ORIGINAL ARTICLE

Differences of BDI-II (Beck Depression Inventory-II) Score before and after Probiotics Administration

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ABSTRACT

Background: Depression is related to the dysregulation of neuroendocrine, neuroimmune, metabolic, and neurotransmitter systems. Gut microbiota is suspected to affect these pathway's dysregulations. Probiotic can improve depression symptoms through the microbiota-gut-brain axis.
Aim: To analyze differences in the BDI-II score before and after 28 days of probiotic administration.
Methods: This study was quasi-experimental, a single-blind, pre-posttest with the control group. The sample was ninety medical students randomized and divided into two groups, probiotic group (*Lactobacillus rhomnosus* and *Lactobacillus helventicus*) (n=50) and placebo group (n=40). A capsule of probiotic or placebo per day was administered for 28 days. The data were gathered using the Beck Depression Inventory-II (BDI-II). Wilcoxon test and Mann Whitney test were used to analyze the data.
Results: Mean of BDI-II score before the intervention was 8.29±8.53, while the mean of BDI-II score after probiotic administration was 2.97±4.1. There was a significant difference BDI-II score after the intervention in the probiotic group (5 (0-27) compared to 2 (0-19), p = 0.001).
Conclusion: This study proves that probiotic administration could reduce depressive symptoms. Therefore, it is recommended for the mental health professional to administer a probiotic supplement to decrease depression symptoms.
Keywords: BDI-II, depression, probiotics

INTRODUCTION

Based on the World Health Organization (WHO), depression affected more than 300 million people worldwide. Depression becomes one of the significant causes of disability and the global burden of diseases[1,2]. In the psychiatry area, 15% of patients diagnosed with depression and had received treatment still committed suicide. The percentage is estimated to be higher in patients who are not receiving treatment[3]. In Indonesia, the prevalence of emotional mental disorders (with depression and anxiety symptoms) in more than 15 years old population reached 6% or 14 million[3,4].

From neurobiological perspective, depression is associated with the dysregulation of neuroendocrine, neuroimmune, metabolic and neurotransmitter systems that corelated with microbiota gut brain axis.[5] There were some evidences from animal studies which showed that depression was influenced by gut microbiota.[5,6] Gut microbiota affects serotonin and its precursor (tryptophan), regulates stress response, modulates cognitive, and behavior via gut-brain axis.[6] The gut-brain axis consists of anatomy-physiological, endocrine, and immunity communication pathway. Intestinal changing can modulate central nervous systems (CNS) function; on the other hand, changes in CNS can modulate intestine. Bidirectional communication between gut and CNS carried by sending information to the intestine via thoracolumbar and lumbosacral vagus nerves pathway or by solutes mediator includes various hormones, neurotransmitter, and cytokines[7].

Intestine dysbiosis condition occurred when intestine was dominated by harmfully potent microbiota. This condition could influence host performance and lead to depression.[7,8] Probiotics have various benefits for health since they can alter pathogenic bacterial growth. The excellent impact of probiotics has been studied. A previous study found that subjects who received probiotic (*Bifidobacterium longum* and *Lactobacillus helventicus*) showed the better results on mood and depression[8]. A recent study reported that consuming probiotics (*Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium bifidum*) could increase mood or feelings. Probiotics can reduce depression symptoms through its effect on the neural and central nervous pathway with the mediation of the microbiota-gut-brain axis and affect the gene expression[9].

The study of the new antidepressants needs to be done to search the ideal antidepressant, which is affordable, useful to reduce depression symptoms, safe, and its side effects can be tolerated.[10] Moreover, it cannot be denied that not all the patients respond to antidepressants that already available in the market, and some of them refuse to receive pharmacological interventions for many reasons. Probiotics that have a lot of benefits in psychiatry are greatly welcomed. There is no doubt that many patients will appreciate the emergence of nonconventional antidepressants in the form of psychobiotics (probiotics)[11]. Moreover, there were limited studies that examined the effect of probiotics (*Lactobacillus rhomnosus and Lactobacillus helventicus*) on depressive symptoms. Therefore, this study aims to investigate and analyze the differences of depressive symptoms before and after the administration of probiotic by using *Lactobacillus rhomnosus* and *Lactobacillus helventicus* for 28 days.

METHODS AND MATERIAL

This study was a quasi-experimental, single-blind, pre-post-test study. The subjects were randomized and divided into two groups; probiotic administered to the treatment group and placebo administered to the control group. The study was conducted in May-June 2017 at the Faculty of Medicine, Diponegoro University, Semarang. The study protocol was approved by the board of the ethical committee at the Faculty of Medicine, Diponegoro University, Semarang, Indonesia.

Research Subject: Subjects in this study were medical students of the Faculty of Medicine Diponegoro University Semarang years of 2016. The inclusion criteria were 18 years old or more, had the willingness to follow the study by signing informed consent first and avoiding consuming other probiotics. Ninety students who meet the inclusion criteria were assigned by simple random sampling into the treatment group and the control group, 50 and 40 subjects, respectively.

Intervention Material: The intervention materials were *Lactobacillus rhomnosus* and *Lactobacillus helveticus* probiotic with the doses $2x10^9$ CFU (Lacidofil) and placebo in the form of fine white sugar inserted into capsule size 00 (same as probiotic capsule size). The shape and size of both supplements were made in the same package.

Data Collection Method: The Beck Depression Inventory-II (BDI-II) is a cheap, fast, self-rating scale that is most commonly used for screening of depression and severity of depression symptoms in adolescents (≥ 13 years) and adults. The BDI-II has been validated on non-psychiatric subjects including students, psychiatric outpatients both adults and adolescents.[12-14]

The data of this study were the primary data obtained from the general characteristic questionnaire and the BDI-II. $BDI\text{-}II_0$ was the BDI-II score, which was measured one day before probiotic administration while the $BDI\text{-}II_1$ was BDI-II score after 28 days of the probiotic administration.

The research was started with the explanation about the background of the study, objectives, benefits, work methods, and research questionnaires through the WhatsApp group and Line group. After the subjects met the sample size, a first encounter was performed for re-scaling the subjects and signing the informed consent sheet. The subjects were then divided into probiotic groups and placebo groups. Subsequently, they were asked to fill in a general characteristic questionnaire and $BDI\text{-}II_0$. Twenty-eight probiotics capsules / placebo were given to the research subjects at the first meeting (P1), which was the day of $BDI\text{-}II_0$ assessment. Probiotic capsules/placebo was consumed once daily before/ simultaneously/ after meals.

All subjects received a short instant message simultaneously at 6:55 pm to remind them to take one capsule of probiotic every day to prevent them from forgetfulness, which can make them drop out of this study. All the subjects also were asked to write down their schedule for drinking probiotics/placebo capsules, other probiotic intakes, fiber from fruit and vegetable intake, drugs consumed, and defecation frequency during the intervention. Then, they were asked to record in weekly reports to evaluate adherence and possible side effects.

During the studies, researchers held five meetings, including a meeting to explain the background of the study and let the subjects signed informed consent (P_1). The second meeting (P_2) was being held on the eighth day of taking probiotics/placebo capsules, the third meeting (P_3) was done on the fifteenth day and the fourth meeting (P_4) on the twenty-second day to evaluate subjects' weekly report. The fifth meeting (P_5) was done a day after all the subjects finished the 28 days of taking probiotic' placebo, then the subjects asked to fill out the $BDI\text{-}II_1$ questionnaire (Figure 1).

Processing and Analysis of Data: The data were analyzed using Saphiro-Wilk test to check the normality. The data were not normally distributed. Therefore, Wilcoxon test for paired groups and Mann Whitney test for unpaired groups were used to analyzed the data in this study.

RESULT

Prospective research subjects who attended the first meeting were 93 students. After re-informed about the studies to all the subjects, one subject resigned because they had an unpleasant experience with probiotic drink and two of the subjects did not meet the inclusion criteria for being under 18 years old. Then, only 90 subjects were left. Subjects were divided into probiotic groups (50 subjects) and placebo groups (40 subjects). After this study was done, five subjects from probiotic groups did not return the questionnaire completely, and six subjects were declared to be dropped out because of consuming antibiotics during the intervention period (2 subjects), and forgot to take probiotics (5 subjects). While in the placebo control group, one subject did not return the questionnaire completely and two subjects were dropped out because they did not take the placebo regularly. It can be concluded that 76 subjects finished the intervention, 39 subjects were probiotic treatment group, and 37 subjects were the placebo control group (Figure 2).

Table 1 showed that for the mean age of subjects was 18.68±0.55 and mean of BDI-II score was 8.29±8.53. There were no significant differences in the subjects' characteristics such as gender, age, body mass index, educational funding source and monthly living cost in both groups ($p> 0.05$) (Table 2). Statistical results showed $p=0.001$; meaning that there was a significant difference between BDI-II score before and after *Lactobacillus helventicus* and *Lactobacillis rhomnosus* administration (Table 3).

Table 1. Subjects' Characteristics

Variable	F	%	Mean ± SD	Median (Range)
Sex				
Man	16	21.1		
Woman	60	78.9		
Age			18.68 ± 0.55	19 (18 – 20)
BMI				
Underweight	11	14.5		
Normal	50	65.8		
Overweight	15	19.7		
Educational Funding				
Parents	75	98.7		
Scholarship	1	1.3		
Living Cost				
≤ 2.000.000	52	68.4		
> 2.000.000	24	31.6		
BDI-II before intervention			8.29 ± 8.53	5 (0 – 49)
BDI-II after probiotic intervention			2.97 ± 4.10	2 (0-19)

Table 2. Comparison of the Characteristics of the Subjects between Groups

Variable	Groups		*P*
	Probiotic	Placebo	
Sex			
Man	5 (12.8)	11 (29.7)	0.071¥
Woman	34 (87.2)	26 (70.3)	
Age	19 (18 – 20)	19 (18 – 20)	0.827‡
BMI			
Underweight	6 (15.4)	5 (13.5)	0.912¥
Normal	26 (66.7)	24 (64.9)	
Overweight	7 (17.9)	8 (21.6)	
Educational Funding			
Parents	38 (97.4)	37 (100)	0.513¥
Scholarship	1 (2.6)	0 (0)	
Living Cost			
≤ 2.000.000	26 (66.7)	26 (70.3)	0.736¥
> 2.000.000	13 (33.3)	11 (29.7)	

Notes: ¥ Chi-Square; ‡ Mann-Whitney

Table 3: Differences in BDI-II Score between Groups

BDI-II	Groups		*p*
	Probiotic	Placebo	
Before intervention	5 (0 – 27)	5 (0 – 49)	0,802‡
After intervention	2 (0 – 19)	2 (0 – 47)	0,420‡
p (paired)	0,000*§	0,001*§	
Differences	-4 (-19 – 3)	-2 (-18 – 6)	0,108‡

Notes : * Significant; ‡ Mann-Whitney; § Wilcoxon

Research Working Process Scheme: The length of study was 9 weeks. 2 weeks for socialization via *WhatsApp/line group*, 28 days did the intervention with probiotic/placebo, 3 weeks spare time to return back the questionnaire.
Placebo: [redacted] Probiotic: : .; Insta[redacted]oadcast message: [redacted]
First meeting (P_1), Second meeting (P_2), Third meeting (P_3), Fourth meeting (P_4), Fifth meeting (P_5).

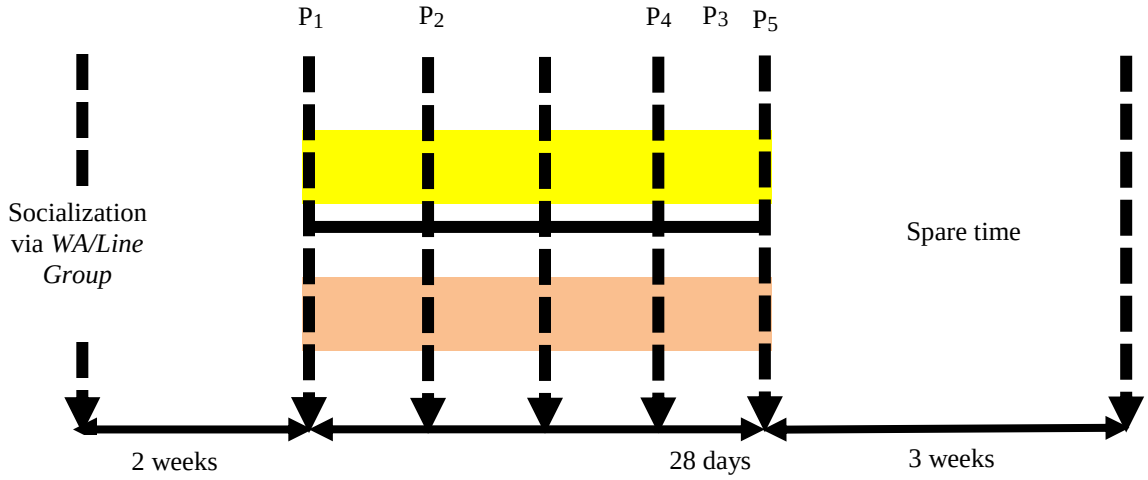
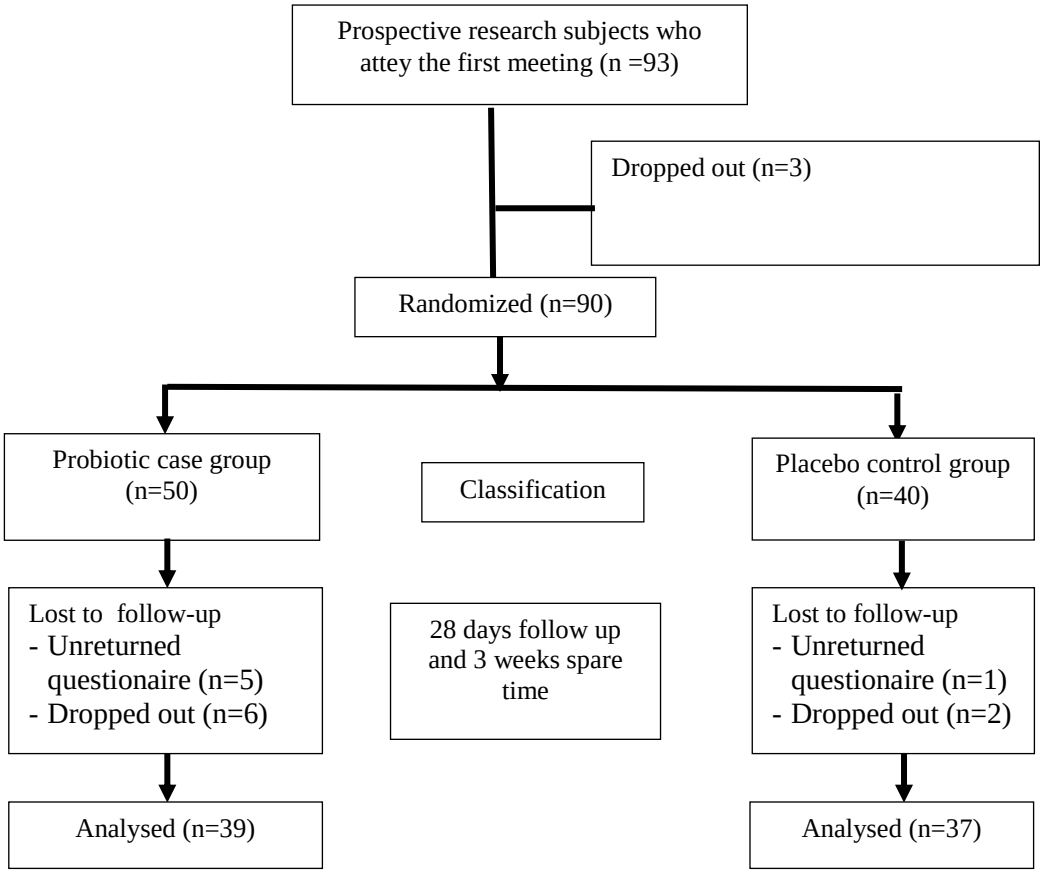


Figure 2. Chart of recruitment and completion research subjects



DISCUSSION

The results showed that the mean of BDI-II for this study was 8.29±8.53 indicating that medical students tend to have moderate depression. This study is in contrast to the mean of medical students' BDI-II score in Poland 13.76±9.99, Germany 8.49±7.64, Portugal 7.37±7.67)[15]. The prevalence of depression in medical students was much higher than the general population. This was possible because the demands of the much heavier task of learning and the adolescent to adult transition period become one of the most stressful times in the life of an individual trying to conform[16]. Other studies obtained various factors that raised susceptibility towards depression on medical students includes lack of sleep, academic stressor, working load and psychological pressure such as student abuse and bullying.[17]

This study also showed that there was significant difference between BDI-II score before and after *Lactobacillus helventicus* and *Lactobacillus rhomnosus* administration. Similarly, in the placebo group, there was a significant difference. Placebo responded towards depression symptoms was oftenly found in many antidepressant clinical trials, with the response rate between 30-40%. On subjects with mild depression symptoms and short duration episode, its response was obtained up to 50% and often difficult to distinguish with the response of antidepressant's studies.[18]

In this study, medical students who got one probiotic capsule that contained *Lactobacillus helventicus* and *Lactobacillus rhomnosus* for 28 days had a significantly lower BDI-II score than the placebo group. These results were consistent with a random, triple-blind study by Steenbergen *et al.*[19] to assess the probiotic effect on the cognitive reaction towards sad mood using the Leiden index of depression sensitivity (LEIDS-r). Forty healthy young adults consumed probiotic supplement or placebo for four weeks and were found that consuming multispecies probiotic formulas *(Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus brevis, Lactobacillus casei, Lactobacillus salivarius,* and *Lactococcus lactis)* significantly reduced overall cognitive reactions towards depression. Probiotics could increase plasma tryptophan levels, potentially increasing serotonin levels in the brain. Similar results were also found in double-blind studies conducted by Akkasheh *et al.*[9] in 40 patients diagnosed with depression who received probiotic supplements *(Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium bifidum)* or placebo for eight weeks. The results showed that the consumption of probiotic supplements significantly lowered BDI scores showing overall improved symptoms, including mood. In another study using *Lactobacillus helventicus* and *Bifidobacterium longum* probiotics for 30 days in healthy volunteers, there were some improvements in Hopskins symptoms checklist (HCL-90) in the somatization, depression and anger-

hostility domains as well as significant improvement in hospital anxiety and depression scale (HADS) in the depression domain compared to plasebo.[20] Similar results obtained in Mohammadi et al. [21]'s study of 75 healthy petrochemical company workers given yoghurt probiotics *(*Lactobacillusacidophilus LA5 and *Bifidobacterium lactis BB12)* or probiotic capsules *(Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhomnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum* and *Streptococcus thermilus)* or conventional yoghurt *(Streptococcus thermilus* and *Lactobacillus bulgaris)* for 6 weeks. In the probiotic yogurt group and probiotic capsule group, there was a significant improvement in Depression Anxiety and Stress Scale (DASS) score.

The action mechanism of probiotics in improving symptoms of depression is not fully known. Preclinical studies explained in rats induced myocardial infarction, with probiotic formulas *Lactobacillus helventicus* and *Bifidobacterium longum* showed a decrease in anxiety and improvement of depressive behavior. The effects of antidepressants on *Lactobacillus helventicus* and *Bifidabacterium longum* allegedly involve its ability to reduce levels of interleukin-1-β (IL-1β) pro-inflammatory cytokines that play an important role in the pathophysiology of depression.[22] In other preclinical studies, the same probiotics were also used showing a recovering depression activity after 2 weeks of administration, allegedly due to its ability to decrease plasma levels of corticosterone, adrenaline and noradrenaline and to increase brain-derived neurotrophic factor (BDNF) expression.[20] *Lactobacillus helventicus* and *Bifidabacterium longum* are thought to reduce not only pro-inflammatory serum levels of interleukin-1-α, interleukin -6, interferon-Y and tumor necrosis factor-α but also capable of enhancing interleukin-4 and interleukin-10 anti-inflammatory cytokines. The inflammatory process itself was believed to underlie the pathophysiology of depression syndrome. In addition, *Lactobacillus helventicus* and *Bifidabacterium longum* were thought to be able to modulate the activity of brain structures involved in the process of anxious emotions, depression and aggression in the septum, central nuclei of the amygdala, bed nucleus stria terminalis and periaqueductal gray through the vagus nerve which do not depend on inflammation.[8,20] Other preclinical studies, mice given probiotics *Lactobacillus rhomnosus* for 28 days showed a reduction in anxiety and depressive behavior. That effect is thought to be due to the ability of *Lactobacillus rhomnosus* to modulate the GABAnergic system in the amygdala and hippocampus through the vagus nerve, preventing corticosterone hormone increases and decreasing the activity of HPA axis[23].

Many works of literature proposed two hypotheses that can explain the mechanism of probiotics in improving symptoms of depression. These theories involve the regulation of inflammatory markers and the transmission of serotonin. Increased expression of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α are repeatedly observed in patients suffering from depression and have been associated with depressive symptoms. Increased inflammation contributes entirely to symptoms of depression by activating the HPA axis, as well as reducing the availability of neurotransmitter precursors and altering neurotransmitter metabolism. Decreased inflammation can result in improved HPA axis activity and neurotransmitter activity. Serotonin itself is the biosynthesis of the essential amino acid tryptophan in the central nervous system and gastrointestinal tract. Serotonin in the central nervous system is involved in regulating stress and emotion, appetite, and sleep. The gastrointestinal tract is responsible for the motility and secretion of the intestine. Changes in microbiota have been shown to have a strong effect on serotonin neurotransmission in the gastrointestinal tract and central nervous system. It leads to the hypothesis that probiotics in the gastrointestinal tract can improve the central nervous system involved in generating depressive symptoms by increasing free tryptophan production, thus increasing serotonin availability. This increase may improve the regulation of the HPA axis and symptoms of depression caused by neurotransmitter deficiency. [24]

Short durations, using single-blind techniques, and daily dietary sources of non-uniform subjects made the weaknesses of this study. There was also a shortage of not measuring the amount of fiber intake and nutritional intake in the subjects and control. Adherence to probiotic or placebo interventions, cigarette use, antibiotics, and probiotics from other sources were conducted through weekly interviews and evaluations, where subjects did not report actual circumstances.

CONCLUSION

There were significant differences in the BDI-II score before and after probiotic administration *(Lactobacillus rhomnosus* and *Lactobacillus helventicus).* Therefore, it is advisable to consume the probiotic supplement to repair depression symptoms. Further research is needed by controlling the confounding variables.

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