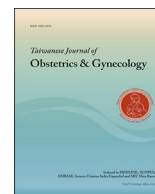




Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

The role of probiotics as adjunct treatment in the prevention and management of gynecological infections: An updated meta-analysis of 35 RCT studies

Mohammad Abavisani ^a, Saeed Sahebi ^a, Farhad Dadgar ^b, Farzaneh Peikfalak ^b, Masoud Keikha ^{c,*}

^a Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran

^b Department of Internal Medicine, School of Medicine, Iranshahr University of Medical Sciences, Iranshahr, Iran

^c Department of Medical Microbiology, School of Medicine, Iranshahr University of Medical Sciences, Iranshahr, Iran



ARTICLE INFO

Article history:

Accepted 3 January 2024

Keywords:

Probiotics
Bacterial vaginosis
Vulvovaginal candidiasis
Randomized controlled trials

ABSTRACT

Objective: The present study aims to conduct a comprehensive meta-analysis of randomized controlled trials (RCTs) investigating the efficacy of probiotics as an adjunct treatment for preventing and treating gynecological infections.

Materials and methods: The study adopted a systematic review of scientific databases including PubMed, Cochrane, and EMBASE, using defined MeSH terms. The inclusion and exclusion criteria were set to refine the search, with the data extraction and quality assessment being conducted by two independent investigators.

Results: A total of 35 articles, comprising 3751 patients, were included in the meta-analysis. The application of probiotics demonstrated a notable increase in the cure rates of bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) as compared to control groups. A significant BV cure rate (OR: 5.972; 95% CI: 2.62–13.59; p-value: 0.01) was noted with probiotic use, which was even more pronounced when used as an adjunctive treatment with antibiotics (OR: 2.504; 95% CI: 1.03–6.06; p-value: 0.04). Additionally, probiotic use significantly reduced the recurrence rates of BV (OR: 0.34; 95% CI: 0.167–0.71; p-value: 0.004). For VVC, a significant increase in the cure rate was observed in the probiotic group (OR: 3.425; 95% CI: 2.404–4.879; p-value: 0.01), along with a lower recurrence rate (OR: 0.325; 95% CI: 0.175–0.606; p-value: 0.01).

Conclusion: Our findings underscore the potential role of probiotics as a beneficial adjunctive treatment for gynecological infections, indicating an improved cure rate and decreased recurrence. However, additional well-designed studies are necessary to corroborate these findings.

© 2024 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are predominant classifications of vaginitis, frequently accompanied by discomforting symptoms such as a malodorous discharge, pruritus, a burning sensation, and pelvic discomfort in the female population. Such conditions are the leading instigators for appointments with clinical obstetricians and gynecologists [1,2].

BV emerges from alterations in the typically lactobacilli-dominant vaginal microbiota, which is instrumental in sustaining a low vaginal pH via the production of H₂O₂ and lactic acid. These

metabolites thwart the transformation of the vaginal microbiota into pathogenic species such as *Gardnerella vaginalis*, *Ureaplasma*, and *Mycoplasma*, among others [3,4]. It is noteworthy that BV does not merely result from the presence of pathogenic organisms but necessitates a pathogenic count escalating to 100 to 1000 times that of the benign vaginal bacteria [5]. Concurrent research highlights that the etiology of BV extends beyond an imbalance and overgrowth of pathogens to involve persistent biofilms. These biofilms significantly contribute to recurrent and resistant conditions by functioning as an immunity-subverting mechanism and obstructing the penetration of antibiotics to the pathogens. This phenomenon could potentially elucidate the antibiotic resistance observed in vaginitis cases [6]. Although BV is generally classified as a mild condition, it may lead to serious complications including miscarriage, premature rupture of membranes (PROM) during

* Corresponding author. Department of Microbiology and Virology, School of Medicine, Iranshahr University of Medical Sciences, Iranshahr, Iran.

E-mail address: masoud.keykha90@gmail.com (M. Keikha).

pregnancy, pelvic inflammatory disease (PID), endometritis, and infertility [7]. VVC is instigated by an overproliferation of yeast organisms, predominantly albicans and non-albicans *Candida* species [8]. In contrast to BV-anaerobe pathogens, *Candida* species demonstrate a high pH tolerance, which facilitates their coexistence with lactobacilli in the vaginal microbiota [2]. The symptomatic manifestation of VVC includes pruritus, follicular vaginal discharge, redness, and dysuria [9]. Existing data indicates that approximately 75% of women will encounter VVC at least once in their lifespan [10]. Triggers such as antibiotic administration, sexual multiplicity, pregnancy, or hormone replacement therapy can precipitate this condition. Nonetheless, a definitive trigger often remains elusive [11].

Standard antifungal and antibiotic treatments have demonstrated efficacy, with the first-line antibiotic regimen for BV showing a 70%–80% cure rate post a four-week treatment course [12]. However, these treatments can exert both physiological and non-physiological influences on the benign vaginal microbiota. The administration of antibiotics may result in the suppression of *lactobacilli* and other vital organisms of the normal vaginal microflora, leading to an increase in vaginal pH, ecological disruption, and subsequent pathogen replacement [13]. Additionally, it has been suggested that an imbalance in the vaginal microbiota could precipitate the onset of hormonal, reproductive, and metabolic disorders [14]. Probiotics, as viable organisms (particularly *Lactobacillus reuteri* RC-14 and *L. rhamnosus* GR-1), have the capacity to integrate themselves into biofilms, resulting in their disintegration and reduction [15,16]. Despite personal hygiene measures, the majority of microbes that constitute the vaginal microflora originate from the gastrointestinal tract [3]. Emerging evidence suggests the potential for genitourinary infection prevention and treatment through the modification of gastrointestinal and vaginal microflora [17]. For oral probiotics to be effective, the organisms must be capable of withstanding the low pH of the upper gastrointestinal tract and successfully colonize the targeted area [18]. Hence, a specific quantity of a targeted probiotic could assist the urogenital tract in regaining a healthy microflora. However, uninformed and inappropriate use of probiotics could lead to undesirable effects, particularly in immunocompromised patients [19]. Although there is a plethora of studies advocating for the benefits of probiotics in the prevention and treatment of vaginitis, the efficacy of probiotics remains a subject of debate. A majority of these studies have assessed the clinical effects of probiotics on gynecological infections, however, potential bias cannot be completely ruled out due to the heterogeneity in treatment protocols, varied follow-up durations, and overall heterogeneity. This study presents an updated meta-analysis of randomized controlled trials (RCTs) studies to decipher the actual role of probiotics as an adjunct treatment in the prevention and treatment of gynecological infections. Additionally, through subgroup analysis, we aim to assess the impact of the species and genus diversity of probiotics, administration routes, and treatment design on therapeutic outcomes.

Methods

Research approach and data collection

This current meta-analysis was undertaken with the objective of elucidating the efficacy of probiotics in the remediation or recurrence of BV and VVC. Relevant studies and literatures were acquired through comprehensive searches of databases such as PubMed, Cochrane, and EMBASE, up until the date of August 4, 2022. MeSH keywords used in the search included “probiotic bacteria”, “*Lactobacillus*”, “urogenital infections”, “bacterial vaginosis”, “vulvovaginitis”, “vaginitis”, and “vulvovaginal candidiasis”. The search

criteria included studies that incorporated both (probiotic bacteria or *Lactobacillus*) and (urogenital infection or bacterial vaginosis or vaginitis or vulvovaginal candidiasis or vulvovaginitis). Each identified study was independently scrutinized by two investigators. Any discrepancies were addressed and resolved via consultation with a third author. Lastly, to preclude potential data omissions, cited references were manually inspected.

Criteria for study selection

The following were the parameters for study inclusion: 1) Availability in English or Chinese languages; 2) Types of studies encompassing randomized control trials and case–controlled studies; 3) Study participants consisting of non-pregnant, non-lactating women; 4) Participants having current or past history of BV and/or VVC according to Nugent score or Amsel's criteria; 5) Studies comparing probiotic treatment versus non-probiotic treatment, with or without antibiotic therapy. Exclusion criteria were as follows: 1) Non-RCT studies including letters, comments, editorials, reviews, retrospective studies, one-arm studies, and other study types apart from RCTs; 2) Studies without a control group; 3) Studies on pediatrics or pregnant or lactating women; 4) Studies on healthy women with no history of gynecological infection.

