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A systematic review and meta-analysis on the efficacy of probiotics for bacterial vaginosis

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Abstract. – OBJECTIVE: The current study aimed at assessing the overall efficacy of probiotics for the treatment of bacterial vaginosis (BV) through the review of relevant studies.

MATERIALS AND METHODS: A systematic literature review was conducted based largely on the following electronic databases updated to May 2021: Embase, the Cochrane Library, and PubMed, with the use of keywords. The investigators also thoroughly reviewed key pertinent sources in the literature for further inclusion.

RESULTS: Eighteen studies including 1651 patients were selected in the present meta-analysis. In comparison with antibiotics, antibiotics plus probiotics significantly decreased the recurrence rate of BV (at 1-3 months and overall analysis) and increased the cure/remission rate of BV (at 1-3 months and overall analysis). Compared with placebo, probiotics decreased the recurrence rate of BV (at 1-3 months and overall analysis) and increased the cure/remission rate of BV (at 1-3 months). Compared with antibiotics, probiotics significantly decreased the recurrence rate of BV (at <1 month, 1-3 months and overall analysis) as well as the incidence of adverse events (AEs) (at less than 1 month) and increased the cure/remission rate of BV (at 1-3 months).

CONCLUSIONS: In comparison with short-term probiotics treatment (<1 month), long-term probiotics treatment (1-3 months) yields superior beneficial outcomes and efficacy in the treatment of BV.

Key Words:
Probiotics, Bacterial vaginosis, Antibiotics, Meta-analysis.

Abbreviations

AE: adverse event; BV: bacterial vaginosis; CI: confidential interval; MD: mean difference; ORs: odds ratios; RR: relative risk.

Introduction

Bacterial vaginitis (BV) is a disorder of the vaginal microflora, which has been acknowledged as the most common type of vaginitis among women of childbearing age. The incidence of the disease is generally related to age and other factors, and ranges from 4.96% to 36.00% in China[1]. The condition is generally caused by an imbalance of the naturally occurring bacteria, typically a decrease in *Lactobacillus bacteria* and an abnormal increase in the total number of several pathogenic bacteria, most of which are strictly anaerobic. Pathogenic bacteria are relatively weak, so it is not just their presence that causes BV, it is their uncontrolled proliferation. BV does not appear until the number of pathogenic bacteria is 100 to 1,000 times that of healthy vaginal bacteria[1,2]. Substantial evidence has shown that BV can lead to a variety of complications and sequelae. It can cause pelvic inflammation and cervicitis. There are more serious health risks to pregnant women, such as an increased risk of miscarriage in early pregnancy such as the first trimester, chorioamnionitis, premature rupture of the membrane and preterm delivery. In addition, changes in the vaginal microecology are associated with urinary tract infections[3,4].

Currently, the main treatments for BV include oral or intravaginal metronidazole or clindamycin, while a high recurrence rate of BV has been reported, from 40% at 3 months after conventional antibiotic treatment to 60% at 6 months[5]. The high recurrence rate may be due to the formation and development of a variety of bacterial biofilms, which adhere to the vaginal epithelial cells, rendering antibiotics unable to completely kill the pathogens. High relapse rates lead to repeated uses of antibiotics, allowing bacteria to develop resistance.

There are a large number of probiotics, such as *Lactobacillus*, in the human vagina. When the number of probiotics is reduced due to changes in the external environment (such as the use of antibiotics), harmful bacteria will

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multiply in large numbers. When the number of noxious bacteria reaches a threshold level, bacterial vaginitis may occur. Exogenous probiotics to treat bacterial vaginitis, through probiotics to inhibit the reproduction and growth of harmful bacteria, have become a new treatment of BV[6,7]. Therefore, the current meta-analysis and review was performed of eligible literature, with an attempt to obtain evidence to evaluate the overall efficacy of probiotics in terms of treating BV, and to offer an insight and theoretical basis for clinical practice.

Materials and Methods

Search Strategy and Study Collection

A thorough search of electronic databases was conducted to identify relevant studies or literature updated to May 2021 on the efficacy of probiotics in terms of treating BV, such as Embase, the Cochrane Library, and PubMed. Our investigators also reviewed and checked the references of all retrieved publications to include other additional studies. The search terms were as follows: probiotics, culturelle, EM, probiotic bacteria, bacterial vaginitis, BV, vaginitis, vaginosis and colpitis. The abovementioned terms were applied during the search process in combination with "AND" or "OR". Two of our investigators independently reviewed the literature, a third investigator contributed to a consensus decision if there were any differences.

The key search terms were included as follows in accordance with the PICOS (Participants, Interventions, Comparisons, Outcomes and Study design) principle: (P) patients with BV; (I) patients received an intervention of probiotics; (C/O) the outcomes included BV recurrence rate, BV cure/remission rate and adverse events (AEs); (S) case-control studies or randomized controlled trials.

The details of literature screening process are shown in the PRISMA 2009 flow diagram **(Supplementary Figure 1).** The checklist of PRISMA 2009 presents the specific framework as well as content of the articles.

Study Selection Criteria

Eligible studies for the current meta-analysis should meet the following criteria: (1) case-control studies or randomized controlled trials; (2) the study participants were BV patients; (3) the experiment group received an intervention of antibiotic plus probiotics or probiotics, and the intervention of the control groups was antibiotic or placebo; (4) Chinese or English publications were available.

Studies with the following should be excluded from our study: (1) duplicate results or articles; (2) evident data errors; (3) meta-analyses, conference reports, case reports, systematic reviews, theoretical research, and other forms of comment or research; (4) studies with no control group; (5) irrelevant outcomes.

Two of our investigators independently assessed all retrieved studies and determined if they met the predefined inclusion criteria. In addition, any differences were settled by enlisting a third investigator.

Data Extraction Process and Quality Assessment

Manuscripts were thoroughly checked by two of our investigators to collect basic information, including names of authors, publication year, age, sample size and intervention, as well as primary study outcomes, including BV recurrence rate, BV cure/remission rate and AEs. Two of our investigators independently assessed all retrieved studies, and any differences were settled with a help of a third investigator.

Statistics Analysis

We applied STATA v10.0 (College Station, TX, USA) for all estimation and analyses across the included trials. The analytic method was on the basis of heterogeneity of chi-squared and I^2 tests to measure and determine ideal analytic models, including fixed-effects or random-effects, describing as follows respectively: $p \leq 0.05$ and $I^2 > 50\%$ (high heterogeneity), random-effects model; $p > 0.05$ and an $I^2 \leq 50\%$ (acceptable heterogeneity), fixed-effects model. As for continuous variables, mean ± standard deviations were applied and compared on the basis of mean difference (MD). On the other hand, categorical data were expressed as percentages and further compared based on relative risk (RR)/odds ratios (ORs). We also analyzed all the indexes of our study with the use of RR and 95% CI.

Results

Literature Search Process

The initial search totally included 439 publications with the use of keywords and excluded

394 articles after primary screening of title and abstract. In addition, 45 publications underwent complete full-text assessment, and 27 were excluded due to failure to meet the predefined inclusion criteria. The causes for exclusion included the following: lack of clinical outcomes (5), theoretical research (15), and duplicated articles (7). A final total of 18 studies[8-25] with 1651 patients were selected and included for this meta-analysis based on the inclusion criteria. Figure 1 describes the detailed process of study selection.

Table I lists the basic information for each study, including names of authors, publication year, age, sample, and interventions, and subgroup analysis was done according to the interventions: antibiotic plus probiotics *vs.* antibiotics, probiotics *vs.* placebo, and probiotics *vs.* antibiotics.

Main Results

In the subgroup analysis of antibiotic plus probiotics *vs.* antibiotics, the antibiotic plus probiotics group had an evidently lower BV recurrence rate at 1-3 months (RR: 0.302, 95% CI: 0.172-0.532) and overall BV recurrence rate (RR: 0.419, 95% CI: 0.238-0.737) than the antibiotics group. The antibiotic plus probiotics group was highly associated with a higher BV cure/remission rate at 1-3 months (RR: 1.217, 95% CI: 1.037-1.429), >3 months (RR: 1.271, 95% CI: 1.111-1.454) and overall BV cure/remission rate (RR: 1.212, 95% CI: 1.105-1.329) than the antibiotics group. Nonetheless, no significant difference was found in the rate of AEs at 1-3 months (RR: 0.644, 95% CI: 0.396-1.047) and overall analysis (RR: 0.910, 95% CI: 0.651-1.273) between the two groups.

In the subgroup analysis of probiotics vs. placebo, the probiotics group had a markedly lower BV recurrence rate at 1-3 months (RR: 0.155, 95% CI: 0.072-0.331) and overall BV recurrence rate (RR: 0.316, 95% CI: 0.184-0.543) than the placebo group. The BV cure/remission rate at 1-3 months (RR: 10.120, 95% CI: 1.457-70.304) was evidently higher in the probiotics group than that of the placebo group.

In the subgroup analysis of probiotics *vs.* antibiotics, the probiotics group had a markedly lower BV recurrence rate at <1 month (RR: 0.387, 95% CI: 0.206-0.726), 1-3 months (RR: 0.180, 95% CI: 0.057-0.571) and overall BV recurrence rate (RR: 0.306, 95% CI: 0.176-0.532) than the antibiotics group. The BV cure/remission rate at 1-3 months (RR: 1.371, 95% CI: 1.071-1.757) was substantially higher in the probiotics group than the placebo group. The incidence of AEs at <1 month (RR: 0.182, 95% CI: 0.046-0.718) was significantly lower in the probiotics group than that of the antibiotics group.

The abovementioned results are presented in Table II.

Quality and Bias Assessment

We applied several complementary methods for the assessment of study quality as well as risk of bias, such as Begg's and Egger's test, and funnel plots. In the subgroup analysis of antibiotic plus probiotics *vs.* antibiotics, clear asymmetry was identified in the log RR funnel plot for BV cure/remission rate for these studies, suggesting a high publication bias risk (Figure 2). According to the results of Begg's test (p=0.003) and Egger's test (p=0.029), a significant risk of bias across the above study results was indeed found. In the subgroup analysis of probiotics *vs.* placebo, clear symmetry was identified in the log RR funnel plot for BV recurrence rate for relevant studies, indicating a low publication bias risk (Figure 3). Based on Begg's test (p=0.133) and Egger's test (p=0.402), we also found a significant risk of bias among the study results. In the subgroup analysis of probiotics *vs.* antibiotics, clear symmetry was shown in the log RR funnel plot for BV recurrence rate in the associated studies, indicating a low publication bias risk (Figure 4). According to the results of Begg's test (p=0.221) and Egger's test (p=0.474), there was a significant risk of bias among the study results.

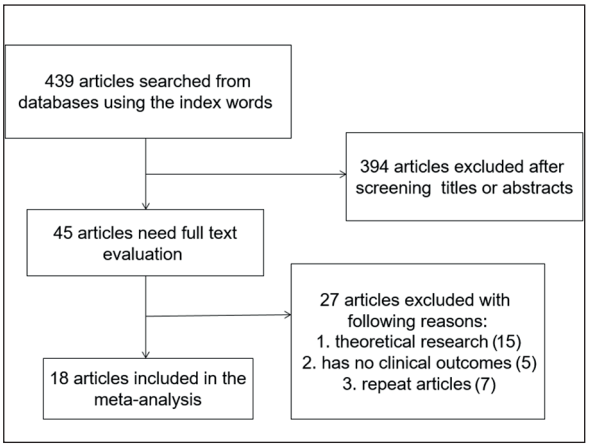

Figure 1. Literature search and selection strategy.

Discussion

BV has been considered as the most common

Table I. The basic characteristics of the included studies.

