

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The efficacy of probiotics in the management of halitosis: A systematic review and meta-analysis
AUTHORS	Huang, Nengwen; Li, Jinjin; Qiao, Xianghe; Wu, Yongzhi; Liu, Yunkun; Wu, chenzhou; Li, Longjiang

VERSION 1 – REVIEW

REVIEWER	Motta, Pamela Universidade Nove de Julho - Campus Vergueiro
REVIEW RETURNED	25-Jan-2022

GENERAL COMMENTS	This manuscript addresses a very interesting and current topic. Although the articles present different ways of analyzing the primary outcomes and different ways of administering probiotics, the authors were able to explore the results well and reach a conclusion.
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REVIEWER	Saiz, Perrine Instituto Universitário Egas Moniz
REVIEW RETURNED	11-Feb-2022

GENERAL COMMENTS	Line 13: replace “Objectives” by “Background” and write “Objective” line 15 before “The present study...” Line 16: complete the sentence by “from a time perspective” Lines 17-29: this part of the abstract is a bit confused Line 19: secondary outcomes are missing Line 30: replace “according to...-analysis “ by “according to the results of this work” ; name probiotics strains used Line 31: add “heterogeneity of clinical trials included” Lines 33-38: I don’t really see an interest to write these lines Line 61: replace “anaerobic microbiota” by “anaerobic oral conditions” Line 62: replace “microbiome” by “microbiota” Line 63: replace “treat” by “manage” Line 64: delete “according to...reports” Line 71: replace “the beneficial...probiotics” by “their beneficial effects are...” ; add others mechanisms of action of probiotics Line 72: give strains examples after “probiotics” Line 75: add “oral mucositis induced by chemo-radiotherapy” Xia C, Jiang C, Li W, Wei J, Hong H, Li J, Feng L, Wei H, Xin H, Chen T. A Phase II Randomized Clinical Trial and Mechanistic Studies Using Improved Probiotics to Prevent Oral Mucositis Induced by Concurrent Radiotherapy and Chemotherapy in Nasopharyngeal Carcinoma. Front Immunol. 2021 Mar 24;12:618150. doi: 10.3389/fimmu.2021.618150. PMID: 33841399; PMCID: PMC8024544.
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	<p>Lines 76-78: "at present, ...halitosis" : delete. Lines 80-82: "in this review...2020": delete</p> <p>Line 85: complete by "this systematic review and meta-analysis"</p> <p>Line 86: simplify : "from a time perspective to provide..."</p> <p>Lines 89-91: mentioned line 312</p> <p>Lines 97-100: remove ?? this part is better explicated in the section "inclusion criteria". Maybe you can merge the two sections.</p> <p>Example line 96: "what is the clinical...placebo treatment ? To answer to our research question, we selected clinical trials according to following inclusion and exclusion criteria": ...</p> <p>Line 106: "some related Chinese journals": which ones ?</p> <p>Lines 23-125: "if the control....were excluded" : belong to a section named "exclusion criteria"</p> <p>Lines 166-167: replace "figure 1 evaluated...exclusion" by "(Figure 1)"</p> <p>Lines 193, 199, : p are missing.</p> <p>Line 215: "Figures 4 and 6"</p> <p>Lines 218-223: belong to the section "Introduction" (lines 40-50), remove from "Discussion"</p> <p>Lines 233-239: why did you put these lines in the "Discussion" and not in the "Primary outcomes" ?</p> <p>Lines 242-247: simplify the sentence</p> <p>Line 242: replace "microbiome" by "microbiota"</p> <p>Line 247: the reference is missing</p> <p>Line 264: the reference is missing</p> <p>Lines 270-272: remove because you already mentioned in the "Introduction"</p> <p>Line 285: terms "heterogeneity of clinical trial" are missing</p> <p>Lines 288-289: simplify the sentence</p> <p>Line 300: name probiotics strains used in the clinical trials included</p> <p>Line 301: add "the heterogeneity of clinical trials included" and "small sample size"</p> <p>Line 303: add "and to evidence the usefulness of probiotics in the management of halitosis".</p> <p>Lines 300-303: Maybe the conclusion needs one or two more sentences.</p> <p>Line 451: replace by "literature search strategy and inclusion, exclusion criteria"</p>
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REVIEWER	Liu, Shan The First Affiliated Hospital of Zhejiang Chinese Medical University
REVIEW RETURNED	13-Jun-2022