Data extraction process and quality evaluation

The extracted data from studies that fulfilled the selection criteria included the following: the name of the first author, the country in which the study was conducted, the year of publication, the genus and species of probiotics used, the interval between antibiotic usage and probiotic intervention, the dosage, the route and duration of intervention, and ultimately, the treatment outcome. All data was independently extracted and reviewed by two investigators, and any discrepancies were resolved by consultation with a third author.

Statistical evaluation

The Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ) was employed for the analysis of the amassed data. To assess the heterogeneity of the results, the Cochrane Q-test ($p < 0.05$ was considered significant) and I-squared (I^2) were utilized. The overall efficacy of probiotic treatment was estimated as a percentage and 95% confidence intervals (CIs) through pooling the data. The most suitable analytic models were determined using random-effect (when $p \leq 0.05$ and $I^2 > 50\%$, implying significant heterogeneity) and fixed-effect (when $p > 0.05$ and $I^2 \leq 50\%$, implying acceptable heterogeneity) measurements. The potential for publication bias was assessed via funnel plot asymmetry. Finally, we performed subgroups analyses based on intervention types, administration route of probiotic application, and the number of species and genus of probiotic bacteria to better understand the impact of treatment.

Results

Search results and process

The initial database inquiry yielded 964 studies, 901 of which were subsequently eliminated after title and abstract screening. Of the 63 full-text articles reviewed, 28 were excluded due to non-compliance with the pre-set inclusion criteria. Reasons for exclusion included duplication, limited full-text availability, irrelevance to the study type, and the withholding of data by the authors

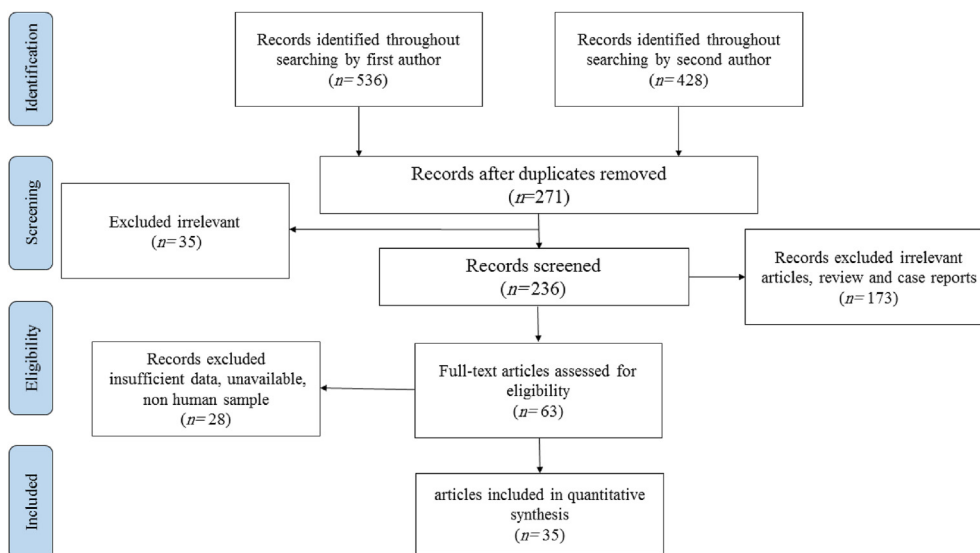


Fig. 1. Flow-diagram of study selection process.

(Fig. 1). Consequently, this meta-analysis includes a total of 35 articles, collectively examining a sample of 3751 patients, all selected based on the outlined inclusion criteria [20–54].

Study characteristics

The meta-analysis encompassed 3751 non-pregnant female participants ranging in age from 18 to 50 years, who were diagnosed with either BV or VVC. The diagnosis of BV/VVC employed various methodologies, including Amsel's criteria, Nugent scores of 7–10, clinical symptoms coupled with microscopy or culture, and clinical signs alone. Follow-up durations ranged from 2 weeks to 12 months for BV and from 5 days to 6 months for VVC. The studies incorporated in this analysis represent a global cross-section of RCTs, with probiotic interventions being delivered either orally or vaginally. Probiotic species utilized in the studies included a broad spectrum of strains, administered as either singular or combined species via oral or vaginal capsules, tablets, or tampons (Table 1).

Statistical results of BV cure

The analysis of 16 articles pertaining to BV cure rates demonstrated a high therapeutic response in BV patients receiving probiotic treatment (ER: 86%, 95% CI: 0.745–0.933; P-value: 0.01; I²: 93%; Egger: 0.06; Begg: 0.26) (Table 2). When compared to controls, probiotic recipients exhibited significantly elevated cure rates (OR: 5.972 95% CI: 2.62–13.59; P-value: 0.01; I²: 89%; Egger: 0.21; Begg: 0.34). Moreover, subgroup analysis indicated that patients using probiotics in conjunction with antibiotics demonstrated higher BV cure rates compared to those on antibiotic therapy alone (OR: 2.504 95% CI: 1.03–6.06; P-value: 0.04; I²: 68%; Egger: 0.75; Begg: 0.8) (Fig. 2). The subgroup analysis also suggested that employing one species or more than two species of probiotics resulted in higher cure rates, regardless of oral or vaginal administration. However, the 'antibiotic vs. probiotic' subgroup analysis revealed a lower heterogeneity, indicating superior cure rates for antibiotics alone compared to probiotics (OR: 3.03 95% CI: 0.96–9.5; P-value: 0.05; I²: 47%; Egger: ND; Begg: ND).

Statistical results of BV recurrence

The analysis of 13 articles indicated a notable reduction in BV recurrence rates in patients using probiotics (ER: 22%, 95% CI:

0.136–0.34; P-value: 0.01; I²: 88%; Egger: 0.17; Begg: 0.5) (Table 3). Furthermore, compared to control groups, those using probiotics displayed a significantly lower risk of BV recurrence (OR: 0.34 95% CI: 0.167–0.71; P-value: 0.004; I²: 0%; Egger: 0.26; Begg: 0.42) (Fig. 3). Additionally, patients using vaginal probiotics showed a reduced risk of BV recurrence, as shown by subgroup analysis with adequate data (OR: 0.18 95% CI: 0.09–0.36; P-value: 0.01; I²: 22%; Egger: 0.75; Begg: 1.00). Subgroup analysis for 'antibiotic + probiotic vs. antibiotic' suggested that the use of probiotics as an adjunct to antibiotics resulted in lower BV recurrence rates (OR: 0.06 95% CI: 0.01–0.28; P-value: 0.01; I²: 0%; Egger: ND; Begg: ND). However, due to data limitations, additional research is required to corroborate these findings. Similar positive outcomes were observed in genus subgroup studies, demonstrating a reduced BV recurrence rate with the use of one or more genera of probiotics.

Statistical results of VVC cure

Further analysis of 6 articles for VVC demonstrated a high cure rate in the probiotic group (ER: 92%, 95% CI: 0.851–0.959; P-value: 0.01; I²: 80%; Egger: 0.001; Begg: 0.008) and a higher cure rate compared to the non-probiotic control group (OR: 3.425 95% CI: 2.404–4.879; P-value: 0.01; I²: 0%; Egger: 0.617; Begg: 0.7) (Table 4) (Fig. 4). Moreover, patients using vaginal probiotics showed a higher VVC cure rate with no significant heterogeneity (OR: 2.85 95% CI: 1.75–4.63; P-value: 0.01; I²: 0%; Egger: 0.23; Begg: 0.73).

