Reviewer’s report

Title: A yeast fermentate improves gastrointestinal discomfort and constipation by modulation of the gut microbiome: results from a randomized double-blind placebo-controlled pilot trial.

Version: 0 Date: 03 Jul 2017

Reviewer: Gerard Mullin

Reviewer's report:

Summary.

The authors report that a yeast fermentate (that is neither a probiotic nor prebiotic fiber) improves gastrointestinal discomfort and constipation by modulation of the gut microbiome in a randomized double-blind placebo-controlled pilot trial. In IBS and its subtypes, the biodiversity is condensed, pathogens are increased and several beneficial species are less abundant. Overall, the gut ecology in IBS is dysbiotic and several lines of evidence show that certain strains of probiotics may ameliorate IBS symptoms. Relative to other subtypes, IBS-C has a paucity of data for studying the benefit of probiotic species in relieving IBS symptomatology. In the submitted manuscript, the authors utilized an EpiCor fermentate which has been shown to have prebiotic-like properties. The study conducted on 80 subjects with IBS-C with randomization in a stratified manner according to symptom severity, resulting in two subgroups of patients: severe and moderate with a 2-week run-in and 6-week intervention (GI symptoms, QOL, Stools). EpiCor fermentate led to a significant improvement of GI symptoms in the moderate subgroup, stool consistency was observed for the total population as well as for the severe subgroup, and a nearly significant increase in stool frequency was detected for the total cohort. These effects were accompanied by an improvement in the constipation-associated quality of life and general perceived stress, particularly in the moderate subgroup. Members of the families Bacteroidaceae and Prevotellaceae, two groups of bacteria that have been previously reported to be deficient in constipated patients, were found to increase with EpiCor fermentate in the severe subgroup. In the moderate subgroup, a significant increase in the beneficial and protective mucin-inducing Akkermansia muciniphila was observed.

Critique.

Fiber is known to help hasten gut transit and improve the biodiversity of the gut microbiome in healthy subjects and in a variety of disease states. The EpiCor fermentate appeared to provide several benefits to moderate and severe IBS-C subjects with measurable improvements in the gut ecology.
Line 102. Is there evidence in this paper that gut barrier function is altered by EpiCor fermentate? If not, please rephrase as the sentence suggests so. Reference 24 used to support the statement does not demonstrate barrier function is altered by this fermentate.

Line 138. The use of probiotics, prebiotics and synbiotics are excluded for 30-days. There are many studies shown the 'washout' time for probiotics can take weeks after cessation. Perhaps address in the methods or discussion.

Line 142. The 5-point GI symptom scale used to assess impact-was this a validated tool such as the IBSSS? Reference 14 is cited.

Line 161. Are any of the university-based authors have commercial ties to the sponsors of the study (Prodigest BVBA Belgium, Embria USA)?

Lines 184-186. The sponsor labelled all bottles but who conducted the randomization using randomization.com? According to line 226, the sponsor labelled all bottles AND conducted the randomization.

Line 372. EpiCor and placebo did not differ (significantly) for its effects on symptoms on those with severe global symptomatology but did show differences in subgroups. Could the placebo have altered GI symptomatology? It was shown to increase the F/B ratio (line 416, Figures 6a, a*) which portends to worse symptoms and has FODMAP subcomponents (oligosaccharides).

Lines 560-1. Serotonin and gastric are referenced to influence neurogastrointestinal function. Consider peptide YY and GLP-2 which are enteric hormones which alter motility and are influenced by SCFA and fermentates.

Lines 625-6. "For instance, a significant increase in Akkermansia muciniphila was observed within this subgroup." Please define "This subgroup" in the sentence.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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None

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