

# The Role of Probiotics in Lowering Severity of Symptoms in Urban Women with Functional Constipation: A Randomized Double-Blind Controlled Trial

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# The Role of Probiotics in Lowering Severity of Symptoms in Urban Women with Functional Constipation: A Randomized Double-Blind Controlled Trial

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**Abstract.** Functional constipation is one of the most common gastrointestinal disorders worldwide, especially in women. Probiotic consumption is commonly used to alleviate symptoms of constipation but the mechanism and the result remain unclear. Hence, this study was conducted to assess the effect of probiotics on constipation symptoms using PAC-SYM© (Patient Assessment of Constipation Symptoms) questionnaire. This was a randomized double-blind controlled trial (RCT) study, consisting of 73 subjects of urban women with functional constipation. This study compared three weeks of probiotic (*Lactobacillus plantarum* IS 10506) administration with placebo and evaluated improvements in PAC-SYM© scores before and after intervention. The subjects were divided into two groups, probiotics group (n = 34) and placebo group (n = 39), then were compared for their mean difference of PAC-SYM© scores. Our study suggested improvements of symptoms after three weeks of probiotic administration, as shown by the total score of PAC-SYM© (mean difference 7.65, 95% CI 3.1-12.20; p=0.001) along with three domains of PAC-SYM©, abdominal symptoms (mean difference 3.0, 95% CI 1.3-4.7; p=0.001), rectal symptoms (mean difference 1.62, 95% CI 0.12-3.13; p=0.034) and stool symptoms (mean difference 3.02, 95% CI 0.58-5.45; p=0.016). Probiotics was superior than placebo in improvements of constipation symptoms in urban women with functional constipation.

## INTRODUCTION

Constipation is a common health problem that affects 5.4% people in Germany and 17.7% people in the United States [1]. A study conducted in Cipto Mangunkusumo Hospital (RSCM) Jakarta, Indonesia from 1998-2005 showed 9% or 216 patients experienced constipation [2]. Another study conducted in Jakarta found 52.9% of 210 female workers had functional constipation [3]. In the United States, constipation leads to approximately 6.3 million outpatient visits and 5.3 million prescriptions annually [4]. The prevalence of constipation and efforts to manage

constipation is significantly higher in women ( $P < 0.05$ ). Women are more likely to use laxatives and seek medical care for the symptoms of constipation [5].

Constipation is characterized by unsatisfactory defecation that results from infrequent stools, difficult stool passage, or both. According to ROME IV Criteria, functional constipation can be diagnosed through diagnostic criteria which must include 2 or more following symptoms: straining, lumpy or hard stools (Bristol stool form scale 1 or 2), sensation of incomplete evacuation during more than 25% of defecations, manual manoeuvre to facilitate defecations (such as digital evacuation or support of the pelvic floor), and fewer than 3 spontaneous bowel movements per week. Those symptoms should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis [6].

Functional constipation can significantly impact the quality of life of the sufferers. A widely used questionnaire called Patient Assessment of Constipation Symptoms (PAC-SYM©) was developed as an important tool to assess the severity of patient-reported symptoms and to measure outcome in clinical trials of constipation. The questionnaire includes 12 questions about symptoms: abdominal, rectal, and stool [7].

Probiotics are commonly used to alleviate symptoms of constipation [8]. The effects of probiotics in constipation has been widely investigated both in human and animal studies. In this study, the probiotic used was *Lactobacillus plantarum* IS 10506 found in traditional fermented milk from Sumatra Barat, Indonesia. It possesses beneficial properties in human gastrointestinal system [9]. However, there is still uncertainty about the results and the mechanism of probiotics in relieving symptoms of constipation [10]. Therefore, the role of probiotic in lowering severity of symptoms in women with functional constipation was investigated.

## **METHODS**

### **Study Design**

This was a Randomized Double-Blind Controlled Trial (RCT) study conducted for 3 weeks, with double-blind procedures and parallel groups applied. This study was conducted at the Petamburan district in the capital city of Jakarta, Indonesia. All prospective subjects were screened for symptoms and signs of functional constipation using the ROME IV criteria. Each subject who fulfilled the inclusion criteria and were willing to complete this study had to fill out the informed consent form. All subjects were randomly divided into 2 groups, group A and group B, and were informed from the start that there were subjects who received placebo and probiotic. Both researchers and participants were blinded to allocation groups and were revealed only after the analysis was completed. Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia with the reference number 0092/UN2.F1/ETIK/2018 before the study was conducted.

### **Participants**

The research team carried out the recruitment of subjects actively by visiting homes and passively by inviting citizens who were experiencing constipation. Then, we screened according to the inclusion and exclusion criteria. All subjects were women, and declared eligible if they met the inclusion criteria while absent of any of the exclusion criteria. The inclusion criteria were women, being generally healthy, fulfilling the symptoms of constipation according to Rome IV criteria, not taking antibiotics a week before intervention, and not drinking other probiotic milk 2 weeks before or during research.[6] In contrast, the exclusion criteria were having certain disorders (e.g. malignancy, intestinal dysfunction and other) causing constipation, having a history of surgery or anesthesia in the last 4 weeks, taking chronic medications (e.g. antidepressants, analgesics, and others) and having severe heart problem. For reducing bias, subjects must not consume laxatives, other probiotics, antibiotics and drugs that affect bowel movements, in the last 1-2 weeks before starting intervention and measurement.

### **Intervention**

In the beginning all subjects were assessed for their general characteristics including body weight, height, age and blood pressure. The severity of symptoms was scored according to PAC-SYM©. For 3 weeks the subjects were given interventions of either probiotic or placebo. At the end of 3 weeks, the severity of symptoms was re-evaluated with PAC-SYM© and compared to the total mean difference. The probiotics used in this study were in the form of curds containing *Lactobacillus plantarum* IS 10506, made in strawberry flavour with a slightly pink colour, a thick

consistency, a slightly sour and sweet taste, and stored at -18°C. The placebo was made accordingly with slightly less viscosity. Each subject did not know which preparations contained probiotics or placebo. Both probiotics and placebo were kept frozen, and then drunk in a cold-liquid state at the same hour every day.

### **Outcomes**

In this study we assessed improvement in symptoms of constipation after probiotics administration when compared to placebo. All subjects were assessed with the PAC-SYM© questionnaire at the beginning of study as baseline value before intervention, and then were re-assessed after 3 weeks of intervention. The main aim of this study was to reduce the symptoms of constipation by administering probiotics as represented by the changes in PAC-SYM© final score. PAC-SYM© was developed by MAPI. The language and culture adaptation were validated into Indonesian in previous studies [11]. The PAC-SYM© score is divided into 3 domains *viz.* abdominal symptoms (Question 1-4), rectal symptoms (Question 5-7), stool symptoms (Question 8-12) and overall score, with a maximum value of 48 and minimum 0. The total scores before and after the intervention were compared to the average probiotic and placebo group and then analyzed according to the domain.

### **Sample size**

The sample size was determined from the prevalence of constipation of 9 percent per year, resulting in the minimum sample of 31 people from each group. However, in this study we obtained more samples, with a total of 73 subjects divided into probiotic and placebo groups.

### **Randomization**

This study used blocked randomization method, where the subjects obtained were grouped into probiotic supplementation group and placebo group according to 10 alternative permutations of random block codes (8 subjects/blocks): AABBAABB, BBAABBAA, ABABABAB, BABABABA, AAAABBBB, BBBBAAAA, ABBABAAB, BAABABBA, ABABBABA, BABAABAB.

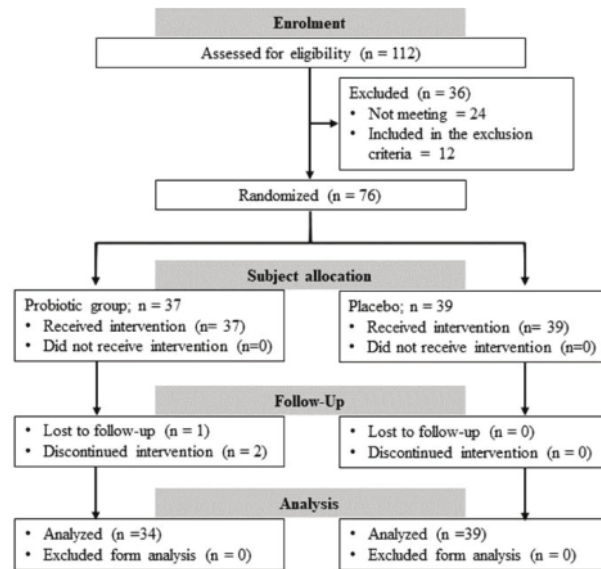
### **Statistical Analysis**

The data were analyzed using SPSS 22 Mac version by calculating the mean and standard deviation of all descriptive data. Afterward we compared the mean difference of PAC-SYM© per domain and overall score before and after intervention. Independent T test was used because the data was normally distributed, as confirmed with Kolmogorov-Smirnov test.

## **RESULTS**

### **Participant's Flow**

There were 112 subjects who experienced constipation and then screened by the research team. While 24 subjects did not meet the inclusion criteria, 12 other subjects had one or more exclusion criteria. 76 subjects were eligible to participate in the study and were randomly allocated into probiotic group and placebo group, with only 3 subjects failed to participate until the end of study, whereby 2 subjects stopped for certain reasons and 1 subject was excluded due to incompletion (Figure 1).



5 **FIGURE 1.** Consolidate standards of reporting trials (CONSORT) flow diagram of participants.

### Baseline Characteristics

From the 73 subjects analyzed in this study, the average age was 39.8 years in the probiotic group and 44.4 years in the placebo group, where most subjects belonged to the productive age. Almost half of the subjects had a normal body mass index (BMI) according to WHO BMI category for Asian population [12], 26 percent in the probiotic group and 19.2 percent in the placebo group. 26 subjects were in the overweight category, 13.7 and 21.9 percent in the probiotic placebo groups, respectively. The majority of all subjects had normal blood pressure according to JNC VII [13], with only 6 subjects were in the category of pre-hypertension, 8 subjects in stage 1 hypertension, and 5 subjects in stage 2 hypertension (Table 1).



5

**TABLE 1.** Participants Sociodemographic and Anthropometric Data at Baseline.

Characteristic	Probiotic (n= 33)	Placebo (n=39)
Age*	39.79 ± 12.8	44.4 ± 10.8
Weight*	63.2 ± 12.1	62.9 ± 11.5
Height*	157.24 ± 5.4	156.2 ± 6.2
BMI*	25.56 ± 4.6	25.8 ± 4.6
Underweight**	1 (1.4)	1 (1.4)
Normal**	19 (26)	14 (19.2)
Overweight**	10 (13.7)	16 (21.9)
Obese Class I**	3 (4.1)	6 (8.2)
Obese Class II**	1 (1.4)	2 (2.7)
Blood Pressure		
Normal**	28 (38.4)	26 (35.6)
Pre-hypertension**	2 (2.7)	4 (5.5)
Hypertension		
Stage 1**	3 (4.1)	5 (6.8)
Stage 2**	1 (1.4)	4 (5.5)

\*The values are expressed as mean ± standard deviation.

\*\* The values are expressed as n (%)

### Functional Constipation Symptoms

The PAC-SYM© questionnaire was divided into 3 domains, abdominal symptoms, rectal symptoms and stool symptoms. The average score in abdominal symptoms domain before intervention was 7.67 in probiotic group and 6.84 in the placebo group. After intervention, the score decreased to 2.44 in probiotic group and 4.61 on placebo group. Similar results also appeared in rectal symptoms and stool symptoms domains. Both probiotics and placebo groups exhibited a reduction of total score after intervention, from 23.91 to 7.79 in probiotics group and 21.84 to 13.38 in placebo group (Table 2). Reduction of score in total score and all domains of PAC-SYM© after intervention indicated that administration of probiotics and placebo both gave improvements of symptoms.

**TABLE 2.** Comparison of the Average PAC-SYM© Score between Probiotic vs. Placebo groups.

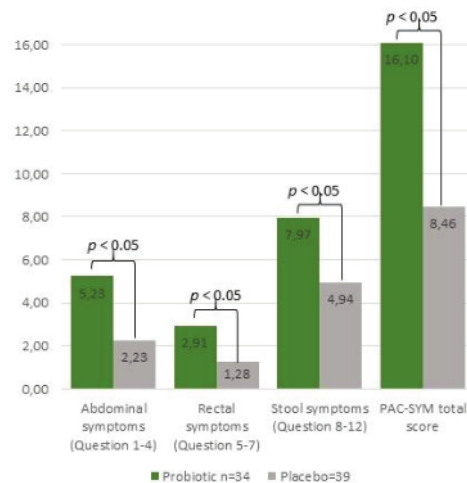
PAC-SYM©	Probiotic (n=34)		Placebo (n=39)	
	Before	After	Before	After
Abdominal symptoms (Question 1-4)	7.67	2.44	6.84	4.61
Rectal symptoms (Question 5-7)	4.11	1.20	4.82	3.50
Stool symptoms (Question 8-12)	12.11	4.14	10.17	5.23
Total score	23.91	7.79	21.84	13.38

The total mean data before and after intervention in each group was calculated into mean difference. The mean difference in probiotic group was then compared to placebo group (Table 3). The aim was to observe which differences were more statistically significant. In the abdominal symptoms' domain, the mean difference of probiotics and placebo groups was 3.00 (p<0.05), meaning that probiotics administration significantly reduced abdominal symptoms compared to placebo. The rectal symptoms domain also gave the same results, with the mean difference of 1.62 between the two groups (p<0.05). Overall, probiotic administration in subjects with functional constipation would further reduce the symptoms than placebo administration, as shown by the mean difference of 7.65 between probiotics and placebo groups (p<0.05) in total PAC-SYM© score (Table 3). As could be seen in Figure 2, there were considerable differences of mean scores between the two groups, all of which were statistically significant (p<0.05).