Statistical results of VVC recurrence

The data analysis of eleven articles focused on VVC recurrence demonstrated a low recurrence rate (ER: 0.09%, 95% CI: 0.055–0.159; P-value: 0.01, I²: 84%; Egger: 0.13; Begg: 0.11) compared to the control group that abstained from using probiotics (OR: 0.325, 95% CI: 0.175–0.606, P-value: 0.01; I²: 77%; Egger: 0.11; Begg: 0.53) (Table 5) (Fig. 5). Moreover, in the subgroup analysis of the 'antibiotic + probiotic vs antibiotic group,' it was suggested that probiotics, when used as adjunct therapy along with antibiotics, could be more effective than antibiotics alone. An evaluation was carried out in the 'one genus' subgroup analysis to examine the efficacy of using a singular genus of probiotic in the prognosis of

Table 1
Characteristics of the included studies in the meta-analysis.

| First author | Country | Year | Study type; interval | Probiotic supplementation intervention | Dosage/rout/duration | Treatment outcome (Cure/Recurrence) | | | | Ref |
|----------------|-----------|------|--|--|--|--|---|------|---------|------|
| | | | | | | BV | | VVC | | |
| | | | | | | Case | Control | Case | Control | |
| Larsson | Norway | 2008 | RCT; Case: Clindamycin + lactobacilli vaginal gelatin capsule Control: clindamycin + placebo | <i>L. gasseri</i> + <i>L. rhamnosus</i> | 10 ⁸ –10 ⁹ colony forming units (CFU); vaginal capsules, 10 days per month for 4 months | 64% Recurrence: 64.9% (24/37) | 78% Recurrence: 46.2% (18/39) | NA | NA | [20] |
| Petricevic | Austria | 2008 | RCT; Case: Clindamycin + probiotics Control: Clindamycin | <i>L. casei</i> + <i>L. rhamnosus</i> | 10 ⁹ colony forming units (CFU); vaginal capsules for 7 days | 6.1% | 10.2% | NA | NA | [21] |
| Mastro-marino | Italy | 2009 | RCT; Case: Probiotics Control: Placebo without any antibiotic | Florisia (<i>L. brevis</i> CD2 + <i>L. salivarius</i> subsp. <i>salicinius</i> FV2 + <i>L. plantarum</i> FV9) | 10 ⁹ colony forming units (CFU); one vaginal tablet; daily for 7 days | 15/18 Recurrence: 7/18 for BV | 2/16 Recurrence: 13/16 for BV | NA | NA | [22] |
| Bradshaw | Australia | 2012 | RCT Case: MTZ-probiotic Control: Clinda + MTZ-placebo | Gynoflor (<i>L. acidophilus</i> KS400 + 0.03 mg estriol) | 10 ⁷ colony forming units (CFU); single vaginal pessary for 12 day | 30 days: 9/133 180 days: 37/133 | 30 days: 18/275 180 days: 78/275 | NA | NA | [23] |
| van de Wijgert | USA | 2020 | RCT: Case: Counseling + Probiotics Control: Counseling + MTZ | Ecologic Femi+ (<i>B. bifidum</i> W28 + <i>L. acidophilus</i> W70 + <i>L. helveticus</i> W74 + <i>L. brevis</i> W63 + <i>L. plantarum</i> W21 + <i>L. salivarius</i> W24) | 1.5 × 10 ⁹ colony forming units (CFU); vaginal capsule per day for the first five days followed by thrice weekly for 2 months | Recurrence of BV at month 2; 5/12 For 6 months:6/9 | Recurrence of BV at month 2; 11/21 For 6 months: 9/19 | NA | NA | [24] |
| Van de Wijgert | USA | 2020 | RCT: Case: Counseling + Probiotics Control: Counseling + MTZ | Gynophilus LP (<i>L. rhamnosus</i> Lcr35) | 1.6 × 10 ⁹ colony forming units (CFU); vaginal capsule once every four days for 2 month | Recurrence of BV at month 2; 6/10 at month 6: 2/7 | Recurrence of BV at month 2; 11/21 at month 6: 2/7 9/19 | NA | NA | [24] |
| Eriksson | Sweden | 2005 | RCT: Case: Clindamycin + probiotics Control: Clindamycin + placebo | <i>L. gasseri</i> + <i>L. casei</i> var <i>rhamnosus</i> + <i>L. fermentum</i> (impregnated tampons) | 10 ⁸ colony forming units (CFU); for 5 days | Recurrence; (41/91) | Recurrence; (34/96) | NA | NA | [25] |
| Hemalatha | India | 2012 | RCT; Case: Probiotics Control: pH-lowering tablet control | Florisia (<i>L. brevis</i> CD2 + <i>L. salivarius</i> subsp. <i>salicinius</i> + <i>L. plantarum</i>) | 10 ⁹ colony forming units (CFU); one daily vaginal tablet for 8 days | 36/75 | 29/73 | NA | NA | [26] |
| Ling | China | 2013 | RCT; Case: Metronidazole + Probiotics Control: Metronidazole | <i>L. delbrueckii</i> subsp. <i>lactis</i> DM8909 | 10 ⁹ colony forming units (CFU); once daily for 10 days | Recurrence; 22/25 | Recurrence; 25/30 | NA | NA | [27] |

| | | | | | | | | | | |
|----------|-----------|------|--|---|---|----------------------|----------------------|--|---|------|
| Bohbot | France | 2017 | RCT: Case: Metronidazole + Probiotics Control: Metronidazole | Physioflor (<i>L. crispatus</i> IP 174178) | 10 ⁹ colony forming units (CFU); once vaginal capsule a day for two menstrual cycles | 8/39 | 16/39 | NA | NA | [28] |
| Czaja | USA | 2007 | RCT: Case: Probiotics Control: placebo | <i>L. crispatus</i> CTV-05 | 5 × 10 ⁸ colony forming units (CFU); vaginal suppository for 5 days | NA | NA | Recurrence; 4/15 | Recurrence; (2/15) | [29] |
| Pirotta | Australia | 2004 | RCT: Case: Probiotics Control: placebo | Femilac (<i>L. rhamnosus</i> + <i>L. delbrueckii</i> + <i>L. acidophilus</i> + <i>S. thermophilus</i>) | a teaspoon of powder twice daily and one pessary at night for 10 days | NA | NA | Recurrence; 17/59 | Recurrence; 9/54 | [30] |
| Witt | Austria | 2009 | RCT; Case: Probiotic + Itraconazole Control: Itraconazole | <i>L. gasseri</i> | 10 ⁹ colony forming units (CFU); Vaginal; one tablet for 6 months | NA | NA | Recurrence rate; 15/45 At 6 months: 6/25 | Recurrence rate; 12/31 At 6 months: 5/23 | [31] |
| Kovachev | Bulgaria | 2015 | RCT: no-intervention Case: Azole topical treatment + Probiotics Control: Azole topical treatment | Lactagyn (<i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>S. thermophilus</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i>) | 10 ⁹ colony forming units (CFU); Vaginal capsules for 10-day | NA | NA | Recurrence: 10/209 | Recurrence: (76/207) | [32] |
| Laue | Germany | 2018 | RCT; NA | yoghurt containing <i>Lactobacillus</i> strains | NA | 100% | 76.5% | NA | NA | [33] |
| Davar | Iran | 2016 | RCT: Case: Probiotics Control: placebo | <i>Lactobacillus acidophilus</i> <i>Bifidobacterium bifidum</i> <i>Bifidobacterium longum</i> | 10 ⁹ colony forming units (CFU); Oral capsule for 10-day | NA | NA | Recurrence; 7.2% | Recurrence; 35.5% | [34] |
| Recine | Italy | 2016 | prospective case–control; metronidazole 500 mg orally twice a day for 7 days plus probiotics | <i>Lactobacillus rhamnosus</i> BMX 54 as adjuvant treatment | 10 ⁴ CFU; vaginal tablets; once a day for 10 days | 90.4% | 79.2% | NA | NA | [35] |
| Heczko | Poland | 2015 | RCT: Case: Metronidazole + Probiotics Control: Metronidazole | <i>L. gasseri</i> and <i>L. rhamnosus</i> | ≥10 ⁸ CFU; One capsule twice daily oral capsule for 10 days | Recurrence; 45.2% | Recurrence; 47.0% | NA | NA | [36] |
| Nouraei | Iran | 2012 | RCT: Case: Fluconazole + Probiotics Control: Fluconazole capsules (2 × 150 mg) + placebo | Protexin probiotic <i>Lactobacillus</i> | Oral capsules for 10 days | NA | NA | Cure; 93.3% | Cure; 82.2% | [37] |
| Marcone | Italy | 2010 | RCT: Case: Metronidazole + Probiotics Control: Metronidazole | Long-term vaginal administration of <i>Lactobacillus</i> <i>rhamnosus</i> | more than 40,000 CFU; 40 mg vaginal capsules once a week for 6 months | Cure; 96% | Cure; 74% | NA | NA | [38] |
| Anukam | Nigeria | 2009 | RCT: Case: Fluconazole + Probiotics Control: Fluconazole (150 mg) | <i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus</i> <i>reuteri</i> RC-14 | (5 billion live organisms per dose); one Oral capsule for 3 months | NA | NA | Cure; 79% | Cure; 43% | [39] |
| Anukam | Nigeria | 2006 | RCT: Case: Metronidazole + Probiotics Control: Metronidazole | oral probiotic <i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14 | 10 ⁹ CFU; vaginally two gelatin capsules for 5 days | Recurrence; 10% | Recurrence; 45% | NA | NA | [40] |

(continued on next page)

Table 1 (continued)

| First author | Country | Year | Study type; interval | Probiotic supplementation intervention | Dosage/rout/duration | Treatment outcome (Cure/Recurrence) | | | | Ref |
|--------------|---------|-------|--|--|---|---|---|--|---|------|
| | | | | | | BV | | VVC | | |
| | | | | | | Case | Control | Case | Control | |
| Anukam | Nigeria | 2006 | RCT: Case: Metronidazole + Probiotics Control: Metronidazole | <i>Lactobacillus rhamnosus</i> GR-1 <i>Lactobacillus reuteri</i> RC-14 | 10 ⁹ CFU; Oral twice daily for 30 days | Cure; 88% | Cure; 40% | NA | NA | [41] |
| Martinez | Brazil | 2009a | RCT: Case: Tinidazole + Probiotics Control: Tinidazole | <i>Lactobacillus rhamnosus</i> GR-1, and <i>Lactobacillus reuteri</i> RC-14 | 10 ⁹ CFU; two Oral capsules Daily for 28 days | Recurrence; 12.5% Cure; 87.5% | Recurrence; 46.9% Cure; 50% | NA | NA | [42] |
| Martinez | Brazil | 2009b | RCT: Case: Fluconazole + Probiotics Control: Fluconazole | <i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14 | 10 ⁹ CFU; two oral capsules for 4 weeks | NA | NA | Recurrence; 10.3% | Recurrence; 38.5% | [43] |
| Yang | China | 2009 | RCT: Case: clotrimazole + Probiotics Control: clotrimazole | <i>Lactobacillus</i> | Vaginal capsule; Once daily for 10 days | NA | NA | Recurrence; 7.1% Cure; 92.86% | Recurrence; 16.7% Cure; 83.33% | [44] |
| Hua | China | 2008 | RCT: Case: Miconazole + Probiotics Control: Miconazole | <i>Lactobacillus</i> | Vaginal capsule; Once daily for 10 days | NA | NA | Recurrence; 4.8% Cure; 70.34% | Recurrence; 13.9% Cure; 67.52% | [45] |
| Marcone | Italy | 2008 | RCT: Case: Metronidazole + Probiotics Control: Metronidazole | <i>Lactobacillus rhamnosus</i> | >40,000 CFU; Vaginal tablet; Once a week for two months | Cure; At 1 month: 96% At 6 months: 98% Recurrence: 2% | Cure; At 1 month: 91% At 6 months: 74% Recurrence: 26% | NA | NA | [46] |
| Ma | China | 2007 | RCT: Case: Miconazole + Probiotics Control: Miconazole | <i>Lactobacillus</i> | Vaginal capsule (0.5 g) once daily for 7 days | NA | NA | Cure; 85.2% | Cure; 70.4% | [47] |
| Mai | China | 2007 | RCT: Case: Clotrimazole + Probiotics Control: Clotrimazole | <i>Lactobacillus</i> | Vaginal capsule (0.25 g); Once daily for 10 days | NA | NA | Recurrence; 5.9% Cure; 94.1% | Recurrence; 15.5% Cure; 83.3% | [48] |
| Han | China | 2006 | RCT: Case: Clotrimazole + Probiotics Control: Clotrimazole | <i>Lactobacillus</i> | Vaginal capsule; Once daily for 10 days | NA | NA | Recurrence; 3.9% Cure; 96.1% | Recurrence; 13.0% Cure; 86.96% | [49] |
| Vicariotto | Italy | 2012 | RCT: Case: Probiotics Control: placebo | <i>L. fermentum</i> LF15 and <i>L. plantarum</i> LP01 | 400 million live cells per dose; Slow-release Vaginal tablets once a day for 7 consecutive days | Recurrence; Day 28: 8.3% Day 56: 83.3% | Recurrence; Day 28: 80% Day 56: 10% | NA | NA | [50] |
| Ya | China | 2010 | RCT: Case: Probiotics Control: placebo | Combination product containing <i>L. rhamnosus</i> A-119 <i>L. acidophilus</i> A-212 <i>Streptococcus. thermophilus</i> A-33 | 8 billion CFU; Vaginal capsule a day for 7 days | Recurrence; 15.78% | Recurrence; 45% | NA | NA | [51] |

| | | | | | | | | | |
|--------|---------|------|--|---|---|--|---------------------------------------|--|------|
| Anders | Sweden | 1991 | RCT: Case: Probiotics Control: placebo | Lyophilized <i>L. acidophilus</i> | 10 ⁹ CFU; Vaginal capsule Twice daily for six days | Cure; 10.3% | NA | NA | [52] |
| Parent | Belgium | 1996 | RCT: Case: Probiotics Control: placebo | <i>L. acidophilus</i> plus 0.03 mg estriol for 6 days | 10 ⁷ CFU; table once daily for 7 days | Cure; 22.2% | NA | NA | [53] |
| Lin | China | 2006 | RCT: Case: Cretrozole + Probiotics Control: Cretrozole | <i>Lactobacillus</i> | Vaginal capsule Once daily for 7 days | NA | Recurrence; 3.8% Cure; 98.1% | Recurrence; 25.0% Cure; 94.2% | [54] |
| Lin | China | 2006 | RCT: Case: Metronidazole + Probiotics Control: Metronidazole | <i>Lactobacillus</i> | Vaginal capsule Once daily for 7 days | Recurrence; 23.5% Cure; 92.2% | NA | NA | [54] |

VVC recurrence. The results indicated that patients who used a singular genus probiotic were notably at a lower risk of VVC recurrence (OR: 0.31, 95% CI: 0.21–0.45, P-value: 0.01; I²: 47%; Egger: 0.17; Begg: 1.00). On the other hand, the data analysis of the ‘more than 1 genus’ subgroup analysis exhibited heterogeneity. Thus, more studies are warranted to affirm the current findings.

Publication bias

The analysis of Begg’s and Egger’s p-value test was revealed the presence of a slight publication bias. Funnel plot was also confirmed the potential publication bias in the eligible studies (Fig. 6); However, the trim-fill method was applied in the case of considerable publication bias. In this regards, there is no changes was observed after the application of trim-fill method in the pooled estimates. Thus, the trim-fill method was approved the stability of overall estimates.

Discussion

Our comprehensive meta-analysis presents a consolidated examination of several RCTs and provides an in-depth perspective on the potential role of probiotics as an adjunctive treatment for gynecological infections. The study underscores the beneficial effects of probiotics in the management of bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC), as indicated by the synthesized data.

A striking observation in our study was the substantial cure rate for BV among patients administered probiotics, an observation that was even more pronounced when probiotics were used in conjunction with antibiotics. This intriguing finding underscores the premise of the potential for a synergistic or complementary action between antibiotics and probiotics. The possible explanation could be that while antibiotics eliminate pathogenic bacteria, probiotics could hasten the restoration of the healthy vaginal microbiota, thereby preventing recolonization by pathogenic bacteria [55]. In another meta-analysis conducted by Chen and co-workers, they resulted that there was no significant difference in the cure rate between the efficacy of probiotics and antibiotics in the treatment of BV [56]. Probiotics are not a homogeneous group of microorganisms, and different strains may have different effects on the vaginal microbiota and immune system [57]. Moreover, the optimal dose and duration of probiotic administration for BV treatment and prevention are still unclear, and may vary depending on the individual characteristics of the patients [58]. Also in a meta-analysis published in 2019, it has been displayed that probiotics alone were more effective in treating BV in both short and long term, whereas probiotics after antibiotic treatment was only effective in the short term [59]. One possible explanation for this finding is that probiotics after antibiotic treatment may not be able to fully restore the diversity and stability of the vaginal microbiota, which are essential for maintaining vaginal health. Antibiotics can kill both harmful and beneficial bacteria in the vagina, creating a disruption in the vaginal ecosystem that may take a long time to recover. Probiotics may help replenish some of the beneficial bacteria, but they may not be able to restore all of them, or they may not be able to compete with the remaining harmful bacteria that may have developed resistance to antibiotics [60,61]. Therefore, probiotics after antibiotic treatment may not be sufficient to prevent BV recurrence in the long run. However, not all probiotics are equally effective for BV treatment and prevention. The type, dose, and delivery method of probiotics may influence their efficacy and safety.

Moreover, the individual characteristics of the patients, such as their vaginal pH, immune status, hormonal levels, and genetic

Table 2
Comparative analysis of BV cure rates using probiotic treatment, antibiotic treatment, and combined therapy.

| Intervention | Random-effects model | | | Heterogeneity | Publication bias | |
|----------------------------------|----------------------|------------|---------|----------------|------------------|--------|
| | OR | 95% CI | p-value | I ² | Egger's | Begg's |
| AB + pro Vs. AB | 2.504 | 1.03–6.06 | 0.04 | 68% | 0.75 | 0.80 |
| AB + pro Vs. AB + placebo | 3.31 | 0.44–24.92 | 0.24 | 95% | 0.45 | 1.00 |
| AB Vs. pro | 3.03 | 0.96–9.5 | 0.05 | 47% | ND | ND |
| Pro Vs. placebo | 16.49 | 3.63–74.93 | 0.01 | 92% | 0.39 | 0.22 |
| 1 species | 4.38 | 1.38–13.91 | 0.01 | 88% | 0.26 | 0.45 |
| More than 2 or 2 species | 6.03 | 1.81–20.13 | 0.01 | 92% | 0.29 | 0.17 |
| Oral | 8.3 | 4.62–14.90 | 0.01 | 00 | ND | ND |
| Vaginal | 5.7 | 2.19–14.87 | 0.01 | 90% | 0.2 | 0.27 |

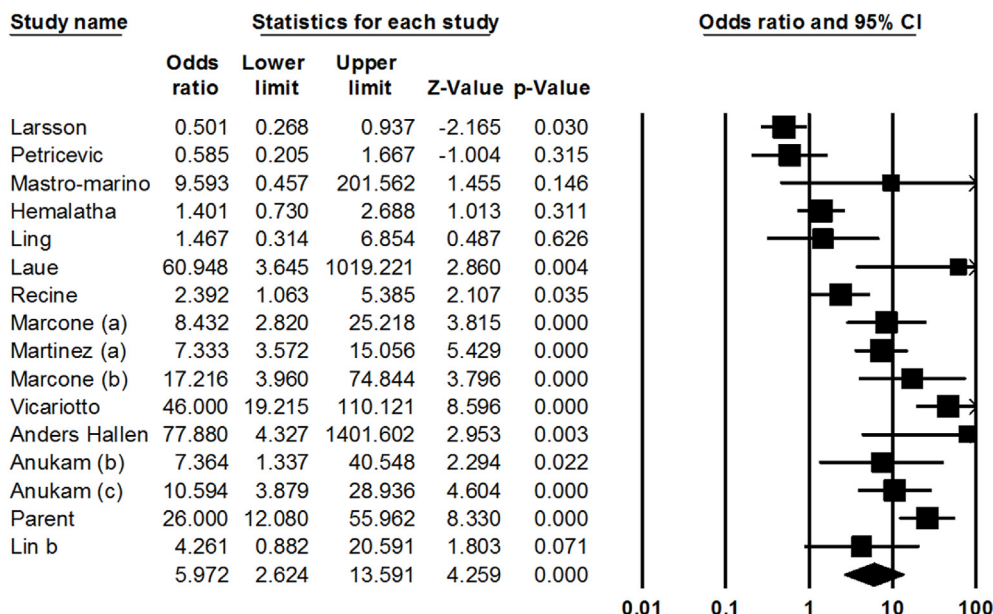


Fig. 2. Forest plot of the meta-analysis on the cure of bacterial vaginosis patients.

Table 3
Comparative analysis of BV recurrence rates with the use of probiotics, antibiotics, and combined therapy.

| Intervention | Random-effects model | | | Heterogeneity | Publication bias | |
|------------------------------------|----------------------|-----------|---------|----------------|------------------|--------|
| | OR | 95% CI | p-value | I ² | Egger's | Begg's |
| AB + pro Vs. AB | 0.06 | 0.01–0.28 | 0.01 | 00% | ND | ND |
| AB + pro Vs. AB + AB' + plc | 0.03 | 0.45–2.37 | 0.01 | 00% | ND | ND |
| AB + pro Vs. AB + plc | 0.54 | 0.24–1.21 | 0.13 | 84% | 0.33 | 0.46 |
| AB Vs. pro | 0.44 | 0.09–1.94 | 0.27 | 77% | 0.09 | 0.29 |
| Pro Vs. plc | 0.08 | 0.01–0.45 | 0.004 | 86% | 0.85 | 1.00 |
| 1 species | 0.43 | 0.13–1.47 | 0.18 | 77% | 0.53 | 0.73 |
| More than 2 or 2 species | 0.27 | 0.11–0.66 | 0.004 | 90% | 0.25 | 0.75 |
| 1 genus | 0.33 | 0.14–0.77 | 0.01 | 89% | 0.26 | 0.27 |
| More than 1 genus | 0.3 | 0.14–0.64 | 0.002 | 32% | ND | ND |
| Oral | 0.4 | 0.07–2.11 | 0.28 | 92% | ND | ND |
| Vaginal | 0.18 | 0.09–0.36 | 0.01 | 22% | 0.75 | 1.00 |

factors, may also affect their response to probiotics and antibiotics. Therefore, more research is needed to identify the optimal probiotic strains, doses, and regimens for different clinical conditions and populations. Moreover, our study revealed a significant decrease in the recurrence rate of BV among probiotic users. Particularly noteworthy was the decreased recurrence rate among patients who received probiotics through vaginal administration. Treatment of BV with currently recommended antibiotics has always been in great dispute with its high rates of recurrence. It may be due to the presence of BV-associated bacteria and multispecies BV biofilm that

some women develop diseases [62]. In compliance with our study, an investigation operated by Marcone et al. demonstrated that the long-term efficacy of probiotics significantly prevented BV recurrence [46]. This finding supports the hypothesis that probiotics can aid in maintaining the stability of the vaginal microbiota by directly colonizing the vagina and exerting their beneficial effects locally.

With regards to VVC, our meta-analysis pointed towards a marked improvement in the cure rate among patients administered probiotics, with a significant decrease observed in the recurrence rate as well. Also another study concluded the enhancing effect in

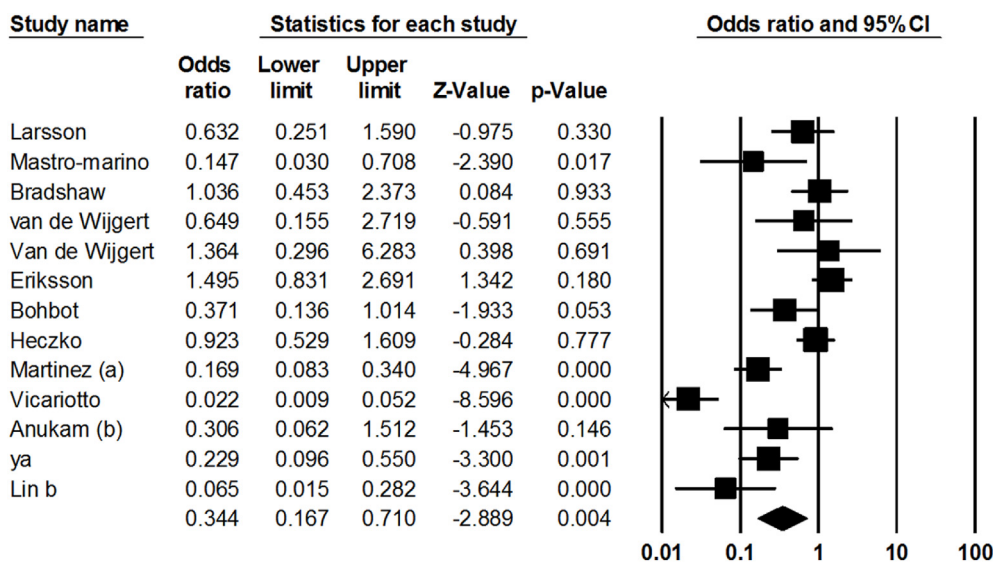


Fig. 3. Forest plot of the meta-analysis on the recurrence of bacterial vaginosis patients.

Table 4
Comparative analysis of VVC cure rates using probiotic treatment, antibiotic treatment, and combined therapy.

| Intervention | Random-effects model | | | Heterogeneity I ² | Publication bias | |
|---------------------------------|----------------------|-----------|---------|---------------------------------|------------------|--------|
| | OR | 95% CI | p-value | | Egger's | Begg's |
| AB + pro Vs. AB | 2.85 | 1.75–4.63 | 0.01 | 0% | 0.23 | 0.73 |
| AB + pro Vs. AB + plc | 4.21 | 2.51–7.06 | 0.01 | 0% | ND | ND |
| 1 species | 2.91 | 1.16–7.33 | 0.02 | 0% | ND | ND |
| More than 2 or 2 species | 4.98 | 2.67–9.29 | 0.01 | 0% | ND | ND |
| Oral | 3.06 | 1.04–9.03 | 0.04 | 71% | ND | ND |
| Vaginal | 2.85 | 1.75–4.63 | 0.01 | 0% | 0.23 | 0.73 |

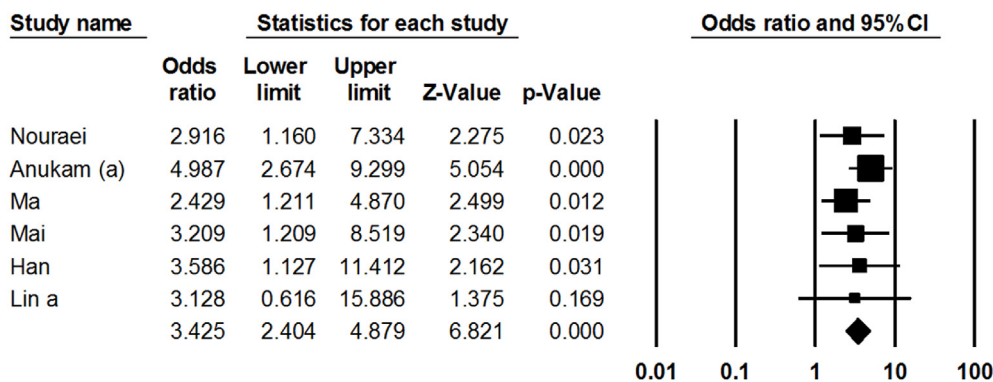


Fig. 4. Forest plot of the meta-analysis on the cure of vulvovaginal candidiasis patients.

improving short-term clinical cure rate when probiotics were added compared with conventional antifungal drugs alone [63]. These findings could be explained by the potential role of probiotics in enhancing the host's immune response, thereby improving the resistance to *Candida* colonization and infection [63]. Additionally, certain probiotic strains may exert direct anti-*Candida* activity [64]. This potential may be due to production of antimicrobial substances, such as hydrogen peroxide, lactic acid, acetic acid, and bacteriocins, that can lower the pH and inhibit the growth and virulence of *Candida* species [65]. Also competition for nutrients and adhesion sites on the mucosa which prevents the colonization and biofilm formation of *Candida* species may be considered as another possible mechanism [66].

Despite these promising outcomes, our study has certain limitations. The presence of considerable heterogeneity among the included studies, due to variations in study designs, probiotic strains used, duration of treatment, and administration routes, may have influenced our results. In addition, there are slight publication bias that originated from clinical heterogeneity as well as methodological heterogeneity of included studies. The studies included in our meta-analysis were relatively short-term, which restricts our ability to draw conclusions about the sustained and long-term effects of probiotics. The lack of data pertaining to certain demographic groups, such as pregnant women and those with specific comorbidities, limits our understanding of the breadth of the benefits and potential risks associated with probiotics.

Table 5
Comparative analysis of VVC recurrence rates with the use of probiotics, antibiotics, and combined therapy.

| Intervention | Random-effects model | | | Heterogeneity | Publication bias | |
|---------------------------|----------------------|-----------|---------|----------------|------------------|--------|
| | OR | 95% CI | p-value | I ² | Egger's | Begg's |
| AB + pro Vs. AB | 0.33 | 0.22–0.51 | 0.01 | 21% | 0.17 | 0.06 |
| AB + pro Vs. AB + placebo | 0.17 | 0.08–0.37 | 0.01 | 0% | ND | ND |
| No intervention control | 0.08 | 0.04–0.17 | 0.01 | 0% | ND | ND |
| Pro Vs. plc | 0.8 | 0.1–6.29 | 0.83 | 90% | 0.73 | 1.00 |
| More than 2 or 2 species | 0.3 | 0.05–1.77 | 0.18 | 93% | 0.08 | 0.29 |
| 1 genus | 0.31 | 0.21–0.45 | 0.01 | 47% | 0.17 | 1.00 |
| More than 1 genus | 0.28 | 0.04–1.82 | 0.18 | 93% | 0.45 | 0.29 |
| Oral | 0.15 | 0.08–0.27 | 0.01 | 0% | ND | ND |
| Vaginal | 0.39 | 0.84–0.18 | 0.01 | 80% | 0.21 | 0.75 |

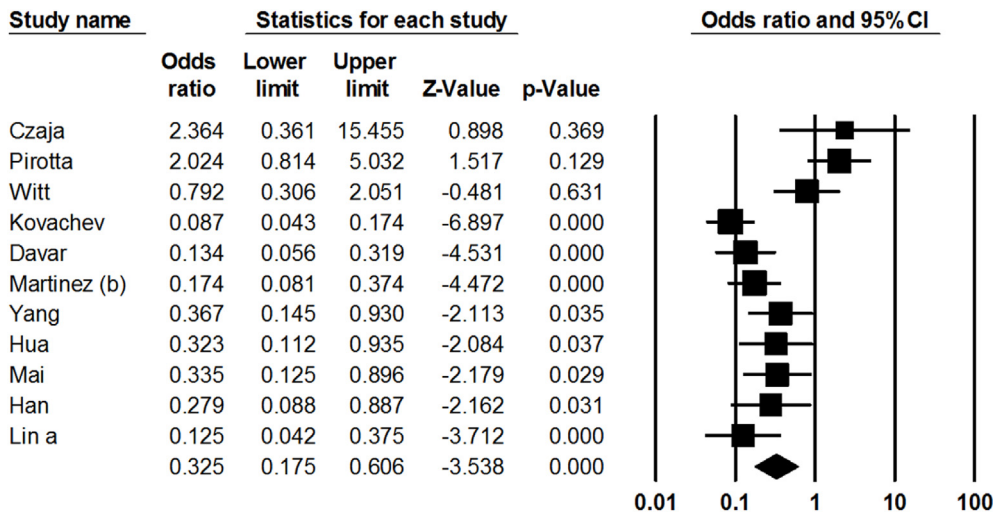


Fig. 5. Forest plot of the meta-analysis on the recurrence of vulvovaginal candidiasis patients.

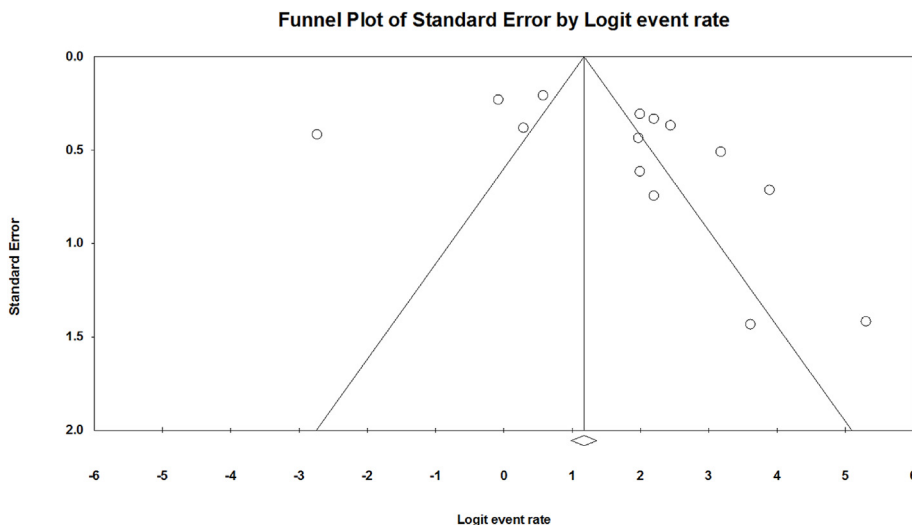


Fig. 6. Funnel plot of the meta-analysis on the cure of bacterial vaginosis patients.

However, despite these limitations, our study has several significant strengths. One of the key strengths of our study is its comprehensiveness, with the inclusion of a large number of RCTs from different geographical locations, thereby enhancing the generalizability of our findings. This diverse representation allows

us to discern the potential effects of probiotics across different populations and ethnicities. Additionally, our study evaluated multiple aspects of gynecological infections, including cure rates and recurrence rates for both BV and VVC, providing a holistic view of the potential benefits of probiotics. Furthermore, our analysis

was not confined to any particular strain or species of probiotics, thus offering a broad perspective on the therapeutic potential of various probiotic strains.

Conclusion and further perspectives

To conclude, the meta-analytical findings of our study present substantial evidence in favor of the potential efficacy of probiotics as an adjunctive therapy for prevalent gynecological infections. This synthesis of existing research provides an encouraging indication of the potential role probiotics can play in women's health, particularly in relation to common gynecological infections. To derive more generalizable results and to cement the use of probiotics as a therapeutic tool, further research should focus on a diverse demographic population. This inclusion will help in understanding the implications of age, ethnicity, genetic predisposition, and socio-economic status on the efficacy of probiotics in treating these gynecological infections. Moreover, conducting such expansive studies will enable us to examine the potential heterogeneity and possible confounders that could be influencing our results. In addition to broadening demographic analysis, it is crucial that future research delineates a comprehensive understanding of the intricate interactions that occur between the probiotics and the host organism. Detailed knowledge about the underlying mechanisms, including the immune responses and genetic factors, which dictate the therapeutic efficacy of probiotics, is essential. By decoding these interplays, it would be possible to optimize therapeutic regimens and personalize treatment, thus advancing the precision medicine approach in women's health. Thus, this study sheds light on an important aspect of women's health, marking an initial stride towards understanding the potential role of probiotics as a therapeutic intervention. Further, it adds a valuable contribution to the academic discourse surrounding probiotics and paves the way for future research in this area, enhancing our knowledge and potentially having far-reaching implications for women's healthcare practices.

Declaration of competing interest

There is no conflict of interest.

References

- [1] Kent HL. Epidemiology of vaginitis. *Am J Obstet Gynecol* 1991;165(4):1168–76.
- [2] Mills BB. Vaginitis: beyond the basics. *Obstet Gynecol Clin North Am* 2017;44(2):159–77.
- [3] Reid G, Dols J, Miller W. Targeting the vaginal microbiota with probiotics as a means to counteract infections. *Curr Opin Clin Nutr Metab Care* 2009;12(6):583–7.
- [4] Kenyon C, Colebunders R, Crucitti T. The global epidemiology of bacterial vaginosis: a systematic review. *Am J Obstet Gynecol* 2013;209(6):505–23.
- [5] Torrone EA, Morrison CS, Chen P-L, Kwok C, Francis SC, Hayes RJ, et al. Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: an individual participant data meta-analysis of 18 HIV prevention studies. *PLoS Med* 2018;15(2):e1002511.
- [6] Reid G, Jewett M, Nickel J, McLean R, Bruce A. Effect of extracorporeal shock wave lithotripsy on bacterial viability: relationship to the treatment of struvite stones. *Urol Res* 1990;18:425–7.
- [7] Ilkit M, Guzel AB. The epidemiology, pathogenesis, and diagnosis of vulvovaginal candidosis: a mycological perspective. *Crit Rev Microbiol* 2011;37(3):250–61.
- [8] Van De Wijgert JH. The vaginal microbiome and sexually transmitted infections are interlinked: consequences for treatment and prevention. *PLoS Med* 2017;14(12):e1002478.
- [9] Sobel JD. Vulvovaginal candidosis. *Lancet* 2007;369(9577):1961–71.
- [10] Gonçalves B, Ferreira C, Alves CT, Henriques M, Azeredo J, Silva S. Vulvovaginal candidiasis: epidemiology, microbiology and risk factors. *Crit Rev Microbiol* 2016;42(6):905–27.
- [11] Watson RR, Preedy VR. Probiotics, prebiotics, and synbiotics: bioactive foods in health promotion. Academic Press; 2015.
- [12] Joesoef M, Schmid G, Hillier S. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy. *Clin Infect Dis* 1999;28(Suppl 1):S57–65.
- [13] López-Moreno A, Aguilera M. Vaginal probiotics for reproductive health and related dysbiosis: systematic review and meta-analysis. *J Clin Med* 2021;10(7):1461.
- [14] Swidsinski A, Mendling W, Loening-Baucke V, Ladhoff A, Swidsinski S, Hale LP, et al. Adherent biofilms in bacterial vaginosis. *Obstet Gynecol* 2005;106(5 Part 1):1013–23.
- [15] McMillan A, Dell M, Zellar MP, Cribby S, Martz S, Hong E, et al. Disruption of urogenital biofilms by lactobacilli. *Colloids Surf B Biointerfaces* 2011;86(1):58–64.
- [16] Bolton M, Van Der Straten A, Cohen CR. Probiotics: potential to prevent HIV and sexually transmitted infections in women. *Sex Transm Dis* 2008;214–25.
- [17] Gardiner GE, Heinemann C, Baroja ML, Bruce AW, Beuerman D, Madrenas Jn, et al. Oral administration of the probiotic combination *Lactobacillus rhamnosus* GR-1 and *L. fermentum* RC-14 for human intestinal applications. *Int Dairy J* 2002;12(2–3):191–6.
- [18] Mombelli B, Gismondo MR. The use of probiotics in medical practice. *Int J Antimicrob Agents* 2000;16(4):531–6.
- [19] Doron S, Snyderman DR. Risk and safety of probiotics. *Clin Infect Dis* 2015;60(Suppl 2):S129–34.
- [20] Larsson P-G, Stray-Pedersen B, Rytting KR, Larsen S. Human lactobacilli as supplementation of clindamycin to patients with bacterial vaginosis reduce the recurrence rate: a 6-month, double-blind, randomized, placebo-controlled study. *BMC Womens Health* 2008;8:1–8.
- [21] Petricevic L, Witt A. The role of *Lactobacillus casei rhamnosus* Lcr35 in restoring the normal vaginal flora after antibiotic treatment of bacterial vaginosis. *BJOG* 2008;115(11):1369–74.
- [22] Mastromarino P, Macchia S, Meggiorini L, Trinchieri V, Mosca L, Perluigi M, et al. Effectiveness of *Lactobacillus*-containing vaginal tablets in the treatment of symptomatic bacterial vaginosis. *Clin Microbiol Infect* 2009;15(1):67–74.
- [23] Bradshaw CS, Pirota M, De Guingand D, Hocking JS, Morton AN, Garland SM, et al. Efficacy of oral metronidazole with vaginal clindamycin or vaginal probiotic for bacterial vaginosis: randomised placebo-controlled double-blind trial. *PLoS One* 2012;7(4):e34540.
- [24] van de Wijgert JH, Verwijs MC, Agaba SK, Bronowski C, Mwambarangwe L, Uwineza M, et al. Intermittent *Lactobacillus*-containing vaginal probiotic or metronidazole use to prevent bacterial vaginosis recurrence: a pilot study incorporating microscopy and sequencing. *Sci Rep* 2020;10(1):3884.
- [25] Eriksson K, Carlsson B, Forsum U, Larsson P. A double-blind treatment study of bacterial vaginosis with normal vaginal *Lactobacilli* after an open treatment with vaginal clindamycin ovules. *Acta Derm Venereol* 2005;85(1):42–6.
- [26] Hemalatha R, Mastromarino P, Ramalaxmi B, Balakrishna N, Sesikeran B. Effectiveness of vaginal tablets containing *Lactobacilli* versus pH tablets on vaginal health and inflammatory cytokines: a randomized, double-blind study. *Eur J Clin Microbiol Infect Dis* 2012;31:3097–105.
- [27] Ling Z, Liu X, Chen W, Luo Y, Yuan L, Xia Y, et al. The restoration of the vaginal microbiota after treatment for bacterial vaginosis with metronidazole or probiotics. *Microb Ecol* 2013;65:773–80.
- [28] Bohbot J, Daraï E, Bretelle F, Brami G, Daniel C, Cardot J. Efficacy and safety of vaginally administered lyophilized *Lactobacillus crispatus* IP 174178 in the prevention of bacterial vaginosis recurrence. *J Gynecol Obstet Hum Reprod* 2018;47(2):81–6.
- [29] Czaja CA, Stapleton AE, Yarova-Yarovaya Y, Stamm WE. Phase I trial of a *Lactobacillus crispatus* vaginal suppository for prevention of recurrent urinary tract infection in women. *Infect Dis Obstet Gynecol* 2007;2007.
- [30] Pirota M, Gunn J, Chondros P, Grover S, O'Malley P, Hurley S, et al. Effect of *Lactobacillus* in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. *BMJ* 2004;329(7465):548.
- [31] Witt A, Kaufmann U, Bitschnau M, Tempfer C, Özbal A, Haytouglu E, et al. Monthly itraconazole versus classic homeopathy for the treatment of recurrent vulvovaginal candidiasis: a randomised trial. *BJOG* 2009;116(11):1499–505.
- [32] Kovachev SM, Vatcheva-Dobrevska RS. Local probiotic therapy for vaginal *Candida albicans* infections. *Probiotics Antimicrob Proteins* 2015;7:38–44.
- [33] Laue C, Papazova E, Liesegang A, Pannenbeckers A, Arendarski P, Linnerth B, et al. Effect of a yoghurt drink containing *Lactobacillus* strains on bacterial vaginosis in women—a double-blind, randomised, controlled clinical pilot trial. *Benef Microbes* 2018;9(1):35–50.
- [34] Davar R, Nokhostin F, Eftekhari M, Sekhvat L, Bashiri Zadeh M, Shamsi F. Comparing the recurrence of vulvovaginal candidiasis in patients undergoing prophylactic treatment with probiotic and placebo during the 6 months. *Probiotics Antimicrob Proteins* 2016;8:130–3.
- [35] Recine N, Palma E, Domenici L, Giorgini M, Imperiale L, Sassu C, et al. Restoring vaginal microbiota: biological control of bacterial vaginosis. A prospective case-control study using *Lactobacillus rhamnosus* BMX 54 as adjuvant treatment against bacterial vaginosis. *Arch Gynecol Obstet* 2016;293:101–7.
- [36] Heczko PB, Tomusiak A, Adamski P, Jakimiuk AJ, Stefański G, Mikotajczyk-Cichońska A, et al. Supplementation of standard antibiotic therapy with oral probiotics for bacterial vaginosis and aerobic vaginitis: a randomised, double-blind, placebo-controlled trial. *BMC Womens Health* 2015;15:1–12.
- [37] Nouraei S, Amir Ali Akbari S, Jorjani M, Alavi Majd H, Afrakhteh M, Ghaforian A, et al. Comparison between fluconazole with oral protexin

