has no effect on serum brain-derived neurotrophic factor (BDNF) levels but beneficially modulates NF-kB and CREB levels in healthy elderly subjects

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1st Editorial decision
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Ref.: Ms. No. JCTRes-D-22-00140
Serum brain-derived neurotrophic factor (BDNF) after 3 months of Bacopa monnieri supplementation
Journal of Clinical and Translational Research

Dear Dr. Keegan,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. 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 and attached to this decision letter.

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 Nov 23, 2022.

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: Please implement the following changes to the manuscript:

1) The title should be reflective of the main outcome of the study. Please rephrase to the effect of "Bacopa monnieri supplementation has no effect on serum brain-derived neurotrophic factor (BDNF) levels but beneficially modulates NF-kB and CREB levels in healthy elderly subjects."

2) Please provide correlation plots for APOE-CREB and APOE-NF-kB and stratification plots for CREB and NF-kB levels for Met carriers vs. Val/Val wild-type subjects. These will attest to the validity of data clustering in Figure 1.

3) Include Western blots of all proteins assayed and give a brief explanation of how the WB were semi-quantitated (e.g., densitometric analysis using XXX software). Also, the baseline bar in Figure 1 should also contain an error bar.

4) Please confirm that the use of parametric statistical tests (t test) was warranted by determining the nature of the data distribution (Gaussian vs. non-Gaussian). This can be performed by employing a D'Agostino-Pearson omnibus test, a Shapiro-Wilk test, or a Kolmogorov-Smirnov test.

5) Add female predominance as study limitation.

Reviewer #3: Several studies established that Bacopa monnieri extract (CDRI-08) improve the cognitive abilities in aged people and regulate the behaviour in hyper active children. The present study examined the effect in clinic participants, not only the behavioural aspects and provided molecular evidence to support the clinical data. However, the manuscript requires additional information.
1.Introduction need more clarity, in this section no single word about ApoE/ TrkB but suddenly appeared in method and result section. Authors should narrate the molecular connectivity of the tested molecules.
2.Why the authors examined the specific genotype - justification should be provided.
3.Authors should rearrange the discussion section, starting with the behavioural profile (improvements) with their medical history and serially the molecules.
4.I do not think the cholinergic section not necessary (discussion part second page line 26-34).

Reviewer #4: In this study, the authors have attempted to explore neuroprotective intracellular signaling processes that could improve the cognitive reserve. For the purpose, they assessed markers in elderly subjects who received Bacopa monnieri (BM) extract for three months. Additionally, they have evaluated if these changes also translate to mood and cognitive improvements.

The authors found significant changes in cyclic AMP response element-binding protein (CREB) and nuclear factor kappa B (NF-κB) phosporylation. However, there was no improvement in brain-derived neurotrophic factor (BDNF) as hypothesized at the outset. Also, the improvement in cognition was limited to delayed-recall subset of the Montreal Cognitive Assessment (MoCA).

While CREB and BDNF have been linked to cognition and depression in several human studies, their improvement in hippocampus after administration of BM extract has been seen mainly in animal models. Hence, in spite of the small sample size and lack of demonstration of elevated BDNF in this study, the limited findings could still be of interest to future researchers.

There are a few suggestions that I would like to give:

Page 4, Line 12, Abstract and Page 9, Line 7, Results:
There are isolated mentions of 'healthy controls' (Page 4, Line 12, Abstract) and 'randomization' (Page 9, Line 7, Results). Can you please clarify and/or mention how cases and controls were selected and randomized?

Page 12, Discussion:
In continuation with previous point; in case this was not a case-control study, please include 'lack of controls' as a limitation of the study.

Page 9, Line 13, Results:
The greater number of female (75%) subjects could impact the interpretation of the depression and mood scores. This should be mentioned as a limitation of the study. Also, please mention the gender-wise scores (before and after) wherever suitable.

Page 12, Line 40, Discussion:
The authors mention that stress reported in LEC-5 didn't 'significantly' change the GDS score. Please show this 'statistical correlation' in the Results section.