Study	Sample		Age		Intervention	
	T	C	T	C	T	C
C. Laue 2018[17]	18	18	≥ 18	≥ 18	Oral metronidazole for 7 days (2×500 mg/d)+125 g yoghurt (containing living strains *L. crispatus* LbV 88) twice daily 4 weeks	Oral metronidazole for 7 days (2×500 mg/d)+ placebo
Nadia Recine 2016[11]	125	125	22-38	19-36	Metronidazole 500 mg orally twice a day for 7 days followed by vaginal tablets containing *L. rhamnosus* BMX 54	Metronidazole 500 mg orally twice a day for 7 days
Robab Davar 2016[12]	28	31	–	–	Probiotic for 6 months + single dose of 150 mg fluconazole	Single dose of 150 mg fluconazole
S. Nouraei 2012[13]	45	45	18-40	18-40	Oral protexin with fluconazole	Fluconazole
Piotr B. Heczko 2015[15]	73	81	18-50	18-50	Oral probiotic preparation (prOVag®) containing three *L.* strains together with standard metronidazole treatment	Standard metronidazole treatment
Per-Göran Larsso 2008[16]	50	50	18.8-53.6	18.8-53.6	Vaginal clindamycin therapy followed by vaginal gelatine capsules containing either 109 freeze-dried lactobacilli for 10 days during 3 menstrual cycles	Vaginal lindamycin therapy followed by identical placebo capsules for 10 days during 3 menstrual cycles
Valentina Marcone 2008[18]	42	42	–	–	One vaginal tablet containing freeze-dried *L. rhamnosus* once a week at bedtime for two months + one vaginal tablet containing freeze-dried *L. rhamnosus* once a week at bedtime for two months	Oral metronidazole 500 mg twice a day for seven days
Valentina Marcone 2010[8]	23	23	–	–	Once-weekly vaginal application of 40 mg of *L. rhamnosus* for 6 months + a twice daily dose of 500 mg oral metronidazole for 7 days	A twice daily dose of 500 mg oral metronidazole for 7 days
Rafael C. R. Martinez 2009[9]	32	32	16-51	16-50	Single dose of tinidazole 2 g with 2 capsules containing *L. rhamnosus* GR-1 and *L. reuteric* RC-14 every morning for 4 weeks	Single dose of tinidazole 2 g for 4 weeks
L Petricevic 2008[10]	83	88	–	–	Vaginal capsules containing 109 colony-forming units of live Lcr35 for 7 days after standard antibiotic therapy for 7 days	Standard antibiotic therapy for 7 days

Continued

Table I *(Continued)*. The basic characteristics of the included studies.

Study	Sample		Age		Intervention	
	T	C	T	C	T	C
Anders Hallen 1991[19]	28	29	–	–	Lyophilized *L.* acidophilus	Placebo
R. Hemalatha 2012[20]	37	30	–	–	Probiotic lactobacilli vaginal tablets (*L. brevis* CD2, *L. salivarius subsp. salicinius*, *L. plantarum*)	Vaginal pH tablet (active comparator)
P. Mastromarino 2008[21]	18	16	≥ 18	≥ 18	One L.-containing tablet daily for 7 days	Placebo daily for 7 days
Franco Vicariotto 2014[22]	24	10	18-50	18-50	*L. plantarum* LP01, once a day for 7 consecutive nights, followed by 1 tablet every 3 nights for a further 3-week application (acute phase) and, finally, 1 tablet per week to maintain a long-term vaginal colonization against possible recurrences.	Placebo
Kingsley C. Anukam 2006[23]	20	20	–	–	*L. rhamnosus* GR-1 and *L. reuteri* RC-14 each night for 5 daysa day (in the morning and evening)	0.75% metronidazole gel, applied vaginally twice
Katarina Eriksson 2005[14]	127	128	20-52	18-53	Clindamycin ovules (DalacinH 100 mg ovule, Pharmacia Upjohn, Stockholm, Sweden) vaginally once daily for 3 days during the open part of the study, lactobacilli tampons were loaded with a mixture of freeze-dried *L. fermentum*, *L. caseivar. rhamnosus* and *L. gasseri*	Clindamycin ovules (DalacinH 100 mg ovule, Pharmacia Upjohn, Stockholm, Sweden) vaginally once daily for 3 days during the open part of the study, placebo
Zongxin Ling 2013[24]	25	30	–	–	10-day probiotics regimen	7-day metronidazole regimen
R.C Martinez 2009[25]	29	26	16-46	16-42	Fluconazole (150 mg) supplemented every morning for the following 4 weeks with two probiotic capsules (containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14)	Fluconazole (150 mg) supplemented every morning for the following 4 weeks with two placebo

vaginal infectious disease in women of childbearing age, which poses a seriously threat to the physical and mental health of women. In addition, the condition is regarded a risk factor for pregnancy complications. It can cause preterm delivery, premature rupture of the membrane, preterm delivery of low-weight infants, recurrent abortion, and chorioamnionitis, and increases the incidence of sexually transmitted diseases, including HIV. At present, the treatment of symptomatic BV patients in China mainly focuses on anti-infection, supplemented by regulating vaginal microecology[1-5].

At present, there is no single bacterium as a specific diagnostic marker of BV, which is probably caused by dysregulation of the vaginal flora.

Table II. The results of meta-analysis.

Index	N (case/control)	Time group	RR (95% CI)	p^*	I^2	$p^\#$	*p*-value	
							Begg's	Egger's
Antibiotic + probiotics *vs.* antibiotics								
BV recurrence rate	245/256	1-3 months	0.302 (0.172,0.532)	0.811	0.0%	< 0.001	0.652	0.189
	56/62	> 3 months	0.719 (0.067,7.671)	0.202	38.6%	0.785	0.999	-
	447/475	overall	0.419 (0.238,0.737)	0.027	50.7%	0.003	0.392	0.023
BV cure/remission rate	338/343	1-3 months	1.217 (1.037,1.429)	< 0.001	78.3%	0.016	0.060	0.142
	111/111	> 3 months	1.271 (1.111,1.454)	0.989	0.0%	< 0.001	0.734	0.553
	658/666	overall	1.212 (1.105,1.329)	0.008	55.5%	< 0.001	0.003	0.029
AE	47/44	1-3 months	0.644 (0.396,1.047)	0.059	71.9%	0.076	0.999	-
	224/222	overall	0.910 (0.651,1.273)	0.247	27.4%	0.583	0.999	0.248
Probiotics *vs.* placebo								
BV recurrence rate	36/32	< 1 month	0.146 (0.004,5.384)	0.010	85.1%	0.296	0.999	-
	48/20	1-3 months	0.155 (0.072,0.331)	0.485	0.0%	< 0.001	0.999	-
	149/111	overall	0.316 (0.184,0.543)	0.030	59.6%	< 0.001	0.133	0.402
BV cure/remission rate	48/20	1-3 months	10.120 (1.457,70.304)	0.786	0.0%	0.019	0.999	-
Probiotics *vs.* antibiotics								
BV recurrence rate	65/70	< 1 month	0.387 (0.206,0.726)	0.540	0.0%	0.003	0.999	0.532
	45/50	1-3 months	0.180 (0.057,0.571)	0.677	0.0%	0.004	0.999	-
	110/120	overall	0.306 (0.176,0.532)	0.623	0.0%	< 0.001	0.221	0.474
BV cure/remission rate	25/30	< 1 month	1.056 (0.851,1.310)	-	-	0.621	-	-
	25/30	1-3 months	1.371 (1.071,1.757)	-	-	0.012	-	-
	50/60	overall	1.195 (0.924,1.546)	0.116	59.4%	0.176	0.999	-
AE	20/20	< 1 month	0.182 (0.046,0.718)	-	-	0.015	-	-

*p value of Heterogeneity chi squared. $^\#p$ value of Pooled statistic.

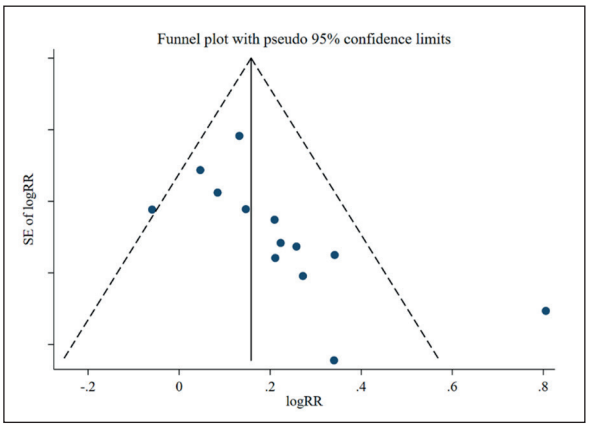

Figure 2. Funnel plot analysis in subgroup analysis of antibiotic plus probiotics *vs.* antibiotics.

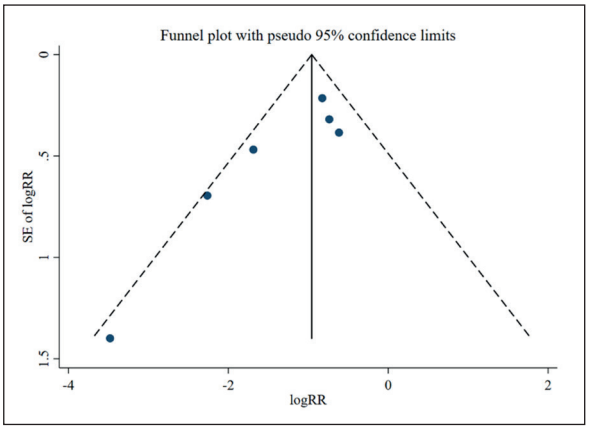

Figure 3. Funnel plot analysis in subgroup analysis of probiotics *vs.* placebo.

