Author's response to reviews

Title: Immune-modulatory Effects of dietary Yeast Beta-1,3/1,6-D-glucan

Authors:

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Version: 2 Date: 13 March 2014

Author's response to reviews: see over
Review title: Immune-modulatory effects of dietary yeast beta-1,3/1,6-D-glucan

Authors: Heike Stier, Veronika Ebbeskotte and Joerg Gruenwald

Point-to-Point response to the concerns of the reviewer

Editorial requirements:

Requesting Acknowledgement Section

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Authors’ answer
We have added two additional paragraphs at the end of the manuscript:

Authors' Information
HS is working as a Scientific Consultant for the CRO analyze & realize GmbH (Germany); JG is the founder of the CRO analyze & realize GmbH (Germany). VE is working as a scientist in the technical service of the animal nutrition department of Leiber GmbH (Bamsche, Germany).

Acknowledgements
We thank I. Wohlfahrt for correction of the manuscript and editing of the English language.
Reviewer 1:

Reviewer's report
Title: Immune-modulatory effects of dietary yeast beta-1,3/1,6-D-glucan
Version: 1
Date: 8 December 2013
Reviewer: Martin O. Weickert

Reviewer's report:
Stier and colleagues provide an interesting and up to date about the immunomodulating effects of yeast beta 1-3, 1-6 D Glucans.

Comments
1. Authors performed a narrative review of the literature. It will be important to give the reader an idea of how the respective studies were selected (e.g. review of which of the data bases, which exact search criteria were used for selection, e.g. presence of a control group, number of subjects, duration of the study, randomised controlled studies etc; and exact criteria for exclusion of studies from this review)

Authors’ answer
We made some modifications within the text to make our selection more retraceable:
Since the results of different β-glucans are heterogeneous we focused on insoluble yeast β-glucans, especially the highly purified, well characterized and intensively studied β-glucans from Spent Brewers’ Yeast (Yestimun®) (see page 4 last paragraph of the manuscript).
We compared the results to the other dietary, insoluble yeast β-glucans preparation available on the market. Only randomized, controlled trials were considered for the purpose of this review. Studies investigating other aspects than the immune system or studies with soluble β-glucans were excluded.

2. Authors are focusing on Yestimmun. A clear statement must be given in the article why authors focus on this specific product. Other comparable products might be around and should be covered as well.

Authors’ answer
Please see also answer to comment 1: We searched in the Pubmed database for other comparable products (insoluble yeast β-glucans preparations with controlled clinical trials in the field of common cold/infection). The cited studies were the only which suited our criteria. Hence, our focus was not exclusively on (Yestimun®)

3. Potential conflicts of interests need to be clearly stated, e.g. the fact that Leiber GmbH has a commercial interest in this study is not obvious.

Authors’ answer
We complied with the reviewers recommendations and added some more information accordingly within the section Competing interests: “This work has been funded by Leiber
GmbH (Barmsche, Germany) the manufacture of the yeast β-glucan preparation Yestimun®.”

“VE is an employee of Leiber GmbH”.

4. Some of the paragraphs would benefit from more moderate statements; e.g. instead of “not any signs of” could be replaced by “no signs of”; or “did not lead to any adverse effects” could be replaced by “no adverse effects” and so on. It also should be appreciated that long term beneficial effects of yeast beta 1-3, 1-6 D Glucans, as well as absence of long term adverse effects are unknown.

Authors’ answer
We complied with the reviewers’ recommendation and rephrased the sentence accordingly. We mainly removed the word “any” as suggested and used more moderate statements instead.

5. The review would greatly benefit from a Figure, pointing out the potential mechanisms that may be involved at conveying Immunomodulatory functions of yeast beta 1-3, 1-6 D Glucans.

Authors’ answer
In our article we tried to focus on general comparison between various β-glucans, the mode of action is one of them. Since the mode of action was not the main focus of the review, we cited the basic literature, which explains the mode of action in more detail (see page 6 and 7). Therefore we have refrained from providing an incomplete figure.

Quality of written English:
Needs some language corrections before being published

Authors’ answer
Has been done.

Statistical review:
No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
This reviewer had received partial funding from Leiber Inc, Bramsche Germany, in 2006; for the conduction of a intervention study investigating a yeast derived (1,3)(1,6)beta-glucan of the company
Reviewer 2:

Reviewer's report
Title: Immune-modulatory effects of dietary yeast beta-1,3/1,6-D-glucan
Version: 1
Date: 19 December 2013
Reviewer: matam Vija-kumar

Reviewer's report:
Minor essential revisions:
The review by Stier et al ‘Immunomodulatory effects of dietary yeast beta 1,3/1,6-D glucan’ covered recent literature mostly on respiratory infections. Introduction is succinct and with appropriate published clinical trials and conclusion. There are numerous changes need to be made as addressed below.

Comments:
1. It requires editing for grammar and typo errors
2. Introduction second line: change strength to strengthen
3. Page 6: PRR are expressed not only by immune cells but also non-immune cells (epithelia, endothelia) and not always cell surface but also expressed in endosomes (TLR3, 7, 8 and 9)
4. PAMP is old terminology and also misleading: Change PAMP to MAMP: Microbial-Associated Molecular Pattern
5. Page 6: Ref 18: induced rat thymocytes ..... what type of induction ?
6. M cells located: add ‘in’
7. Page #7: Change synthetically synthesized to chemically synthesized
8. Page 8: Phagozytosis or phagocytosis?
9. Page 8: ‘The activation of the CR3 leads than in combination ..... Do not make any sense
10. [Previously called Biolex-Beta HP]: Mentioned twice on Page 8 and 11
11. Page 9: LPS is not a lectin
12. Page 9: change lack of Vitamins to specific vitamin deficiency

Authors’ answer
All this helpful comments were addressed and the corresponding sections within the text were changed accordingly. We only haven’t changed point 7, since the term “synthetic glucan” was used by the authors of that reference.