**TABLE 3.** The Mean Difference of PAC-SYM© score Between Probiotics vs. Placebo groups.

PAC-SYM©	Delta Mean		Mean Difference	95% CI of the Difference		Statistical significance
	Probiotic (n=34)	Placebo (n=39)		Lower	Upper	
Abdominal symptoms (Question 1-4)	5.23 ± 4.09*	2.23 ± 3.19*	3.00	1.30	4.70	(p<0.05)
Rectal symptoms (Question 5-7)	2.91 ± 2.65*	1.28 ± 3.62*	1.62	0.12	3.13	(p<0.05)
Stool symptoms (Question 8-12)	7.97 ± 5.83*	4.94 ± 4.58*	3.02	0.58	5.45	(p<0.05)
Total score	16.10 ± 10.73*	8.46 ± 8.75*	7.65	3.10	12.20	(p<0.05)

\*The values are expressed as mean ± standard deviation.



**FIGURE 2.** The mean difference comparisons of PAC-SYM© between probiotic vs. placebo groups.

## DISCUSSION

This randomized controlled trial (RCT) was conducted to determine the benefits of probiotics administration in lowering severity of symptoms on subjects with functional constipation using PAC-SYM© as the measurement tool. While prior studies had been carried out, to our knowledge this was the first study in Indonesia to evaluate improvements of constipation symptoms using PAC-SYM©. In accordance with our hypothesis, our study suggests that urban women with functional constipation experienced a significant improvement of symptoms after 3 weeks of probiotics supplementation.

An RCT study conducted in Malaysia compared 12 weeks of synbiotics administration placebo on improvements of PAC-SYM© score in subjects with constipation. The study concluded that there were no statistically significant differences in improvements of PAC-SYM© score between synbiotic group and placebo group, 49.6% and 43.7% in synbiotic and placebo groups respectively (p = 0.65) [14]. Another RCT study comparing 4 weeks of synbiotic administration to placebo on 60 subjects with constipation found no significant differences between synbiotic and placebo groups (p = 0.5), with the baseline PAC-SYM© scores of 1.61 ± 0.49 (placebo group) and 1.37 ± 0.46 (synbiotic group), and the final score of 0.52 ± 0.51 (placebo group) and 0.81 ± 0.48 (synbiotic group) [15]. On the contrary, in our study with 3 weeks of intervention, there was a significant difference between probiotics and placebo group, with a mean difference of 7.65 in the total PAC-SYM© score (p = 0.001).

A 4-week RCT of probiotics and prebiotics supplementation was carried out to evaluate improvements of constipation symptoms in patients with constipation and Parkinson disease. In comparison to the placebo group, the



probiotics-prebiotics group exhibited further improvement of constipation symptoms, as shown by the number of complete bowel movements (CBMs). There was a higher number of patients in the probiotics-prebiotics group vs. the placebo group reported 3 or more CBMs ( $p = 0.030$ ; 58.8% vs 37.5%; odds ratio = 2.4, 95% CI 1.1 – 5.2) and an increase by one or more CBMs ( $p = 0.004$ ; 53.8% vs 25.0%; odds ratio = 3.5, 95% CI 1.8 – 8.1) during the third and fourth weeks. (Barichella, 2016) A systematic review and meta-analysis of RCTs on the effect of probiotics on functional constipation in adults found that probiotics improved whole gut transit time, stool frequency, and stool consistency compared to placebo. Thus, probiotics would generate a better pattern of defecation [17].

Another study investigating the effect of a probiotic fermented milk (*Lactobacillus casei* strain Shirota) in 90 subjects with functional constipation found no significant differences between the probiotic and placebo groups on improvements of stool frequency, consistency, and quantity by fourth week ( $\alpha = 5\%$  level). But after being re-evaluated ( $\alpha = 10\%$  level), the probiotic group approached a borderline of statistically significant improvement in constipation severity ( $p = 0.058$ ) [18].

Our study found significant differences of improvements in PAC-SYM© scores between probiotics and placebo groups. Even though improvements were found in both groups, the probiotics group exhibited further improvements than the placebo group. Reduction of PAC-SYM© scores found in placebo group might happen due to a placebo effect or a laxative effect of the placebo. Lactose intolerance is a common problem in Asians, including Indonesian, thus the laxative effect of the placebo such as diarrhea could be mistaken as improvement of constipation symptoms.

## CONCLUSION

This research concluded that probiotics administration for 3 weeks in urban women with functional constipation significantly improved their symptoms as shown by reduction of PAC-SYM© scores, specifically abdominal symptoms, rectal symptoms and stool symptoms. Although placebo provided some improvements in this clinical trial, it was less significant than probiotics. Therefore, further research is needed to investigate the underlying mechanisms of placebo on reducing constipation symptoms.

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