Postbiotic Treatments for Alcohol-Associated Intestinal Dysbiosis

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Introduction

Postbiotics are the metabolites, and structural components produced by beneficial bacteria. These include bacterial-derived:

- Indoles
- Short-chain fatty acids
- Secondary Bile acids
- LPS, LTA, etc.

Postbiotics have been shown to be improve alcohol-associated:

- Gut barrier dysfunction
- Intestinal dysbiosis
- Inflammation

Postbiotic Treatments for Alcohol-Associated Liver Disease

Several studies have been conducted to examine the effects of postbiotics on ALD. Two prime examples of the beneficial effects of postbiotics on ALD are the use of Butyrate and Indole-3-acetic acid (IAA).

Butyrate is a SCFA that is produced by the fermentation of fiber by the intestinal microbiota.

Indole-3-acetic acid (IAA) is a bacterial catabolic product of tryptophan metabolism.

The study by Han, et al., showed that alcohol-fed animals treated with butyrate had mitigated:

- LSEC damage with Beta-Catenin significant decreases
- Gut microbiota phylogenetic and beta diversity increased

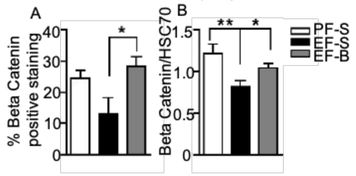


Fig. 1. (A) Beta-Catenin immunofluorescent images and (B) Beta-Catenin immunoblot results quantified. * p<0.05, ** p<0.001

The study by Hendrikx, et al., showed that alcohol-fed animals treated with IAA had mitigated:

- Inflammation and intestinal barrier damage
  - IL-22 levels increased significantly
- Bacterial translocation to liver
  - REG3G increased significantly
  - Total hepatic bacteria decreased

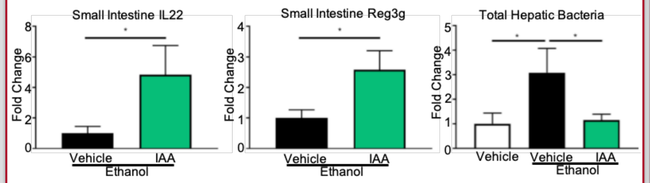


Fig. 2. Expression of IL22 and Reg3g mRNA in ileum of mice following chronic-binge alcohol diet with IAA supplement shown. Total bacteria in liver measured by qPCR for 16s rRNA results shown. * p<0.05

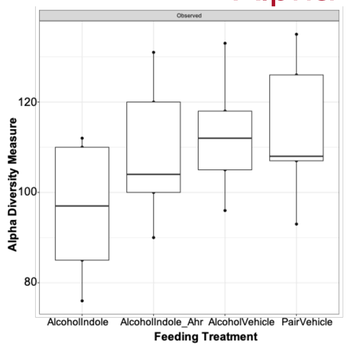
Does indole effect the composition of the intestinal microbiota in alcohol-fed mice?

Methods: Microbiome Analysis

Microbiome analysis was performed using R with data from indole treatment and these R packages: DADA2, phyloseq, DEseq2, ggplot, and vegan.

- DNA sequencing of the 16s rRNA gene was performed on an Illumina MiSeq
- DADA2 was used to filter, trim and produce an OTU sequence table from the raw sequence reads.
- Phyloseq was used to calculate alpha and beta diversity.
- DESeq2 was used to determine the differentially abundant genera.
- Significant was determined via PERMANOVA analysis using vegan.
- All plots were generated using ggplot.

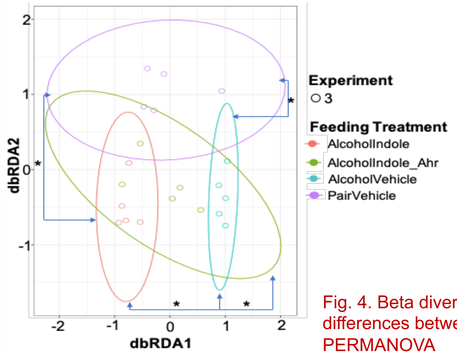
Alpha Diversity



There were no significant differences in alpha diversity between the groups.

Fig. 3. Alpha diversity plot shows the number of species present in each sample separated by treatment group.

Beta Diversity

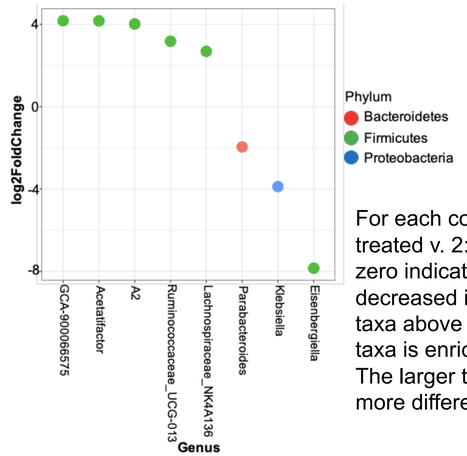


Significant differences in beta diversity were observed between:

- Pair-fed mice and indole treated mice
- Alcohol-fed and pair-fed mice
- Indole-treated and alcohol-fed mice
- Indole and AHR inhibitor-treated and alcohol-fed mice

Fig. 4. Beta diversity plot shows phylogenetic differences between the different groups. * p<0.05 via PERMANOVA

Differentially Abundant Genera



For each comparison (1: indole-treated v. 2: alcohol-fed): Taxa below zero indicates that the taxa is decreased in 1 compared to 2, while taxa above zero indicates that the taxa is enriched in 1 compared to 2. The larger the taxa number indicates more differences in genera.

Fig. 5. Genus plot shows the differentially abundant genera between indole-treated and alcohol-fed mice. Significantly differentially abundant taxa. Adjust P value < 0.05 by negative binomial generalized linear models for each taxa and Wald test for significances.

Conclusions

- Postbiotic treatments have proven to be a potential treatment for alcoholic liver disease and intestinal dysbiosis.
- Butyrate treatments improved phylogenetic and beta diversity, as well as LSECs function.
- Indole treatments reduced bacterial translocation and improved inflammation and intestinal barrier damage.
- Microbiome analysis showed significant differences in beta diversity and abundant genera between indole-treated and alcohol-fed mice. Evidence suggests indole supplementation affects intestinal microbiota.
- In the future, studies need to further assess postbiotic treatments in humans for longer durations of treatment and investigate possible side effects and best treatment combinations.

References

- Han, S. H., Suk, K. T., Kim, D. J., Kim, M. Y., Baik, S. K., Kim, Y. D., et al. (2015). Effects of probiotics (cultured lactobacillus subtilis/Streptococcus faecium) in the treatment of alcoholic hepatitis: Randomized-controlled multicenter study. *European Journal of Gastroenterology & Hepatology, 27*(11), 1300-1306.
- Hendrikx, T., Duan, Y., Wang, Y., Oh, J. H., Alexander, L. M., Huang, W., et al. (2019). Bacteria engineered to produce IL-22 in intestine induce expression of REG3G to reduce ethanol-induced liver disease in mice. Gut, 68(8), 1504-1515.