Quality of written English:
Needs some language corrections before being published

Authors’ answer
Has been done.

Statistical review:
No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
None
Reviewer 3:
Reviewer's report
Title: Immune-modulatory effects of dietary yeast beta-1,3/1,6-D-glucan
Version: 1
Date: 29 December 2013
Reviewer: Girish Kirimanjeswara

Reviewer's report:
This is a well-researched and well-written synopsis of mechanism and usefulness of yeast beta-glucans. Although, it mainly focuses on Yestumin, the authors do write about a few other preparations.

Major Compulsory Revisions:
There are number of grammatical errors in the manuscript which need to be addressed before publication.

Authors’ answer
Has been done.

Quality of written English:
Needs some language corrections before being published

Authors’ answer
Has been done.

Statistical review:
No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
None.
Reviewer 4:
Reviewer's report
Title: Immune-modulatory effects of dietary yeast beta-1,3/1,6-D-glucan
Version: 1 Date: 6 January 2014
Reviewer: Venkatesh Hegde

Reviewer's report:
This review article focuses on an important area of immunomodulation by yeast-derived beta glucans and its significance which could be interesting to the readers of ‘Nutrition Journal’. The insoluble or particulate [1,3]-[1,6] branched chain # glucans are believed to possess more profound immunomodulatory properties compared to other soluble glucans. The major focus in this article is on review of animal studies and human clinical trials using Yestimun®, a proprietary Brewer’s yeast-derived particulate beta glucan preparation. The need for and importance of such a focused review is reasoned based on the significance of immune stimulating effects of insoluble 1,3/1,6 # glucans as well as variation in functionality of such glucans depending on the quality, purity, average molecular mass of the preparations as well as on the manufacturing processes used. The topic as such is important.

Major Compulsory Revisions
1. While the favorable report from European Food Safety Authority on the safety of the product (“EFSA Panel on Dietetic Products NaAN: Scientific Opinion on the safety of ‘yeast beta-glucans’ as a Novel Food ingredient. EFSA Journal 2011, 9:2137”[22 pp]) has been cited by the authors, the following two reports from the same panel have not been mentioned: Scientific Opinion on the substantiation of a health claim related to Yestimun® and immune responses pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2010; 8(5):1607 [11 pp.]. doi:10.2903/j.efsa.2010.1607.
   In this report the Panel concludes that a cause and effect relationship was not established between the consumption of Yestimun® and the initiation of appropriate innate and adaptive immune responses.
   Secondly, Scientific Opinion on the substantiation of a health claim related to Yestimun® and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2013;11(4):3159 [12 pp.]. doi:10.2903/j.efsa.2013.3159 in which the Panel notes that in the absence of an effect of Yestimun® in humans on defense against pathogens in the upper respiratory tract the submitted human, animal and in vitro studies pertaining to a possible mechanism by which Yestimun® could exert the claimed effect do not provide any scientific evidence for the substantiation of the claim. Since these reports from the expert panel are based on review of data/ evidence as well as conclusions from some of the important studies/ trials on Yestimun discussed in this article, these reports should be cited and discussed and the limitations of the studies in purview of these should be elaborated more thoroughly to arrive at more balanced conclusions.

Authors’ answer
We changed this as recommended and included the two EFSA opinions on Yestimun within the appropriate sections (please refer to page 13 last paragraph as well to the conclusion).

2. Authors state that they aim to ‘present the in vitro and in vivo data, and results from
clinical trials on Yestimun and compare with other yeast dietary β-glucan findings’. However, except for listing of brief descriptions of clinical trials on other glucans in section 4.1, an in-depth comparative discussion of studies and findings is lacking.

Authors’ answer
We have included some more information regarding the studies described under section 4.3. There is now comparable information on the studies performed with Yestimun and the other β-glucans preparation Wellmun WGP®.

3. Information and discussion on the average molecular mass of proprietary Yestimun and other dietary yeast β-glucans and its significance on the observed structure-function relationship is lacking and should be included. Isn’t this (intermediate/high molecular mass) an important factor contributing to their biological activity? and an important difference among β-glucans derived from different sources and different manufacturing processes?

Authors’ answer
This is a very important point, since different β-glucan induce different immune reactions. We tried to address this as good as it gets. However, for insoluble, particulate β-glucans it is nearly impossible to determine the molecular mass. The molecular mass can only determine for soluble beta-glucans. To determine the molecular weight of particulate insoluble beta-glycans they have to be transformed into a soluble form (which probably also changes the molecular weight). For Yestimun so far no determination of the MW has been performed.

In this article we try to elucidate effects of insoluble, particulate yeast β-glucans. Therefore no molecular mass is given. To compare these insoluble particulate β-glucans we have included the relative linkage percentage from β-1,6 glucan (for Yestimun as well a for the other preparations if available) and the information on the manufacturing process (at least for Yestimun).

Since the structure function relationship for is an very important issue we try to explain the structure function differences of β-glucans (at least for dectin binding) by citing the article by Adams et al., 2008. They analyzed synthetically designed β-glucans regarding structure, molecule size, branching etc. and the effect on dectin 1 receptor binding.

Minor Essential Revisions:
There are a number of typos and grammatical errors throughout the manuscript. The article needs to be carefully edited for such errors and revised to improve language and clarity.

Authors’ answer
Has been done.

Quality of written English:
Needs some language corrections before being published

Authors’ answer
Has been done.

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