GENERAL COMMENTS	<p>I appreciate the meaningful work done by the team. This paper systematic review the efficacy of probiotics in the management of halitosis. The research question is interesting and scientific sounds. However, the authors should address the following concerns:</p> <ol style="list-style-type: none"> 1. A detailed search strategy as supplemental material would be better to assess the quality of literature search. 2. A study seemed be missed, "Benic GZ, Farella M, Morgan XC, Viswam J, Heng NC, Cannon RD, et al.. Oral probiotics reduce halitosis in patients wearing orthodontic braces: a randomized, triple-blind, placebo-controlled trial. J Breath Res. (2019) 13:036010. 10.1088/1752-7163/ab1c81". Please refine your search strategy. 3. The inclusion criteria demonstrated the detailed criteria of included studies, however, excluded criteria was also very important for the selection of literature. Please add relevant methods.
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	<p>4. In Page 153-154, please add corresponding references for the evaluation methods of heterogeneity model selection.</p> <p>5. In Fig 1, please add reasons for the excluded records(n=116). Moreover, it should be 14 not 7 in “full-text articles assessed for eligibility”.</p> <p>6. Publication bias and leave-one-out analysis should be included.</p> <p>7. I have noticed that in Page 301, eliminating pathogens was mentioned in conclusion. However, I could not connect the results to this conclusion.</p> <p>8. In Page 183-216, I am confused why quantitative synthesis was a separate paragraph. The detailed overalls results of the outcomes be demonstrated in primary outcomes and secondary outcomes would be clearer.</p> <p>9. Add discussion the difference of your manuscript with “Nansi López-Valverde, Antonio López-Valverde, Bruno Macedo de Sousa, et al. Role of Probiotics in Halitosis of Oral Origin: A Systematic Review and Meta-Analysis of Randomized Clinical Studies. Front Nutr. 2022 Jan 21;8:787908. doi: 10.3389/fnut.2021.787908. eCollection 2021.”</p>
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REVIEWER	Thornley, Simon The University of Auckland, Section of Epidemiology and Biostatistics
REVIEW RETURNED	22-Jul-2022

GENERAL COMMENTS	<p>The study uses appropriate methods to address the question it poses relating to the effect of probiotics.</p> <p>It would be useful to have more description of the assessment of the primary outcome, so that non-specialist readers understand how this data is collected. In particular, it would be useful to know whether this is subjective or objectively measured. There is some material related to this in the discussion, but it should also be addressed in the methods.</p> <p>I notice that no attempt has been made to look for publication bias, such as using funnel plots. This could be investigated. Given the high rate of heterogeneity, random effect trials are known to be biased in the presence of publication bias, even though the number of studies included is low. Considering the heterogeneity, it may also be useful to group trials together if they have methods for assessing the outcome that are similar.</p> <p>The inconsistency of the pooled results with some positive and some negative could also be discussed, as a factor that undermines the conclusion that these results indicate a positive effect.</p>
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VERSION 1 – AUTHOR RESPONSE

For reviewer 1

This manuscript addresses a very interesting and current topic. Although the articles present different ways of analyzing the primary outcomes and different ways of administering probiotics, the authors were able to explore the results well and reach a conclusion.

Response: We appreciate your taking time out of your busy schedule to review our manuscript. We also appreciate your recognition of our research.

For reviewer 2

Dear reviewer:

We thank you for the positive and constructive comments and suggestions on our manuscript. The comments are all valuable and helpful for revising and improving our paper. We have studied all comments carefully and have made conscientious corrections. Please see below for the point-point responses to your comments. These responses to the reviewers' comments in bold blue text are as follows. Revised portions are marked in red in the manuscript.

1. Line 13: replace "Objectives" by "Background" and write "Objective" line 15 before "The present study..."

Response: We thank the reviewer for this suggestion. We have revised the expression in the text. Please see the revised expression line 13 and line 16.

2. Line 16: complete the sentence by "from a time perspective"

Response: We thank the reviewer for pointing out this issue. We have completed the sentence in the text according to your suggestion. Please see the revised expression, lines 16-17.

3. Lines 17-29: this part of the abstract is a bit confused

Response: We are sorry for the confusion brought to the reviewer. We have revised this part of the abstract in the text. Please see the revised Abstract, lines 18-32.

