

PEER REVIEW HISTORY

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ARTICLE DETAILS

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| TITLE (PROVISIONAL) | Use of probiotics to correct dysbiosis of normal microbiota following disease or disruptive events: a systematic review. |
| AUTHORS | McFarland, Lynne |

VERSION 1 - REVIEW

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| REVIEWER | Dan Merenstein Georgetown University, USA I have been an expert witness for a few probiotic products. |
| REVIEW RETURNED | 27-Mar-2014 |

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| GENERAL COMMENTS | <p>Overall a very important and interesting topic. They did a tremendous amount of work and really should be commended for undertaking this work.</p> <p>My main concern is that there is so much data presented that it confuses the reader. For example here is the abstract Results: 63 trials (with 69 treatment arms) are included. Complete restoration of the microbiota was found in 83% of 12 probiotic products, altered microbiota was documented in 56% of 18 probiotics and no change in microbiota was found in 79% of 19 probiotics. Clinical efficacy was associated with strains capable of restoration of the normal microbiota.</p> <p>Conclusions: Only five (10%) of the 49 probiotic strains have evidence for normal microbiota restoration or alteration with supportive clinical efficacy trial results. The health claim for correctingdysbiosis is poorly supported for most probiotic strains and requires further research.</p> <p>This is not clear at all, in fact there is a # 10% in the conclusion that is not in the results. This totally confuses the reader. In general the entire paper is way too long. That said it is a great paper that just needs shortened and clarified. I think a lot of what you present can just be linked to a website as the mass majority of readers wont want or need that info.</p> <p>Few other minor points.</p> <p>They state this in the intro and something similar in the Discussion, "In the U.S., unlike approved prescription drugs, which are regulated by the Food and Drug Administration (FDA), probiotics are typically available as over-the-counter medications or as dietary supplements and thus are limited to 'structure or function health claims' and are not permitted to claim to 'treat' or 'cure' disease." This is not entirely</p> |
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| | <p>true as probiotics can be drugs, medical foods, regular foods or supplements.</p> <p>Line 29 needs rewritten.</p> <p>They state this in Results but do we know exactly what is a normal biota? “The study design with the highest quality capable of documenting the recovery of normal microbiota due to a probiotic treatment requires that subjects be enrolled with a normal, undisrupted microbiota”</p> <p>I am not sure this is correct, “The U.S. Food and Drug Administration has struggled with appropriate evidence-based health claims for probiotic products a...” I tried to look up the link but it didn’t work. The word struggled is strange is that really what the FDA stated?</p> <p>As important as I think this study is I feel it may be nearly outdated, at they state, “Most of the studies (80%) using Model A to document restoration of the normal microbiota only used microbiologic culturing techniques” I don’t think anyone is still using the older methods.</p> <p>I am not comfortable enough with the stats for this type of paper</p> |
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| REVIEWER | Ger Rijkers University College Roosevelt, Middelburg, The Netherlands |
| REVIEW RETURNED | 16-Apr-2014 |

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| GENERAL COMMENTS | <p>This paper gives a comprehensive overview of the published studies on the effects of probiotics on restoring or maintaining a balanced gut microbiota.</p> <p>I only have a couple of remarks:</p> <p>1) I think that EFSA has accepted only 1 or 2 health claim applications for probiotics, and therefore the rejection rate is >> 80%</p> <p>2) restoration or maintainance of a balanced gutmicrobiota as such is not accepted by EFSA as a health clean. Only in the context of a functional effect, such as AAD. This should be stated more clearly.</p> <p>3) Finally: probiotic effects are not only species specific but eve strain specific. In the majority of cases (text as well as tables) the strain is not indicated, with just a few exceptions. I recognize that in many publications the strain identifiacion is lacking, but that is an Achillis heel of many studies on probiotics.</p> |
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Dan Merenstein

Institution and Country Georgetown University, USA

Please state any competing interests or state ‘None declared’: I have been an expert witness for a few probiotic products.

3. Overall a very important and interesting topic. They did a tremendous amount of work and really should be commended for undertaking this work.

Thank you for your kind comment!

4. My main concern is that there is so much data presented that it confuses the reader. For example here is the abstract Results: 63 trials (with 69 treatment arms) are included. Complete restoration of the microbiota was found in 83% of 12 probiotic products, altered microbiota was documented in 56% of 18 probiotics and no change in microbiota was found in 79% of 19 probiotics. Clinical efficacy was associated with strains capable of restoration of the normal microbiota. Conclusions: Only five (10%) of the 49 probiotic strains have evidence for normal microbiota restoration or alteration with supportive clinical efficacy trial results. The health claim for correcting dysbiosis is poorly supported for most probiotic strains and requires further research.