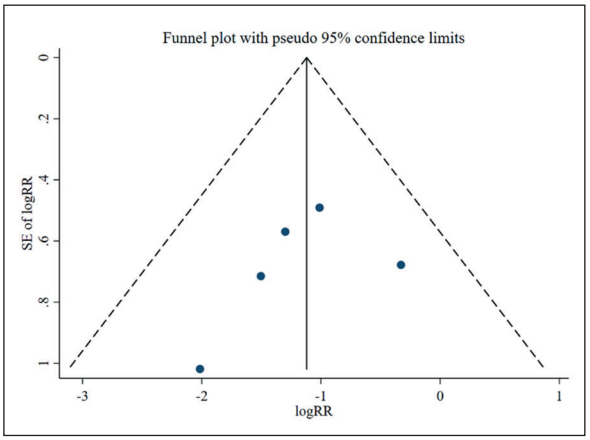

Figure 4. Funnel plot analysis in subgroup analysis of probiotic *vs.* antibiotics.

Therefore, drugs that restore and rebuild the normal vaginal flora dominated by *Lactobacillus* remain pivotal to the treatment of BV. However, the current first-line regimens in the clinical guidelines of all countries are the standard therapy of metronidazole and clindamycin. With increasing drug resistance of the vaginal flora, the effective rate of the standard therapy is gradually reduced, while the recurrence rate is rising. Finding novel alternative therapy and elucidating the mechanism of bacteria-restoring drugs can be helpful and bring great benefit to the clinical treatment of BV.

Clinical trials using single strains or combinations of strains to treat bacterial vaginitis have been carried out for many years. These probiotics contain a family of *Lactobacillus* bacteria and are given either orally or vaginally. There are two treatment options for BV: probiotics alone or probiotic adjuvants after conventional antibiotics. It remains unclear whether probiotics are used alone for BV treatment or probiotics combined with antibiotics for BV treatment, which is related to the uniqueness of probiotics. There are many kinds of probiotics, and there are great differences among various probiotics, which have great differences in the treatment of BV. Secondly, the method and time of administration also have a great impact on therapeutic effect.

When antibiotics are used to treat BV, pathogenic bacteria are quickly killed, but non-pathogenic bacteria are also killed, briefly forming a sterile environment. If certain probiotics are given at this time, the probiotics can quickly colonize the vagina and occupy the colonization site of the original pathogenic bacteria so as to prevent the recurrence of BV. Probiotics are good candidates for the treatment of BV, which is highly associated with the treatment of BV as well as the prevention of recurrence. Probiotics also is pivotal to the treatment of vaginitis in women. They inhibit the growth of pathogenic microorganisms by producing a variety of antimicrobial compounds and lactic acid, and by stimulating the immune system through competitive adhesion to achieve the effect of treating BV[21-25].

In our meta-analysis, compared with antibiotics, antibiotic plus probiotics significantly decreased the BV recurrence rate (at 1-3 months and overall analysis) and increased the BV cure/remission rate (at 1-3 months and overall analysis). Compared with the placebo, probiotics decreased the BV recurrence rate (at 1-3 months and overall analysis) and increased the BV cure/

remission rate (at 1-3 months). Compared with antibiotics, probiotics significantly decreased the BV recurrence rate (at <1 month, 1-3 months and overall analysis) and the incidence of AEs (at <1 month), and increased the BV cure/remission rate (at 1-3 months). In the treatment of BV, antibiotic plus probiotics was superior to antibiotics, and probiotics was superior to antibiotics. In terms of the length of treatment, most of the significant benefits were achieved over long periods of treatment (at 1-3 month).

Limitations

However, there were several limitations that should be acknowledged: (1) the current studies have limited sample size; (2) different selection criteria were used in individual studies; (3) different strains and doses of probiotics were used in individual studies; (4) patients experienced different severities of the disease; (5) our study only analyzed pooled data as no individual patient data was available, limiting comprehensive analyses.

Conclusions

In comparison with short-term probiotics treatment (<1 month), long-term probiotics treatment (1-3 months) yielded superior beneficial outcomes and efficacy in the treatment of BV. Besides, probiotics were indeed evidently more effective than antibiotics, and antibiotic plus probiotics produced better results than antibiotics.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Contributionss

Each author made substantial contributions to the creation of this paper. All authors have read and approved the final manuscript.

Data Availability Statement

No datasets have been generated related to this published article

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