4. Line 19: secondary outcomes are missing

Response: We thank the reviewer for the correction. We have added the missed in the text. Please see the revised expression, line 21.

5. Line 30: replace "according to...-analysis" by "according to the results of this work"; name probiotics strains used

Response: We thank the reviewer for pointing out this issue. We have revised the expression and added the name probiotics strains used in the text. Please see the revised expression, lines 33-34.

6. Line 31: add "heterogeneity of clinical trials included"

Response: We thank the reviewer for pointing out this issue. We have added the expression in the text. Please see the revised expression, lines 35-36.

7. Lines 33-38: I don't really see an interest to write these lines

Response: We thank the reviewer for pointing out this issue. According to the requirements of this journal, we need to list the strengths and limitations of study. We have revised these lines in the text. Please see the revised expression, lines 38-43.

8. Line 61: replace "anaerobic microbiota" by "anaerobic oral conditions"

Response: We thank the reviewer for this suggestion. We have revised the expression in the text. Please see the revised expression, lines 65-66.

9. Line 62: replace "microbiome" by "microbiota"

Response: We thank the reviewer for pointing out this issue. We have revised the expression in the text. Please see the revised expression, line 67.

10. Line 63: replace “treat” by “manage”

Response: We thank the reviewer for pointing out this issue. We have revised the expression in the text. Please see the revised expression, line 67.

11. Line 64: delete “according to...reports”

Response: We thank the reviewer for this suggestion. We have deleted the expression in the text. Please see the revised expression, line 68.

12. Line 71: replace “the beneficial...probiotics” by “their beneficial effects are...” ; add others mechanisms of action of probiotics

Response: We thank the reviewer for pointing out this issue and your suggestions. We have revised the expression and added mechanisms of action of probiotics in the text. Please see the revised expression, lines 75-77.

13. Line 72: give strains examples after “probiotics”

Response: We thank the reviewer for pointing out this issue. We have given the strains examples after probiotics in the text. Please see the revised expression, line 77.

14. Line 75: add “oral mucositis induced by chemo-radiotherapy”

Response: We thank the reviewer for your suggestion. We have added the “oral mucositis induced by chemo-radiotherapy” and the corresponding reference in the text. Please see the revised expression, lines 80-81.

VERSION 2 – REVIEW

REVIEWER	Liu, Shan The First Affiliated Hospital of Zhejiang Chinese Medical University
REVIEW RETURNED	26-Sep-2022

GENERAL COMMENTS	I appreciate the meaningful work done by the team. The research question is interesting and scientific sounds.I agree this manuscript to publish.
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REVIEWER	Thornley, Simon The University of Auckland, Section of Epidemiology and Biostatistics
REVIEW RETURNED	11-Oct-2022

GENERAL COMMENTS	<p>I agree with the author's interpretation of no obvious publication bias, however, in the abstract the line "There was no risk of publication bias" is puzzling. It should read "There was no evidence of publication bias".</p> <p>The leave-one-out analysis does not address the issue of the inconsistency in effect between different outcome measures. This is a broader issue for interpretation, since if there were a consistent benefit for various different outcomes, this would be more persuasive evidence for causation, according to the Bradford-Hill criteria. I believe a comment to this effect should be made.</p>
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VERSION 2 – AUTHOR RESPONSE

Responses to the reviewer's comments:

For reviewer 3

I appreciate the meaningful work done by the team. The research question is interesting and scientific sounds. I agree this manuscript to publish.

Response: We appreciate your taking time out of your busy schedule to review our manuscript. We also appreciate your recognition of our research.

For reviewer 4

Dear reviewer:

We thank you for the positive and constructive suggestions on our manuscript. The comments are all valuable and helpful for revising and improving our paper. We have studied all comments carefully and have made conscientious corrections. Please see below for the point-point responses to your comments. These responses to the reviewers' comments in bold blue text are as follows. Revised portions are marked in red in the manuscript.

1. I agree with the author's interpretation of no obvious publication bias, however, in the abstract the line "There was no risk of publication bias" is puzzling. It should read "There was no evidence of publication bias".

Response: We thank you for pointing out this issue. We have revised the expression. Please see the revised expression, lines 31, 239, 254.

VERSION 3 – REVIEW

REVIEWER	Thornley, Simon The University of Auckland, Section of Epidemiology and Biostatistics
REVIEW RETURNED	27-Oct-2022
GENERAL COMMENTS	Happy with responses.