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Effectivity and efficacy probiotics for Bacterial Vaginosis treatments: Meta-analysis

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ABSTRACT

Introduction: Bacterial Vaginosis (BV) is the most common cause of vaginal discharge. However, in some cases, side effects and resistance rates have been reported when antibiotics are administered. This problem has prompted several investigations on the administration of probiotics as an adjunct therapy to treat this infection.

Objection: This study aims to conduct a meta-analysis based on evidence to determine the efficacy and safety of probiotic and antibiotic treatments.

Methods: The meta-analysis was performed using PRISMA guidelines. The literature review was conducted in December 2020 using PubMed, Science Direct, Cochrane Library, and RevMan V.5.3.

Result: The results showed a high and significant cure rate from the analysis of 1006 and 528 samples of probiotics and non-probiotics or control in 16 studies. The recurrence rate was statistically significant with probiotic treatment. Furthermore, neither procedures nor therapy failure showed a significantly lower adverse event rate than the control group.

Conclusion: Probiotic shows better results compared to the control group. However, both have the same occurrence of adverse event.

1. Introduction

Bacterial Vaginosis (BV) is the most common cause of vaginal discharge characterized by dysbiosis due to Lactobacilli producing lactic acid as well as facultative and anaerobic proliferation (Muzny et al., 2019a). It is common in the reproductive age and occurs with or without symptoms. The symptoms of this infection in 50% of women include an unpleasant vaginal odor, discharge, itching, and an increase in vaginal pH (Makella S Coudray1, 2021).

Abbreviations: BV, Bacterial Vaginosis; CDC, Centers for Disease Control; RCTs, Randomized Control Trials; CRISPR, Clustered regularly interspaced short palindromic repeat-associated.

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The prevalence of BV in different parts of the world varies at approximately between 19 and 24%, and its incidence is higher in developing countries. According to national data from the CDC, the prevalence of this infection in women of reproductive age is about 29%, or approximately 21 million persons (Homayouni et al., 2014).

The CDC has approved the administration of antibiotics such as metronidazole and tinidazole in treating BV. However, in some cases, these drugs showed some side effects and resistance rates (Bacterial Vaginosis, 2021). This problem has prompted several investigations on the administration of probiotics as an adjunct therapy to treat BV. These are believed to increase and reduce BV's cure and recurrence rates, respectively. However, its effectiveness and safety need to be further examined since the use of antibiotics is under development (Larsson et al., 2011).

2. Material and methods

2.1. Literature search

This meta-analysis was conducted following the PRISMA guidelines, as shown in Fig. 1 (Page et al., 2021). The literature search was performed using Cochrane, Sciencedirect, and PubMed. The keywords used are probiotics, antibiotics, and Bacterial Vaginosis. Finally, all randomized control trials from 2006 to 2019 were included.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this study include (1) randomized control trials (RCTs); (2) comparisons of probiotics with placebo or antibiotics, and (3) a report of at least one of the following outcomes, such as cure rates, failure medication, recurrence rates, and adverse event. Meanwhile, the exclusion criteria are (1) unclear reports of the outcomes as mentioned

