PROPOSAL

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TITLE

Lactobacillus Plantarum IS 10560 Supplementation in Women With Functional Constipation: Molecular Profile of Fecal Microbiome With NGS Method

INVESTIGATORS

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BACKGROUND

Functional constipation as a part of Irritable Bowel Disorder is a physiological malfunctioning mechanism that occurs in the digestive tract where one of the main functions of the luminal gastrointestinal (intestinal) microbiota experiences a balance disorder that has an impact on the disruption as well as the expression of Short Chain Fatty Acid (SCFA) excreted by the intestinal microbiota. The imbalance of microbiota in the digestive tract will affect metabolites of Short Chain Fatty Acid (SCFA) as a result of fermentation of carbohydrates and proteins in the lower digestive tract. SCFA has a role in physiological processes (cytokine formation also activates nuclear factor κB (NF κB), maintains mucosal defence balance, neurotransmission regulation (SERT, TPH1 and serotonin), affects peristalsis and motility) Measurement of SCFA titers is one of the scientific bases It was established in the parent study to look at the mechanisms underlying the improvement of symptoms and signs of functional constipation with the supplementation of probiotics Lactobacillus plantarum IS 10506 indigenous to fermented West Sumatra curd.

OBJECTIVE

1. Test the role of Short Chain Fatty Acid (SCFA) in relation to improvement of symptoms and signs of Jakarta Women with Functional Constipation
2. Test the concentration ratio of SCFA (Acetate, propionate and butyrate) as SCFA profiles of Jakarta Women with Functional Constipation with measurements GCMS and GCFID
3. Test the relevance of changes in SCFA titers with supplementation probiotics during the 3-week period of supplementation of Lactobacillus plantarum IS 10506

METHOD

1. Design

This study is a laboratory experimental study with two blind double randomized clinical trials using female subjects with functional constipation. Metabolite analysis of Short Chain Fatty Acid (SCFA) with GCMS is carried out after supplementation of indigenous Lactobacillus plantarum IS 10506 and placebo (2 variations of treatment) for three weeks. The analysis is carried out at the DKI Jakarta Regional Health Laboratory (DKI Jakarta Labkesda).

2. Interventions

Drug : Fermented milk containing probiotic Lactobacillus plantarum for three weeks
Placebo : Fermented milk containing placebo for three weeks

3. Patients

Inclusion Criteria

- Women aged 18 to 60 years
- Being declared healthy based on initial examination and the Structured Interview Questionnaire (SIQ)
- Having the symptoms and signs of functional constipation refer to ROME-IV criteria
- Able to communicate well
- Able to consume 1 bottle of fermented milk each day for three weeks
- Not using antibiotic no later than one week before supplementation

Exclusion Criteria

- Diagnosed with functional bowel disorder
- Using anesthesia at least 4 weeks before treatment
- Having a serious pathological disorder (carcinoma)
- During healing phase of acute gastrointestinal disorders at least 4 weeks before treatment
- Having severe heart disease
- Taking chronic medications such as antidepressants or analgesics

4. Procedure

Samples will be taken from 62 (plus 10% DO predictions to 70 people) women from Jakarta community with a diagnosis of Functional Constipation based on ROME-IV established by the Medical Team of the Gastroenterology Department FK UI.

Subjects will be given supplies of fermented milk containing probiotic or placebo 1-3 days/time of arrival of researchers while monitoring compliance. Supplement is taken one bottle/day. During the supplementation of fermented milk, it should be kept in the refrigerator to a minimum of 8^0C.

Functional constipation symptom improvement parameter (PAC Sym and PAC QoL), faecal samples, and blood samples will be collected three times (pre-interval-post). Faecal samples will be obtained using pot faeces then will be inserted in the cool box and ice pack stored in -20^{0}C freezer. From the faecal samples, SCFA titer will be analyzed by Gas chromatography–mass spectrometry (GCMS) and microbiome profile will be analyzed with NGS (Next Gen Sequencing) method with MiSEq Reporter software (MSR).

5. Statistical Analysis

For normally distributed data Kolmogorov-Smirnov, Non parametric test Mann-Whitney will be used to evaluate the differences between treatment and SCFA titer. Spearman Rho test will be performed to evaluate the correlation between variation of treatment and SCFA titer and functional constipation symptom improvement parameter. P value < 0.05 is considered statistically significant.

6. Ethical Committee Approval

Approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia must be obtained before starting the trial.

REFERENCES

1. Drossman DA, Hasler WL. Rome IV - Functional GI disorders: Disorders of gut-brain interaction. Gastroenterology. 2016;150(6):1257–61. http://dx.doi.org/10.1053/j.gastro.2016.02.032
2. Schoenfeld PS. Advances in IBS 2016 : A Review of Current and Emerging Data. Gastroenterol Hepatol (N Y). 2017;12(8):S3–11.
3. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology. 2016;150(6):1393–1407e5. http://dx.doi.org/10.1053/j.gastro.2016.02.031
4. Stephanie NS, Mawe GM. Non-conventional features of peripheral serotonin signalling — the gut and beyond. Nature Reviews Gastroenterology & Hepatology.2017:51
5. Zhu L, Liu W, Alkhouri R, Baker RD, Bard JE, Quigley EM, et al. Structural changes in the gut microbiome of constipated patients. Physiol Genomics. 2014;46(18):679–86. doi:10.1152/physiolgenomics.00082.2014.
6. Schippa S, Conte M. Dysbiotic Events in Gut Microbiota: Impact on Human Health. Nutrients 2014, 6, 5786-5805; doi:10.3390/nu6125786.
7. National consensus on the management of constipation in indonesia 2010.Indonesian Society of Gastroenterology (ISG). Acta Med Indones. 2011 Oct;43(4):267- 74.(abstrak)
8. Wald A, Mueller-lissner S, Kamm MA, Hinkel U, Richters E, Schujit C, Mandel KG. Survey of laxative use by adults with self-defined constipation in South America and Asia: a comparison of six countries. Aliment Pharmacol Ther . 2010;31: 274–284 doi:10.1111/j.1365-2036.2009.04169.x