This is not clear at all, in fact there is a # 10% in the conclusion that is not in the results. This totally confuses the reader. In general the entire paper is way too long. That said it is a great paper that just needs shortened and clarified. I think a lot of what you present can just be linked to a website as the mass majority of readers wont want or need that info.

The abstract and text have been revised for clarity and extraneous text was deleted when possible. As this is the first time this body of literature has been assessed for the ability of probiotics to correct dysbiosis, sufficient data needs to be presented to allow readers to assess this relationship. Unfortunately, no website exists to link this data.

5. Few other minor points. They state this in the intro and something similar in the Discussion, "In the U.S., unlike approved prescription drugs, which are regulated by the Food and Drug Administration (FDA), probiotics are typically available as over-the-counter medications or as dietary supplements and thus are limited to 'structure or function health claims' and are not permitted to claim to 'treat' or 'cure' disease." This is not entirely true as probiotics can be drugs, medical foods, regular foods or supplements.

Clarified and revised as suggested, See Introduction, 1st paragraph, page 4. I agree, probiotics may be available as drugs (no current probiotics have achieved FDA approval for this yet), medical foods (although this isn't really a good fit under the regulations of medical foods) or dietary supplements. However, probiotics should not be classified as "regular foods" if they state they are probiotics on their labels.

6. Line 29 needs rewritten.

Revised as suggested, see Introduction, 1st paragraph, page 4, "Probiotics are active during this susceptible window..." .

7. They state this in Results but do we know exactly what is a normal biota? "The study design with the highest quality capable of documenting the recovery of normal microbiota due to a probiotic treatment requires that subjects be enrolled with a normal, undisrupted microbiota"

Excellent point! The issue of a lack definition for 'normal' microbiota has been added to the text. See: Introduction (3rd paragraph, page 5), Methods (see outcomes and definitions, page 7) and Discussion (see Strengths and Weaknesses, page 22).

8. I am not sure this is correct, "The U.S. Food and Drug Administration has struggled with appropriate evidence-based health claims for probiotic products a..." I tried to look up the link but it didn't work. The word struggled is strange is that really what the FDA stated? 'Struggled' is not a direct quote from the FDA document quoted, rather it is the author's appreciation of the long duration of debate and meetings that the FDA has held to agree on a consensus for these regulations. See revised text in Discussion (page 17). The reference (#108) has been corrected.

9. As important as I think this study is I feel it may be nearly outdated, at they state, "Most of the studies (80%) using Model A to document restoration of the normal microbiota only used microbiologic culturing techniques" I don't think anyone is still using the older methods.

Currently, not all researchers have access to metagenomic tools in their laboratories. Some of the more recent trials still report doing microbiologic cultures (as recently as 2010 in this paper).

10. I am not comfortable enough with the stats for this type of paper

As this is a descriptive paper and a systematic review, the typical statistics used in meta-analysis were not appropriate. The only statistical test used was the chi-squared test to compare frequencies of single strains versus multiple strains (see Results, page 11).

Reviewer: 2

Reviewer Name Ger Rijkers

Institution and Country University College Roosevelt, Middelburg, The Netherlands

Please state any competing interests or state 'None declared': None declared

This paper gives a comprehensive overview of the published studies on the effects of probiotics on restoring or maintaining a balanced gut microbiota.

I only have a couple of remarks:

11) I think that EFSA has accepted only 1 or 2 health claim applications for probiotics, and therefore the rejection rate is >> 80%.

Revised as suggested (see Introduction, 1st paragraph, page 4).

12) restoration or maintenance of a balanced gutmicrobiota as such is not accepted by EFSA as a health claim. Only in the context of a functional effect, such as AAD. This should be stated more clearly.

Revised as suggested (see Introduction, 1st paragraph, page 4 and in the Discussion, 1st paragraph, pages 17-18).

13) Finally: probiotic effects are not only species specific but even strain specific. In the majority of cases (text as well as tables) the strain is not indicated, with just a few exceptions. I recognize that in many publications the strain identification is lacking, but that is an Achilles heel of many studies on probiotics.

Excellent point! Please see revised Tables 1-4, where probiotic strains are provided where reported in studies. Note, not all studies report strain identification. This issue has also been added to the Discussion (see Opportunities for Future Research, 3rd paragraph, page 21).

VERSION 2 – REVIEW

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| REVIEWER | Dan Merenstein Georgetown University USA Have been a paid expert on a few class action lawsuits |
| REVIEW RETURNED | 04-Jun-2014 |

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| GENERAL COMMENTS | answered all concerns. I do feel it would work better if journal allowed for some data only on website. |
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