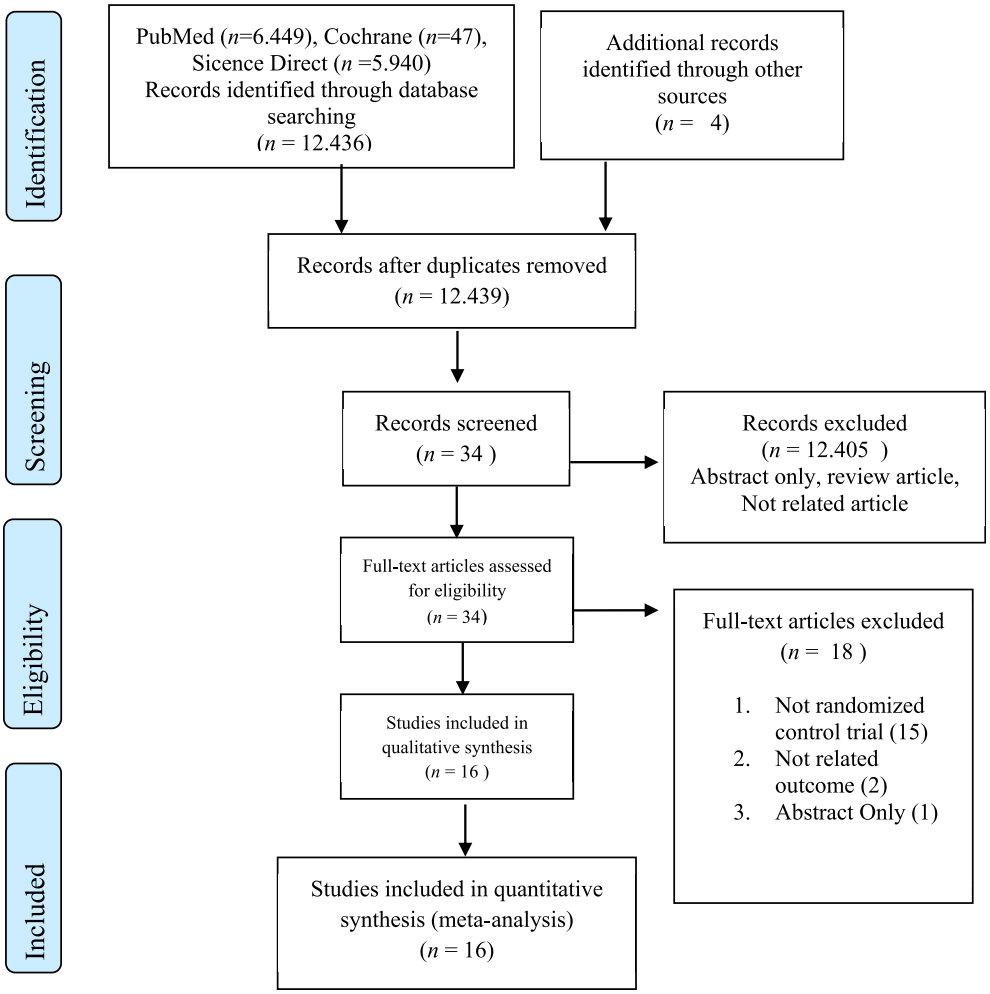

Fig. 1. Record screening article with PRISMA flow chart.

earlier, (2) unextractable or uncomputable data, and (3) non-RCTs. The authors independently screened the studies, extracted relevant data, and discussed each outcome.

2.3. Outcome and study quality

The assessed results include cure rates, medication failure, recurrence, and adverse events. The quality of the RCTs was determined using a Jadad score with a scale range of 0–5. Furthermore, the score was considered high, moderate, and low quality when it was >4, 3–4, and <3, respectively. Table 1 present the score assessment (Luchini et al., 2021). Finally, the level of evidence was evaluated for each study based on the available criteria of the Oxford Center for Evidence-Based Medicine (OCEBM Levels of Evidence, 2011).

2.4. Statistical analysis

The statistical analysis Review Manager version 5.3 was used to calculate each parameter, while Mantel-Hanzel methods combined results across studies. The data type was dichotomous or categorical and expressed as OR with a 95% confidence interval (CI). Furthermore, the Cochrane Chi-squared test and inconsistency (*I2*) examine the studies' heterogeneity. A *P-value* <0.05 was considered statistically significant; hence, heterogeneity was significant when I2 >50%. The effect models used were random and fixed, and they were applied when heterogeneity was >50% and <50%, respectively.

3. Result

3.1. Baseline characteristic

A total of 12,436 related articles and four from other sources were analyzed in the form of a bibliography with the final screening results of 16 studies. The total sample obtained was 1534 patients in each treatment group. Furthermore, this includes 1006 and 528 samples of probiotics and probiotics or control, respectively, as shown in Fig. 1.

Table 2 shows the characteristics of the included studies (Anukam, Osazuwa, Ahonkhai, et al., 2006; Anukam, Osazuwa, Osemene, et al., 2006; Bohbot et al., 2018; Cohen et al., 2020; Eriksson et al., 2005; Happel et al., 2020; Hemmerling et al., 2010; Hummelen et al., 2010; Larsson et al., 2011; Laue et al., 2018; Marcotte et al., 2019; Martinez et al., 2009; Mastromarino et al., 2009; Russo et al., 2019; Sgibnev & Kremleva, 2020; Vujic et al., 2013). The evidence base determination level was 1b for 16 RCTs, and the studies attained a significant level of quality, with Jadad scores in the range of 3–5.

3.2. Cure rate

Fig. 2 shows eleven articles with 717 patients in the probiotic group and 470 in control. The prebiotic group has a high cure rate (OR 3.30; 95% CI, 1.45 to 7.50; p = 0.004) with a reasonably high heterogeneity as indicated by the chi-Squared test to be I2 = 85%.

Table 1
Jadad Score assesment.

Article	Randomization	Blinding	Withdrawals or Dropouts	Jadad Scale
Anukam a 2006 (Anukam et al., 2006a)	2	1	1	4
Anukam b 2006 (Anukam et al., 2006b)	2	0	1	3
Bohbot 2017 (Bohbot et al., 2018)	1	2	1	4
Cohen 2020 (Cohen et al., 2020)	1	2	1	4
Erikson 2005 (Eriksson et al., 2005)	1	2	1	4
Happel 2020 (Happel et al., 2020)	2	2	1	5
Hemmerling 2010 (Hemmerling et al., 2010)	2	2	1	5
Hummelen 2010 (Hummelen et al., 2010)	2	2	1	5
Larson 2008 (Larsson et al., 2008)	1	2	1	4
Laue 2017 (Laue et al., 2018)	2	2	1	5
Marcotte 2019 (Marcotte et al., 2019)	2	1	1	4
Martinez 2009 (Martinez et al., 2009)	2	1	1	4
Mastromarino 2008 (Mastromarino et al., 2009)	2	2	1	5
Russo 2019 (Russo et al., 2019)	2	1	1	4
Sgibnev 2009 (Sgibnev & Kremleva, 2020)	2	2	1	5
Vujic 2013 (Vujic et al., 2013)	2	2	1	5

*Randomization: 1 point; give additional 1 point if randomization method is appropriate (eg. Computer generated)*Blinding: 1 point; give additional 1 point if blinding method is appropriate (eg.indetical placebo) *Withdrawals: 1 point if the number and the reasons was stated.

Table 2
Characteristic of study quality and articles.

Article	Intervention	Country	Study design	LE	Jadad Scale	Case (*n*)	
						Probiotic	Control
Anukam a 2006 (Anukam et al., 2006a)	Antibiotic + Placebo vs Antibiotic	Nigeria	RCT	1b	4	49	57
Anukam b 2006 (Anukam et al., 2006b)	Probiotic vs Antibiotic	Nigeria	RCT	1b	3	17	18
Bohbot 2017 (Bohbot et al., 2018)	Antibiotic + Probiotic vs Antibiotic + Placebo	France	RCT	1b	3	50	48
Cohen 2020 (Cohen et al., 2020)	Probiotics vs Placebo	USA	RCT	1b	4	152	76
Erikson 2005 (Eriksson et al., 2005)	Antibiotic + Probiotic vs Antibiotic + Placebo	Finland	RCT	1b	3	91	96
Happel 2020 (Happel et al., 2020)	Antibiotic + Probiotic vs Antibiotic + Placebo	South Africa	RCT	1b	5	12	18
Hummerling 2010 (Hemmerling et al., 2010)	Antibiotic + Probiotic vs Antibiotic + Placebo	USA	RCT	1b	5	6	18
Hummelen 2010 (Hummelen et al., 2010)	Antibiotic + Probiotic vs Antibiotic + Placebo	Holland	RCT	1b	4	23	28
Larson 2008 (Larsson et al., 2008)	Antibiotic + Probiotic vs Antibiotic + Placebo	Sweden	RCT	1b	4	37	39
Laue 2017 (Laue et al., 2018)	Antibiotic + Probiotic vs Antibiotic + Placebo	German	RCT	1b	5	18	18
Marcotte 2019 (Marcotte et al., 2019)	Antibiotic + Probiotic vs Antibiotic	Sweden	RCT	1b	4	12	14
Martinez 2009 (Martinez et al., 2009)	Antibiotic + Probiotic vs Antibiotic + Placebo	Brazil	RCT	1b	4	32	32
Mastromarino 2008 (Mastromarino et al., 2009)	Probiotics vs Placebo	Italy	RCT	1b	3	18	16
Russo 2019 (Russo et al., 2019)	Antibiotic + Probiotic vs Antibiotic + Placebo	Italy	RCT	1b	3	24	24
Sgibnev 2009 (Sgibnev & Kremleva, 2020)	Antibiotic + Probiotic vs Antibiotic + Placebo	Rusian	RCT	1b	5	44	42
Vujic 2013 (Vujic et al., 2013)	Probiotics vs placebo	Croatia	RCT	1b	4	394	149

LE: Level of Evidence Base, 1b: Level of Evidence Randomized control trial.

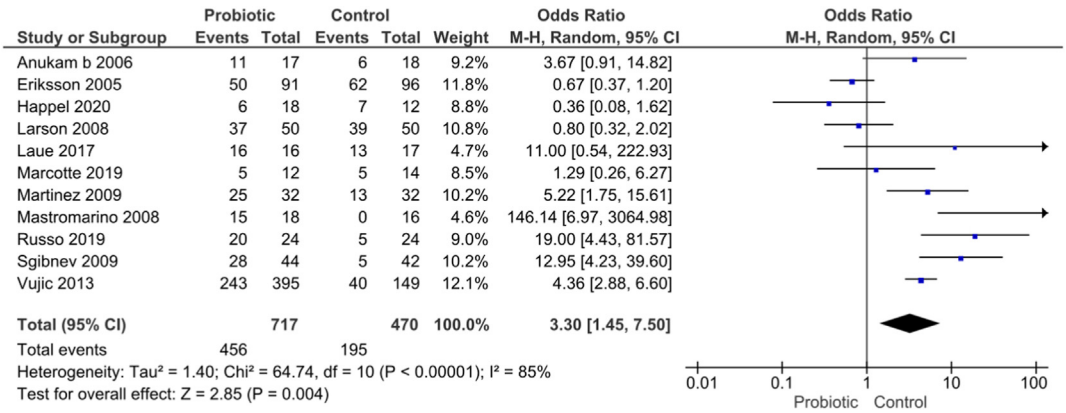

Fig. 2. Forest plot cure rate.

3.3. Recurrence rate

The recurrence rate was compared in four studies, as shown in Fig. 3. The total subgroup reported had a significant difference where the recurrence rate was less in the probiotic group of patients (OR 0.50; 95% CI, 0.32 to 0.078; p = 0.002) without heterogeneity I2 = 0%.

3.4. Adverse event

The five articles in this subgroup showed that abnormalities of itching and burning had no significant difference between the two groups (OR 1.02; 95% CI,0.30 to 3.51; p = 0.97) I2 = 77%, and unpleasant vaginal odor was significantly less in probiotics groups (OR 0.30; 95% CI,0.12 to 0.75; p = 0.01) I2 = 55%. Furthermore, vaginal discharge showed no difference in

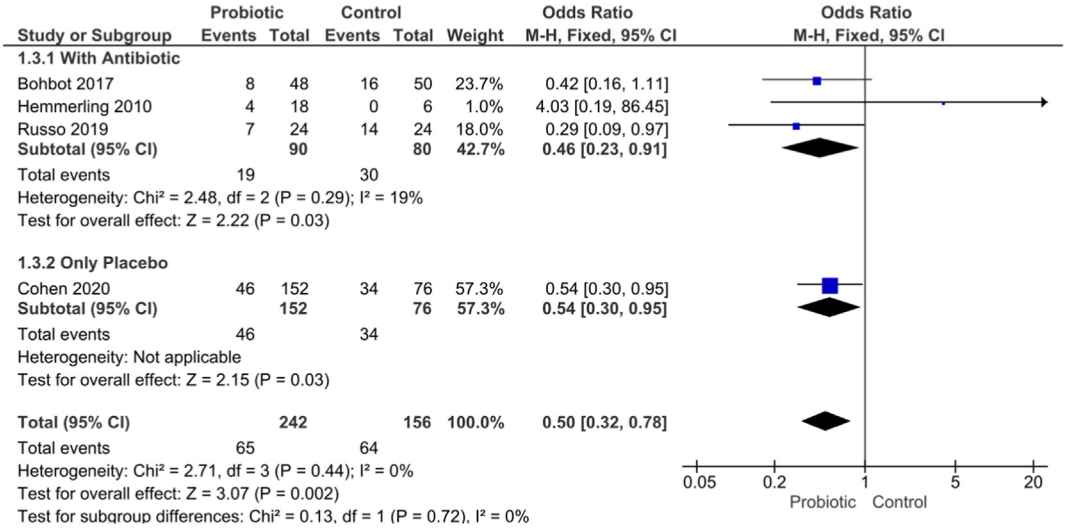

Fig. 3. Forest plot recurrence rate.

the two groups (OR 0.54; 95% CI,0.16 to 1.80; p = 0.32) I2 = 79% with an overall analysis (OR 0.57; 95% CI, 0.30 to 0.095; p = 0.03) and had high heterogeneity I2 = 75% as indicated in Fig. 4.

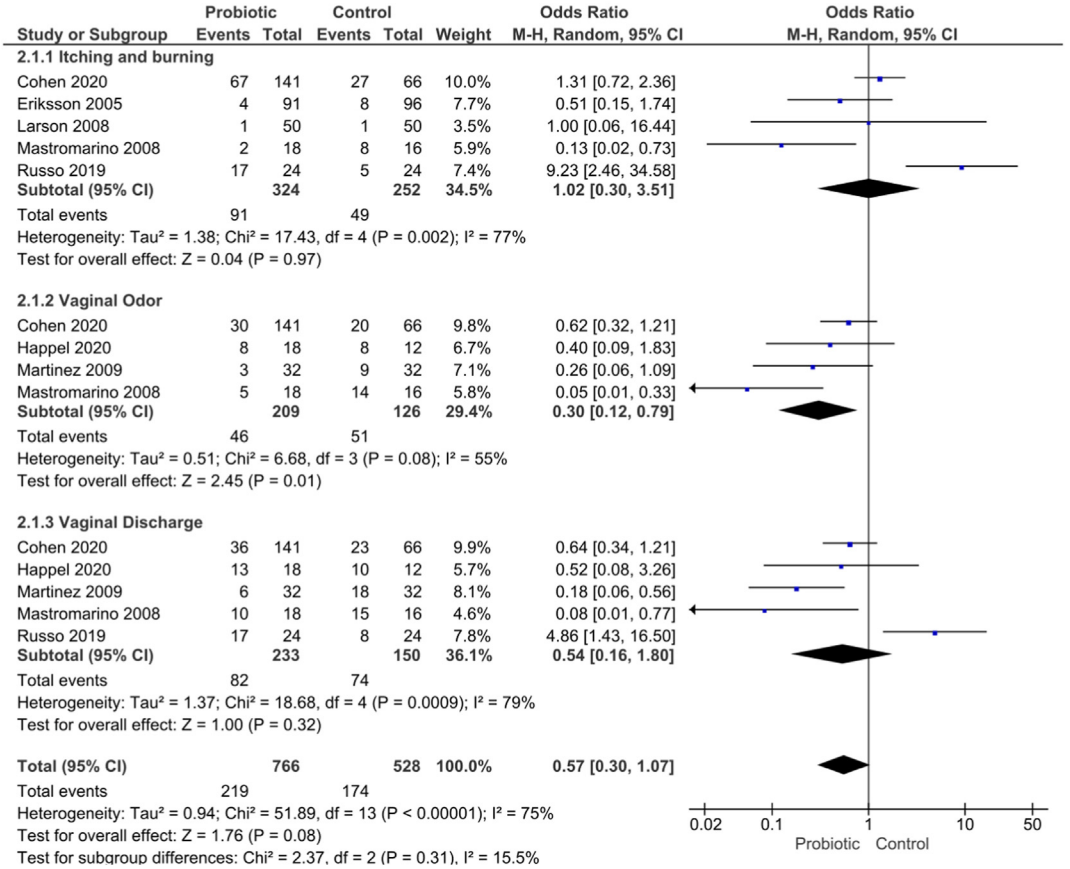

Fig. 4. Forest plot adverse event.

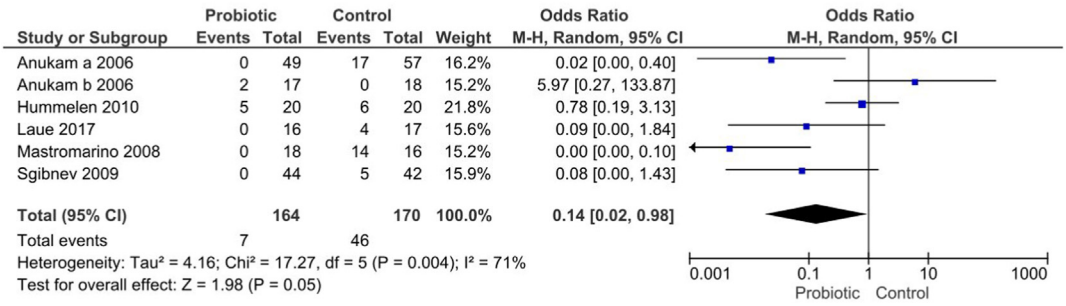

Fig. 5. Forest plot failure of therapy.

3.5. Failure of therapy

Six articles in the analyzed studies showed significant differences in the probiotic groups, which have less incidence of therapy failure (OR 0.14; 95% CI, 0.02 to 0.98; p = 0.05) with high heterogeneity of I2 = 76% as presented in Fig. 5.

4. Discussion

Probiotics are believed to be reasonably effective in dealing with cases of vaginal discharge caused by bacteria or BV (Han & Ren, 2021). Meta-analysis was conducted on 16 RCT articles with good quality jaded scores of 3–5 to determine the effectiveness, efficacy, and safety of using probiotics to treat this infection. A high heterogeneity could be due to insufficient samples or different methods in each article.

The cure rate analysis showed a significant difference where its high level is observed in the probiotic group. In treating BV cases, prebiotics has a good effect because exogenous Lactobacilli maintain the pH of the vagina in an acidic state and help colonize endogenous Lactobacilli to restore normal conditions (Chee et al., 2020; Muzny et al., 2019b). The mechanism of these drugs is to decrease increased phosphorylation of nuclear factor-kappa B p65 in vaginal tissue and inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, for restoring the vaginal micro-ecological environment (Zhou et al., 2019). The use of probiotics in the vaginal and orally has the same positive effect. However, it has a fast therapeutic effect when applied to the vaginal than the oral administration (Anukam et al., 2006b; Reznichenko et al., 2020; TesterFarage and Al-Ghazzewi, 2018). Cure rate and diagnosis are determined by Gram stain Nugent scoring (a score of 0–3 was considered optimal, 4–6 intermediate microbiota, and 7–10 BV), or modified Amsel criteria (defined as the presence of at least 2 of the following criteria: vaginal pH > 4.5, positive whiff test, and 20% clue cells) (Amsel et al., 1983; Nugent et al., 1991).

The recurrence rate analysis showed significantly lower results in the probiotic group. These are in accordance with existing research, stating that antibiotics without probiotics have a high recurrence rate (Hillier et al., 2017; Nyirjesy & Schwebke, 2018; Schwebke et al., 2017). Metronidazole is the recommended treatment option for BV (van Schalkwyk et al., 2015; Workowski et al., 2015). However, its recurrence rate is reported to be 21.2%–25.5% compared to probiotics which are 10.6%–11% (Faught & Reyes, 2019). The several factors that play a role in recurrence include the persistence of a BV-associated biofilm, failure to recolonize the vagina with Lactobacilli, reinfection from an untreated partner, and host genetic or immune factors (Vodstrcil et al., 2021).

The treatment failure in BV is significantly high in the control group. Probiotic reduce the inflammatory response in the vagina and inhibits the growth of pathogenic microbiota by restoring pH (Zhou et al., 2019). Clustered regularly interspaced short palindromic repeat-associated (CRISPR)-genes reduce the metronidazole treatment's effectiveness and protect bacteria like *G. vaginalis*. Furthermore, metronidazole can eliminate low to modest concentrations but cannot make it when a biofilm contains a high *G. vaginalis* (Deng et al., 2018; Verwijs et al., 2020).

There is no difference between the two groups in the incidence of vaginal discharge, vaginal odor, itching, and burning. This explains the potential of the two groups in reducing these complaints. Zhang et al. reported no serious adverse events due to probiotics and metronidazole therapy (Javed et al., 2019; Zhang et al., 2021).

5. Conclusion

This meta-analysis showed several significant advantages of probiotic treatment regarding cure rate, recurrence rate, and therapy failure. The two groups had a similar adverse event occurrence. However, the insufficient RCT data resulted in a lack of potential outcomes, hence, it appears that extensive follow-up investigations are necessary.

Disclosure

There is no conflict of interests and funding

Ethical approval

Not required.

Patient consent

Not required.

Declaration of competing interest

The authors declare no conflict.

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