Page 12, Limitations:
A similar recent study (McPhee GM 2021, PMID: 33692683) has demonstrated promising neuroimaging results in addition to elevation of BDNF in elderly subjects who received BM extract. The authors have already cited this study. It would benefit the readers if the authors summarized the relevant findings of this study while making a case for future research.

Page 2, Title:
This study compares biochemical markers (a) with clinical correlates of cognition (b) in the elderly (c) after BM supplementation (d) for three months (e). A title that reflects these points

would be more succinct. This is an optional suggestion left to the discretion of the authors.

Reviewer #5: Dear Authors, I like your paper overall, but your acceptance for publication is dependent on several edits that you need to make. First, the use of the word "there" is vague and distracting in technical and scientific writing. When you use that word, you are distorting the subject and the object in your sentences. For example, the first sentence where you used there, should be instead, "Over the 3 months, the GDS and the total MoCA did not significantly change, but the delayed-recall subscale significantly improved." Please reword all sentences where you used there to be more grammatically clear. If you intend to continue writing for publication in peer-reviewed journals, I encourage you to practice a better writing style from this point forward and avoid the use of the word "there" to begin sentences. Second, you are not using and creating acronyms correctly. The first time you need to create an acronym, you spell out the words first and put the acronym in parentheses. You have the order reversed in several instances. You also used at least one acronym, MCI, where you did not spell it out at all. Also, do not create an acronym if you only use it the one time that you create it. You also do not create the same acronym more than one time in the body of your paper. You have quite a few errors, typos, and misuse of punctuation that I have highlighted on the .pdf of your manuscript. It does not look favorably for you when you have so many simple mistakes that could have been avoided prior to submission. I suggest that you ask a colleague who is not a co-author and never read the paper to review it and edit it for you the next time before you submit a paper. You probably failed to have a fresh set of eyes review your paper, and after a while, you no longer even notice the mistakes because you have read the text too many times. Nonetheless, you can only make one first impression and you have way too many typos. I encourage you to be much more of a perfectionist moving forward. Figure 1 is nonsensical. Delete it and provide the actual data in a table for the 4 biomarkers that you are reporting. Your limitations section is weak. You might consider expanding some other potential issues, such as you did not collect any dietary data that might have played a role in the results. The GDS is a valid measure, but you should acknowledge that other measures such as the BDI or HAM-D might have been more sensitive to change. Consider providing some justification for the dose of Bacopa you selected. Since you studied a sample of healthy people, you might have needed a bigger dose to affect BDNF and the MoCA. Otherwise, I think you did a nice job running the study and collecting some interesting biomarkers that set up the next step in your research program. If you can accurately make all of the changes that I have suggested, then I would be in favor of accepting your paper on the next submission.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors’response

Reviewer #1: Please implement the following changes to the manuscript:

1) The title should be reflective of the main outcome of the study. Please rephrase to the effect of "Bacopa monnieri supplementation has no effect on serum brain-derived neurotrophic

factor (BDNF) levels but beneficially modulates NF-kB and CREB levels in healthy elderly subjects."

Thank you for this suggestion. We have made this change.

2) Please provide correlation plots for APOE-CREB and APOE-NF-kB and stratification plots for CREB and NF-kB levels for Met carriers vs. Val/Val wild-type subjects. These will attest to the validity of data clustering in Figure 1.

We have provided additional figures below to show the clustering of the data and this was performed in reference to the genetics as requested. The request for APOE-CREB and APOE-NFkB was unclear and we welcome any further requests. The Figures below provide individual subjects' data relative to their baseline visit (line at 1 defines no change and above is an increase and below is a decrease between visits). Please recall that subject's two visits were run on the same gel, but not all subjects were run on the same gel.

2nd Editorial decision
23-Nov-2022

Ref.: Ms. No. JCTRes-D-22-00140R1
Bacopa monnieri supplementation has no effect on serum brain-derived neurotrophic factor (BDNF) levels but beneficially modulates NF-kB and CREB levels in healthy elderly subjects
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.
Please notify our assistant editor/production editor when you receive the proofs if your article should belong to a special issue specifying the issue's title.

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: