ARTIKEL ASLI

Print ISSN: 2580-2925
Online ISSN: 2580-2933

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 8, No. 1: 2024; 12-18

The effect of probiotics on inflammatory bowel disease Remission and relaps rate: A systematic review and meta-analysis

Louis Edwin Wirya[1*], Heinz Purwadi Gunawan Schoeck[2,3], Epistel Pangujian Simatupang[1]

Crossref Crossmark
DOI : 10.36216/jpd.v8i1.240

Introduction: Nowadays, dysbiosis, an imbalance of intestinal microbiota composition, is believed to play a role in the pathogenesis of Inflammatory Bowel Disease (IBD). Therefore, there is a hope that giving probiotics can be an addition to standard IBD treatment. This study aims to examine the efficacy of probiotics on the remission and relapse rates of IBD and its safety profile.

Methods: The authors collected studies from PubMed, Scopus, Embase, Cochrane, and Google Scholar. Inclusion criteria included all randomized controlled trials that compared groups of adult IBD patients (>18 years) who received probiotics and placebo on their standard treatment.

Results: Twenty-four studies met the inclusion criteria with a total sample of 2,233. The mean age of the sample was 39.1 ± 12.4 years in the probiotic group and 38.2 ± 12.3 years in the placebo group. Men compose 50.1% of the total sample. The remission rate in the probiotic group was higher than placebo (OR 1.58, 95% CI 1.28-1.95, p<0.0001). Moreover, the relapse rate in the probiotic group was significantly lower than in the placebo group (OR 0.70 CI 95% 0.53-0.93, p=0.01). There was no significant difference in the incidence of adverse events in the probiotic group compared to placebo (RR 1.04, CI 95% 0.85-1.29, p=0.68). Multistrain probiotics increased the remission rate(OR 2.68, CI 95% 1.88 -3.83, p=<0.00001). Meanwhile, only *Bifidobacterium sp*. significantly reduced the relapse rate (OR 0.07, CI 95% 0.01-0.38, p=0.002).

Conclusion: Probiotics can significantly ameliorate the remission rate and reduce the relapse rate in IBD patients. Giving probiotics that contain particular strains can increase the remission rate and reduce the relapse rate in IBD.

Keywords: *Probiotic, Inflammatory Bowel Disease, Remission, Relapse.*

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic relapsing inflammatory disorders of the gastrointestinal tract characterised by a multifactorial etiology and evolving in a relapsing and remitting manner.[1,2,3,4,5] The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which are similar in etiology, pathogenesis, and clinical manifestations.[6] CD is a chronic inflammatory and progressive disease that can affect all segments of the gastrointestinal, which typically characterizized by segmental, asymmetrical, and transmural lesion.[7] While, UC is a non-specific colorectal erosive chronic inflammatory condition, characterized by inflammation of the mucosa, erosion and ulceration, giving the symptomp of bloody diarrhea and abdominal pain.[8,9] Epidemiological studies show that the incidence of IBD is on the rise, mainly in Europe and North America, and a large number of patients are young and often with a lifelong risk of recurrence.[6]

The medical management of IBD can be separated into two phases: induction and maintenance treatment.[10] The aim of treating IBD is to reach a remission, prevent the relapse, and increase the quality of life (QoL).[11] In recent studies, The Short Form-36 Health Survey (SF-36), European HRQoL Index, and IBD Questionnaire (IBDQ) scale have been applied to evaluate general health and QoL status in IBD.[11] However, despite an intensive treatment, recurrency in patients with IBD is common.[11] Sequential colonoscopy in a cohort of Belgian patients showed that one year after surgery, 73% of CD patients developed endoscopic recurrence, and 44% had severe lesions.[12] A meta-analysis confirmed a pooled severe endoscopic recurrence rate of approximately 50%.[12]

Although there are so many IBD

[1]Department of Internal Medicine Siloam Hospitals Kebon Jeruk, Jakarta;
[2]Department of Internal Medicine Prof. Dr. IGNG Ngoerah Hospitals, Denpasar;
[3]Division of Gastroenterohepatologi Siloam Hospitals Kebon Jeruk, Jakarta;
[4]Division of Gastroenterohepatologi Prof. Dr. IGNG Ngoerah Hospitals, Denpasar;
[5]Faculty of Medicine Udayana University, Denpasar.

*Korespondensi:
Louis Edwin Wirya;
Department of Internal Medicine Siloam Hospitals Kebon Jeruk, Jakarta;
louis_edwin92@yahoo.com

Received : 01 January 2024
Accepted : 01 Februari 2024
Published : 01 April 2024

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 8, No. 1: 2024; 12-18

Print ISSN: 2580-2925
Online ISSN: 2580-2933

therapies, including, corticosteroids, and other novell immunosuppressant agents to suppress intestinal inflammation, or even a surgery, treatment with 5-aminosalicylic acid containing drugs is still the gold standard for the treatment of mild-to-moderate active IBD.[13] However, there is sometimes, a considerable intolerance not only to classic aminosalicylate sulphasalazine, but also to sulphur-free compounds such as mesalazine or olsalazine.[13] In such patients, there is no effective drug therapy for relapse prevention.[14] Furthermore, there were a subpopulation of patients is intolerant or refractory to these therapies because of their significant adverse effects.[14] In this regard, treatments that directly modulate gut microbiota have been studied as adjunctive therapies or as alternative options to conventional drug therapies, because it is believed that the bacteria were well tolerated without serious side effects.[15,16]

Based on a fact that there is still no definitive results regarding the efficacy of probiotic and several significant flaws however limit the importance of many probiotic trials, such as inclusion of too few patients, too limited a period of observation, or the association of the probiotic with other drugs.[17] Therefore will conduct a systematic review and meta analysis to evaluate the effect of probiotic as an additional therapy to IBD standard therapy in order to increase remission rate and decrease refractory rate, as well as its safety profile.

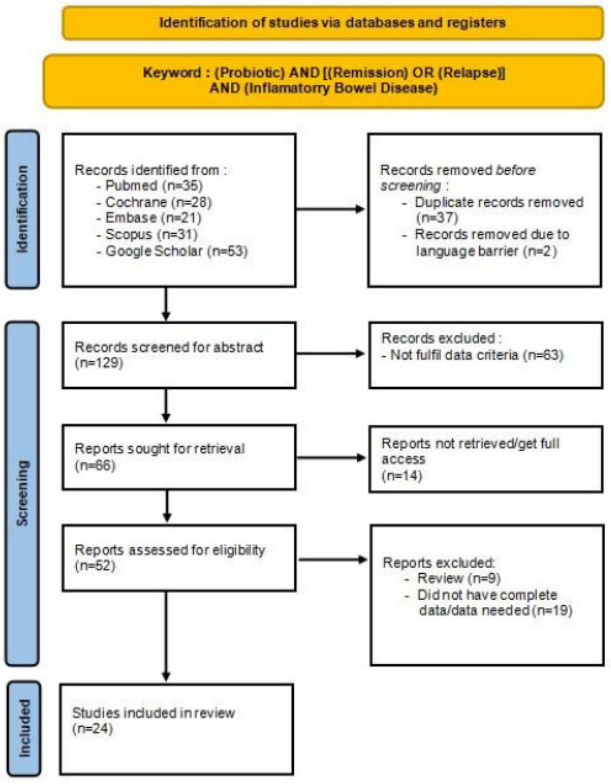


Figure 1. Prisma 2020 Flow Diagram for Systematic Review.

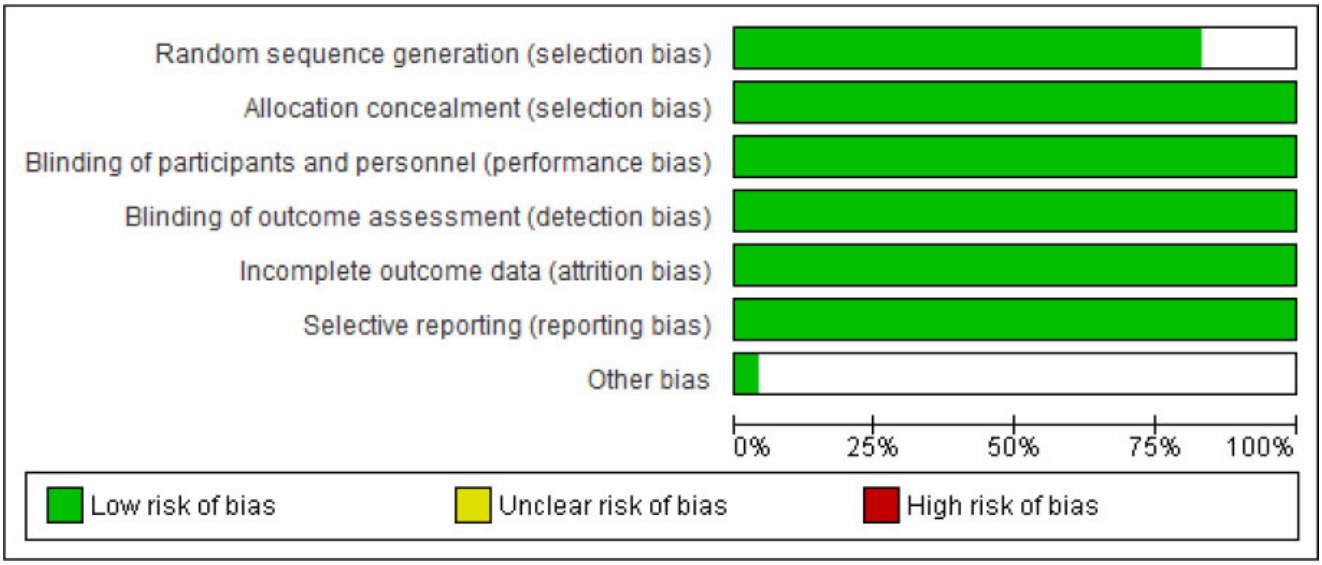
Table 1. Demographic Data of Eligible Studies

No.	Author (et al)	Year	Country	Σ	Sample		Sex Distribution			
					P	C	P		C	
							M	F	M	F
1.	Fan H[6]	2019	China	40	21	19	10	11	10	9
2.	Park SK[12]	2022	South Korea	118	58	60	43	24	48	18
3.	Fedorak[13]	2015	United States	120	58	62	30	28	32	30
4.	Bjanarsson[14]	t	United Kingdom	143	73	70	n/s	n/s	n/s	n/s
5.	Boureille A[10]	2013	France	159	80	79	22	58	23	56
6.	Schultz[17]	2004	Germany	11	5	6	n/s	n/s	n/s	n/s
7.	Kruis W[15]	2004	Germany	327	162	165	92	70	87	78
8.	Yoshimatsu[16]	2015	Japan	46	23	23	16	7	12	11
9.	Sood A[18]	2009	India	147	77	70	43	34	45	25
10.	Altun HK[11]	2011	Turkey	36	18	18	10	8	9	9
11.	Petersen[19]	2014	Denmark	100	50	50	20	30	18	32
12.	Guslandi M[20]	2000	Italy	32	16	16	11	5	9	7
13.	Matsuoka K[9]	2018	Japan	192	97	95	50	47	50	45
14.	Tamaki H[21]	2016	Japan	56	28	28	11	17	16	12
15.	Tursi A[29]	2004	Italy	60	30	30	21	9	18	12
16.	Zocco MA[23]	2006	Italy	122	62	60	34	28	34	26
17.	Matthes A[22]	2010	Germany	43	23	20	13	10	12	8
18.	Kato K[25]	2004	Japan	20	10	10	5	5	5	5
19.	Rembacken[26]	1999	United Kingdom	116	57	59	29	18	32	27

ARTIKEL ASLI
Print ISSN: 2580-2925
Online ISSN: 2580-2933
Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 8, No. 1: 2024; 12-18

No.	Author (et al)	Year	Country	Σ	Sample		Sex Distribution			
					P	C	P		C	
							M	F	M	F
20.	Wildt S[8]	2010	Denmark	32	20	12	6	14	4	8
21.	Brandimarte[24]	2010	Italy	144	71	73	49	22	44	29
22.	Schutz E[28]	1997	Germany	103	50	53	29	21	26	27
23.	Prantera C[27]	2001	Italy	45	23	22	14	9	15	7
24.	Ishikawa[30]	2014	Japan	21	11	10	6	5	5	5
	Σ	Total Sample								
	M	Male								
	F	Female								
	n/s	Not stated								
	P	Probiotic								
	C	Control								

Table 2. The Assessment of Study Bias



METHODS

Study Selection and Characteristics

A total of 168 studies were retrieved from PubMed, Scopus, Embase, Cochrane, and Google Scholar with the keyword of (Probiotic) AND [(Remission) OR (Relapse)] AND (Inflammatory Bowel Disease). After screening titles, abstracts and removing the duplicates, 129 articles were assessed for eligibility through reading the full-text form. Among these eligible studies, 66 articles were further excluded, fourteen articles did not share full access, nine were review articles, and eighteen studies did not have complete data, therefore resulting in the final number of 24 *randomized controlled trial* with a total of 2.233 patients with IBD for the analysis (Figure 1).

Sample sizes ranged from 20 to 327. Those included studies are accrossing multicountry. Athough most of studies comes from western country, there are still eight studies that covers asian populations. Nearly 50% of those population were female, so the distribution of sex are quite balance. The details of each included studies were summarized in Table 1.

Eligibility Criteria

The inclusion criteria for selecting the study were as follows: (1) Types of studies: all randomized clinical trials discussing the use of probiotic in IBD; (2) Types of participants: patients at age more than 18 year and diagnosed with IBD; (3) Types of intervention: received a placebo in its protocol; (4) Types of comparison: receiving only standard of care or placebo; (5) Types of outcome: Odds Ratio (OR) probiotic to remission and reccurance rate. Studies in which do not have data needed were excluded. Studies without the control group, any other articles besides primary studies

ARTIKEL ASLI
Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 8, No. 1: 2024; 12-18
Print ISSN: 2580-2925
Online ISSN: 2580-2933

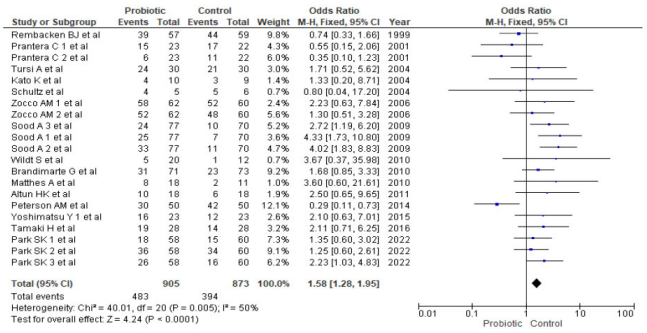


Figure 2. Forrest Plot The Effect of Probiotic on Remission Rate.

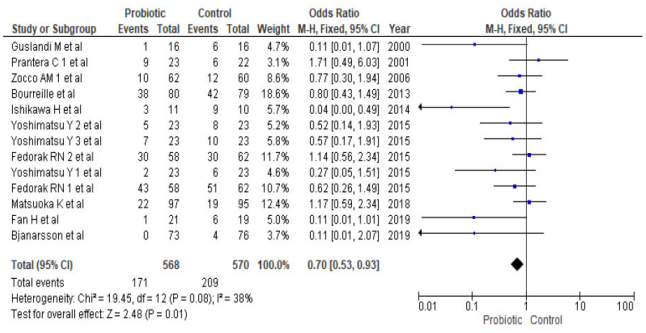


Figure 3. Forrest Plot The Effect of Probiotic on Relapse Rate.

(review articles, editorials, correspondences), and articles in non-English language will also be excluded.

Quality of Study Assessment

Risk of Bias version 2 (RoB v2) from Cochrane was used to evaluate the quality of studies. Those twenty four studies have low-risk of bias in all five domains of methodological evaluation. (Table 2).

RESULTS

Twenty four studies met the inclusion criteria with a total sample of 2.233. The mean age of the sample was 39,1 ± 12,4 years in the probiotic group and 38,2 ± 12,3 years in the placebo group. Men compose 50,1% of the total sample. In our study, patients were predominantly caucasian and male. This is may caused due to all study included were come from western country population.[4]

In the probiotic group, the remission rate was significantlly higher compared to placebo (OR 1.58, 95% CI 1.28-1.95, p<0.0001), with overall effect Z = 4.24.

Moreover, the relapse rate in the placebo group was also significantly lower than in the placebo group (OR 0.70 CI 95% 0.53-0.93, p=0.01) by overall Z effect 2.48. This two findings means that by adding probiotic to standard therapy can dramatically promote remission rate and prevent the reccurance of IBD.

There was no significant difference in the incidence of adverse event in the probiotic group compared to placebo (RR 1.04, CI 95% 0.85-1.29, p=0.68). Adverse events occurred based on its spesific strain given by the clinician. For example, probiotic that contain *Saccharomyces boulardii* often cause diarrhea, arthralgia, constipation, and abdominal pain.[18] Admission of *Echerischia colii* Nissle 1917 (EcN) reported several side effects, such as itching, nausea, bloating, and abdominal pain.[19] While, patient with *Lactobacillus GG* experienced a suture stitch suppuration and a mild increase in alanine aminotransferase.[20] Probiotic rarely cause serious adverse events, but Ishikawa et al reported three serious side effect following administration of probiotic containing *Bifidobacterium breve* : avascular necrosis of bilateral femoral head, development of granuloma in the throat, and pulmonary thromboembolism (in one patient in the placebo group).[21] However, a causal relationship with the study beverage was ruled out for all these events.[21]

Interestingly, probiotics that contain spesific multistrain (*Bifidobacterium sp., Lactobacillus sp.*, and *Streptococcus thermophilus*) (OR 2.68, CI 95% 1.88 -3.83, p=<0.00001) apparently had an effect to increase the remission rate. Other probiotic strains are seems not statistically related to ameliorate the remission rate, including strain of *Escherichia colii* (OR 1.09, CI 95% 0.77-1.53, p=0.63), strain *Bifidobacterium sp.* (OR 1.88, CI 95% 0.74-4.80, p=0.19), *Lactobacillus GG* (OR 0.94, CI 95% 0.54-1.62, p=0.81), or other multistrain probiotic, such as, *Lactobacillus sp.* and *Bifidobacterium sp.* (OR 3.67, CI 95% 0.37-35.98, p=0.26) or *Streptococcus sp.*, *Clostridium sp.*, and *Bacillus sp.* (OR 2.10, CI 95% 0.63-7.01, p=0.23).

Meanwhile, only *Bifidobacterium sp.* which significantly proved reducing the relapse rate OR 0.07, CI 95% 0.01-0.38, p=0.002). Contrastly, other probiotic Strains are not statistically related to reduce of remission rate. For example, strain of *Escherichia colii* (OR 1.18, CI 95% 0.72-1.93, p=0.52), *Lactobacillus GG* (OR 0.98, CI 95% 0.49-1.99, p=0.97), *Saccharomyces boulardii* (OR 0.66, CI 95% 0.37-1.18, p=0.16), or other multistrain probiotic, such as, *Lactobacillus sp.* and *Enterococcus sp.* (OR 0.11, CI 95% 0.01-2.07, p=0.14) or *Streptococcus sp.*, *Clostridium sp.*, and *Bacillus sp.* (OR 0.47, CI 95% 0.21-1.02, p=0.06).

DISCUSSION

The pathogenic role of luminal bacteria in IBD has been a source of controversy but the leading hypothesis is that resident bacterial flora are an essential cofactor in driving the inflammatory process in IBD.[22] The gut contains numerous species of bacteria (microbiota) that maintain

ARTIKEL ASLI

Print ISSN: 2580-2925
Online ISSN: 2580-2933

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 8, No. 1: 2024; 12-18

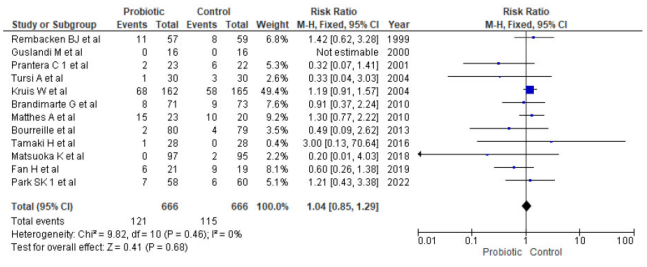


Figure 4. Forrest Plot Probiotic *Safety Profile* Probiotic vs Placebo.

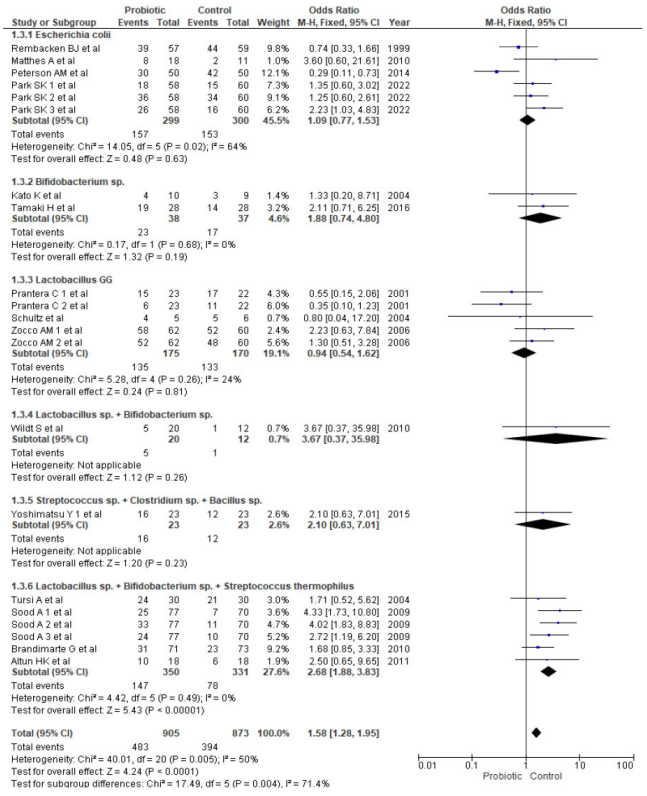


Figure 5. Forrest Plot The Effect of Spesific Probiotic Strain on Remission Rate.

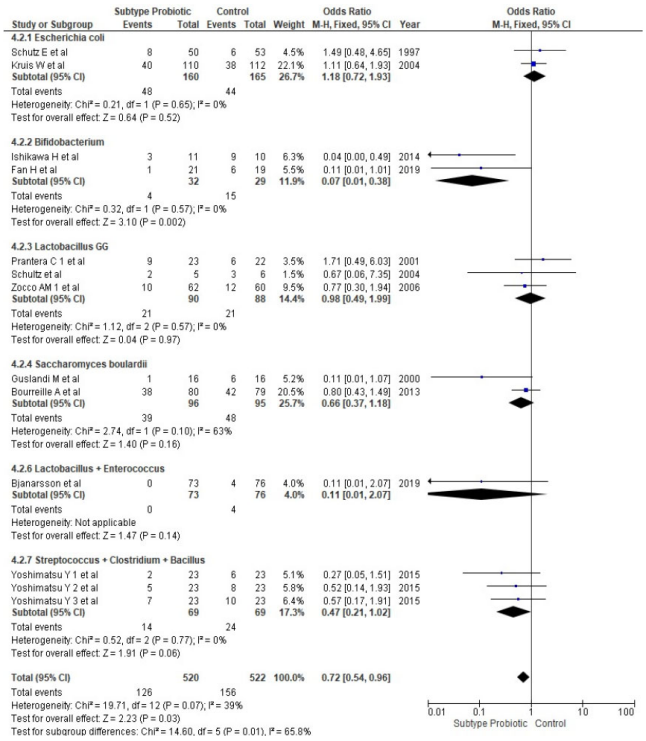


Figure 6. Forrest Plot The Effect of Spesific Probiotic Strain on Relapse Rate.

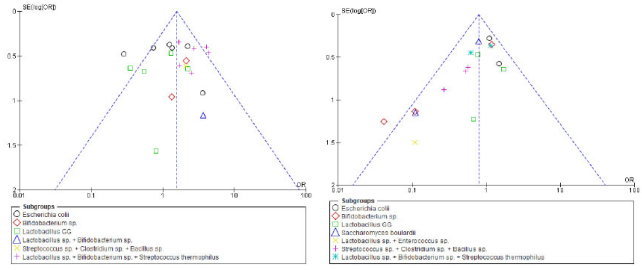


Figure 7. Funnel Plot The Effect of Spesific Probiotic Strain on Remission and Relapse Rate.

the mucosal barrier and aid digestion.[22] The microbiota was recently shown to affect development of the immune system. Because the microbiota exists in homeostasis with the human host, the dysregulation of bacterial species (dysbiosis), caused by a change in diet, infections, stress, overwork, or the use of antibiotic and nonsteroidal anti-inflammatory drugs, might be involved in development and exacerbation of IBD pathogenesis by breaking immunologic tolerance, leading to an abnormal infammatory response to the presence of commensal bacteria.[23,24,25]

Giving probiotic as an additional therapy may possibly help to reach and mantain remission that are very effective and safe with good compliance when used on a long-term basis.[26] Probiotics are viable non-pathogenic microorganisms that confer health benefits to the host by improving the microbial balance of the indigenous microflora.[27] The interest in probiotics has been fueled by new technologies that demonstrate that the intestinal microbiome is signifcantly altered in a number of intestinal and extra-intestinal diseases, suggesting that bacterial dysbiosis may have an etiological or pathogenic role in some of these disorders.[28] Probiotic can be composed by either single microbes or a combination of a few microbes, such as, VSL#3, a high-concentration probiotic preparation of live, freeze-dried bacterial strains, including 4 strains of *Lactobacilli* (*L. paracasei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subspecies *bulgaricus*), 3 strains of *Bifidobacteria* (*B. longum*, *B. breve*, and *B. infantis*), and *Streptococcus thermophilus*.[16] Therefore, recently, probiotic microorganisms received much scientific attention due to reports of successful treatment of various intestinal, mainly

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 8, No. 1: 2024; 12-18

Print ISSN: 2580-2925
Online ISSN: 2580-2933

infectious disorders.[29]

Despite the promising treatment of probiotic, several previous studies provided different conclusion regarding the efficacy. In the present trial, clinical relapses of CD were observed to a significantly lesser extent in patients on maintenance treatment with mesalamine plus *Saccharomyces boulardii* (6.25%) than in subjects receiving mesalamine alone (37.5%).[14] Moreover, it has been found that the probiotic *Escheriscia colii* Nissle (EcN) as supplementary treatment option to topically applied aminosalicylates or glucocorticoids has the ability to induce remission and preventing disease flares in patients with active UC that equivalent to mesalazine (5-ASA).[12,15]

Contrastly, other study says probiotic containing *Lactobacillus* GG and *Eschericia colii* strain were ineffective in preventing recurrence after curative resection in CD or maintaining medically induced remission. Bourreille et al also stated that the probiotic yeast *Saccharomyces boulardii* is safe and well tolerated, but it does not appear to have any beneficial effects for patients with CD in remission after steroid or salicylate therapies.[10] Furthermore, Fedorak et al found that there were no statistical differences in endoscopic recurrence rates at day 90 between patients who received VSL#3 and patients who received placebo.[13] But clearly through this meta analysis, we can draw a conclusion that, eventhough was not statistically proved, remission rate in probiotic group was higher compared to placebo and the relapse rate in the its group was significantly lower than in the probiotic group. This means that probiotic will be a promissing treatment to generate remission and prevent the reccurance of IBD. However, there are reports clarify that in spite of successful induction and maintenance of remission in UC, but treatment of CD with probiotic preparations still proved difficult.[30]

In the terms of safety profile, probiotic is statistically proved has no different, comparing to placebo group, which is mean that probiotic can be a new therapy without giving significant adverse effect. This finding is in line with most of the previous trials. The limitations of our study is nearly half of the trials that met inclusion criteria came from up to 10 years trial. The main strengths are the design and the high number of patients which allow us to draw firm conclusions about the effects of probiotic in IBD. In summary, based on those results above, we can recommend to use probiotic as an additional to standard therapy given in order to increase the remission rate and relapse rate in patient with IBD.

CONCLUSION

The use of probiotics can significantly increase the remission rate and reduce the relapse rate in IBD patients. Furthermore, there was no significant difference in the incidence of side effects in the probiotic group compared to placebo. Giving probiotics that contain particular strains can increase the remission rate and reduce relapse rate in IBD. Therefore, probiotic can be used as an additional to standard therapy given in order to increase the remission rate and relapse rate in IBD patients, and thus, reach better quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

REFERENCE

1. Liu, S, et al. The Microbiome in Inflammatory Bowel Diseases: From Pathogenesis to Therapy. *Protein Cell 2021*, 12(5):331–345
2. Santana PT, Rosas SLB, Ribeiro BE, Marinho Y, de Souza HSP. 2022. Dysbiosis in Inflammatory Bowel Disease: Pathogenic Role and Potential Therapeutic Targets. *Int J Mol Sci.* 2022 Mar 23;23(7):3464
3. Shaw, K.A., Bertha, M., Hofmekler, T. *et al.* Dysbiosis, Inflammation, and Response to Treatment: a Longitudinal Study of Pediatric Subjects with Newly Diagnosed Inflammatory Bowel Disease. *Genome Med* 8, 75
4. Tamboli CP, Neut C, Desreumaux P, Colombel JF. Dysbiosis in Inflammatory Bowel Disease. *Gut.* 2004 Jan;53(1):1-4
5. Yu, L.CH. 2018. Microbiota Dysbiosis and Barrier Dysfunction in Inflammatory Bowel Disease and Colorectal Cancers: Exploring a Common Ground Hypothesis. *J Biomed Sci* 25, 79
6. Fan H, Du J, Liu X, Zheng WW, Zhuang ZH, Wang CD, Gao R. Effects of pentasa-combined probiotics on the microflora structure and prognosis of patients with inflammatory bowel disease. Turk J Gastroenterol. 2019 Aug;30(8):680-685
7. Torres, J., Mehandru, S., Colombel, J.-F., & Peyrin-Biroulet, L. (2017). Crohn's disease. The Lancet, 389(10080), 1741–1755.
8. Wildt S, Nordgaard I, Hansen U, Brockmann E, Rumessen JJ. A randomised double-blind placebo-controlled trial with Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp. lactis BB-12 for maintenance of remission in ulcerative colitis. J Crohns Colitis. 2011 Apr;5(2):115-21
9. Matsuoka K, Uemura Y, Kanai T, Kunisaki R, Suzuki Y, Yokoyama K, Yoshimura N, Hibi T. Efficacy of Bifidobacterium breve Fermented Milk in Maintaining Remission of Ulcerative Colitis. Dig Dis Sci. 2018 Jul;63(7):1910-1919
10. Bourreille A, Cadiot G, Le Dreau G, Laharie D, Beaugerie L, Dupas JL, Marteau P, Rampal P, Moyse D, Saleh A, Le Guern ME, Galmiche JP; FLORABEST Study Group. Saccharomyces boulardii does not prevent relapse of Crohn's disease. Clin Gastroenterol Hepatol. 2013 Aug;11(8):982-7
11. Kamarli Altun H, Akal Yildiz E, Akin M. Impact of Synbiotic Therapy on the Quality of Life in Patients with Mild-to-Moderately Active Ulcerative Colitis. J Gastrointestin Liver Dis. 2022 Dec 17;31(4):417-423
12. Park SK, Kang SB, Kim S, Kim TO, Cha JM, Im JP, Choi CH, Kim ES, Seo GS, Eun CS, Han DS, Park DI. Additive effect of probiotics (Mutaflor) on 5-aminosalicylic acid therapy in patients with ulcerative colitis. Korean J Intern Med. 2022 Sep;37(5):949-957
13. Fedorak RN, Feagan BG, Hotte N, Leddin D, Dieleman LA, Petrunia DM, Enns R, Bitton A, Chiba N, Paré P, Rostom A, Marshall J, Depew W, Bernstein CN, Panaccione R, Aumais G, Steinhart AH, Cockeram A, Bailey RJ, Gionchetti P, Wong C, Madsen K. The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. Clin Gastroenterol Hepatol. 2015 May;13(5):928-35.e2
14. Bjarnason I, Sission G, Hayee B. A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease. Inflammopharmacology. 2019 Jun;27(3):465-473

Print ISSN: 2580-2925
Online ISSN: 2580-2933

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 8, No. 1: 2024; 12-18

15. Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut. 2004 Nov;53(11):1617-23
16. Yoshimatsu Y, Yamada A, Furukawa R, Sono K, Osamura A, Nakamura K, Aoki H, Tsuda Y, Hosoe N, Takada N, Suzuki Y. Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. World J Gastroenterol. 2015 May 21;21(19):5985-94
17. Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. BMC Gastroenterol. 2004 Mar 15;4:5
18. Sood A, Midha V, Makharia GK, Ahuja V, Singal D, Goswami P, Tandon RK. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. Clin Gastroenterol Hepatol. 2009 Nov;7(11):1202-9, 1209.e1
19. Petersen AM, Mirsepasi H, Halkjær SI, Mortensen EM, Nordgaard-Lassen I, Krogfelt KA. Ciprofloxacin and probiotic Escherichia coli Nissle add-on treatment in active ulcerative colitis: a double-blind randomized placebo controlled clinical trial. J Crohns Colitis. 2014 Nov;8(11):1498-505
20. Guslandi M, Mezzi G, Sorghi M, Testoni PA. Saccharomyces boulardii in maintenance treatment of Crohn's disease. Dig Dis Sci. 2000 Jul;45(7):1462-4
21. Tamaki H, Nakase H, Inoue S, Kawanami C, Itani T, Ohana M, Kusaka T, Uose S, Hisatsune H, Tojo M, Noda T, Arasawa S, Izuta M, Kubo A, Ogawa C, Matsunaka T, Shibatouge M. Efficacy of probiotic treatment with Bifidobacterium longum 536 for induction of remission in active ulcerative colitis: A randomized, double-blinded, placebo-controlled multicenter trial. Dig Endosc. 2016 Jan;28(1):67-74
22. Matthes H, Krummenerl T, Giensch M, Wolff C, Schulze J. Clinical trial: probiotic treatment of acute distal ulcerative colitis with rectally administered Escherichia coli Nissle 1917 (EcN). BMC Complement Altern Med. 2010 Apr 15;10:13
23. Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Novi M, Rigante D, Cazzato IA, Ojetti V, Armuzzi A, Gasbarrini G, Gasbarrini A. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 2006 Jun 1;23(11):1567-74
24. Tursi A, Brandimarte G, Giorgetti GM, Forti G, Modeo ME, Gigliobianco A. Low-dose balsalazide plus a high-potency probiotic preparation is more effective than balsalazide alone or mesalazine in the treatment of acute mild-to-moderate ulcerative colitis. Med Sci Monit. 2004 Nov;10(11)
25. Kato K, Mizuno S, Umesaki Y, Ishii Y, Sugitani M, Imaoka A, Otsuka M, Hasunuma O, Kurihara R, Iwasaki A, Arakawa Y. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. Aliment Pharmacol Ther. 2004 Nov 15;20(10):1133-41
26. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet. 1999 Aug 21;354(9179):635-9
27. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut. 2002 Sep;51(3):405-9
28. Kruis W, Schütz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 1997 Oct;11(5):853-8
29. Tursi A, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, Forti G, Morini S, Hassan C, Pistoia MA, Modeo ME, Rodino' S, D'Amico T, Sebkova L, Sacca' N, Di Giulio E, Luzza F, Imeneo M, Larussa T, Di Rosa S, Annese V, Danese S, Gasbarrini A. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2010 Oct;105(10):2218-27
30. Ishikawa H, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. J Am Coll Nutr. 2003 Feb;22(1):56-63