- combination and fluconazole in the treatment of vulvovaginal candidiasis. *Int Sch Res Notices* 2012;2012.
- [38] Marcone V, Rocca G, Lichtner M, Calzolari E. Long-term vaginal administration of *Lactobacillus rhamnosus* as a complementary approach to management of bacterial vaginosis. *Int J Gynecol Obstet* 2010;110(3):223–6.
- [39] Anukam KC, Duru MU, Eze CC, Egharevba J, Aiyebilehin A, Bruce A, et al. Oral use of probiotics as an adjunctive therapy to fluconazole in the treatment of yeast vaginitis: a study of Nigerian women in an outdoor clinic. *Microb Ecol Health Dis* 2009;21(2):72–7.
- [40] Anukam KC, Osazuwa E, Osemene GI, Ehigiagbe F, Bruce AW, Reid G. Clinical study comparing probiotic *Lactobacillus GR-1* and *RC-14* with metronidazole vaginal gel to treat symptomatic bacterial vaginosis. *Microbes Infect* 2006;8(12–13):2772–6.
- [41] Anukam K, Osazuwa E, Ahonkhai I, Ngwu M, Osemene G, Bruce AW, et al. Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14*: a randomized, double-blind, placebo-controlled trial. *Microbes Infect* 2006;8(6):1450–4.
- [42] Martinez RC, Franceschini SA, Patta MC, Quintana SM, Gomes BC, De Martinis EC, et al. Improved cure of bacterial vaginosis with single dose of tinidazole (2 g), *Lactobacillus rhamnosus GR-1*, and *Lactobacillus reuteri RC-14*: a randomized, double-blind, placebo-controlled trial. *Can J Microbiol* 2009;55(2):133–8.
- [43] Martinez R, Franceschini SA, Patta MC, Quintana SM, Candido RC, Ferreira JC, et al. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14*. *Lett Appl Microbiol* 2009;48(3):269–74.
- [44] Yang Q, Zhao W, Zheng J. Clinical observation of *Mycobacterium lacticola* preparation in treatment of vaginal viny candidiasis using clotrimazole effervescent tablets. *Chin Hosp Pharm J* 2009;29:1377–9.
- [45] Hua Y, Lin M, Wang L, Xia L. Observation of curative effect of miconazole and *Lactobacillus* on vulvovaginal candidiasis treated. *Chin J Microecol* 2008;20:386–7.
- [46] Marcone V, Calzolari E, Bertini M. Effectiveness of vaginal administration of *Lactobacillus rhamnosus* following conventional metronidazole therapy: how to lower the rate of bacterial vaginosis recurrences. *New Microbiol* 2008;31(3):429.
- [47] Ma L, Li L. Miconazole plus Lactasin capsules to treat vulvovaginal candidiasis (54 cases). *Herald Med* 2007;26:1041–2.
- [48] Mai X. Analysis of probiotic *Lactobacillus*'s effect on vulvovaginal candidiasis. *Chin J Microecol* 2007;19(4):362–3.
- [49] Han Y, Zhao S. Clinical observation of Ding JunSheng and clotrimazole vaginal tablet in the treatment of vulvovaginal candidiasis. *Anh Med J* 2006;27:528–9.
- [50] Vicariotto F, Mogna L, Del Piano M. Effectiveness of the two microorganisms *Lactobacillus fermentum LF15* and *Lactobacillus plantarum LP01*, formulated in slow-release vaginal tablets, in women affected by bacterial vaginosis: a pilot study. *J Clin Gastroenterol* 2014;48:S106–12.
- [51] Ya W, Reifer C, Miller LE. Efficacy of vaginal probiotic capsules for recurrent bacterial vaginosis: a double-blind, randomized, placebo-controlled study. *Am J Obstet Gynecol* 2010;203(2). 120. e1–e6.
- [52] Anders H, Jarstrand C, Pahlson C. Treatment of bacterial vaginosis with lactobacilli. *Sex Transm Dis* 1992;19(3):146–8.
- [53] Parent D, Bossens M, Bayot D, Kirkpatrick C, Graf F, Wilkinson F, et al. Therapy of bacterial vaginosis using exogenously-applied *Lactobacilli acidophili* and a low dose of estriol: a placebo-controlled multicentric clinical trial. *Arzneimittel-Forschung* 1996;46(1):68–73.
- [54] Lin H, Meng X. Clinical application of Lactasin capsules in vaginitis. *J Pract Med* 2006;22:1927–8.
- [55] Wieërs G, Verbelen V, Van Den Driessche M, Melnik E, Vanheule G, Marot J-C, et al. Do probiotics during in-hospital antibiotic treatment prevent colonization of gut microbiota with multi-drug-resistant bacteria? A randomized placebo-controlled trial comparing *Saccharomyces* to a mixture of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*. *Front Public Health* 2021;8:578089.
- [56] Chen R, Li R, Qing W, Zhang Y, Zhou Z, Hou Y, et al. Probiotics are a good choice for the treatment of bacterial vaginosis: a meta-analysis of randomized controlled trial. *Reprod Health* 2022;19(1):137.
- [57] Hu S, Wang L, Jiang Z. Dietary additive probiotics modulation of the intestinal microbiota. *Protein Pept Lett* 2017;24(5):382–7.
- [58] Parma M, Stella Vanni V, Bertini M, Candiani M. Probiotics in the prevention of recurrences of bacterial vaginosis. *Altern Ther Health Med* 2014;20(Suppl 1):52–7.
- [59] Wang Z, He Y, Zheng Y. Probiotics for the treatment of bacterial vaginosis: a meta-analysis. *Int J Environ Res Public Health* 2019;16(20):3859.
- [60] Webb L. Probiotics for preventing recurrent bacterial vaginosis. *JAAPA* 2021;34(2).
- [61] Éliás AJ, Barna V, Patoni C, Demeter D, Veres DS, Bunduc S, et al. Probiotic supplementation during antibiotic treatment is unjustified in maintaining the gut microbiome diversity: a systematic review and meta-analysis. *BMC Med* 2023;21(1):262.
- [62] Swidsinski A, Loening-Baucke V, Mendling W, Dörrfel Y, Schilling J, Halwani Z, et al. Infection through structured polymicrobial *Gardnerella* biofilms (StPM-GB). *Histol Histopathol* 2014;29(5):567–87.
- [63] Xie HY, Feng D, Wei DM, Mei L, Chen H, Wang X, et al. Probiotics for vulvovaginal candidiasis in non-pregnant women. *Cochrane Database Syst Rev* 2017;11(11):Cd010496.
- [64] De Angelis M, Scagnolari C, Oliva A, Cavallari EN, Celani L, Santinelli L, et al. Short-term probiotic administration increases fecal-anti *Candida* activity in healthy subjects. *Microorganisms* 2019;7(6).
- [65] Kunyeit L, K AA-A, Rao RP. Application of probiotic yeasts on *Candida* species associated infection. *J Fungi* 2020;6(4):189.
- [66] Ribeiro F, Rossoni R, De Barros P, Santos J, Fugisaki L, Leão M, et al. Action mechanisms of probiotics on *Candida* spp. and candidiasis prevention: an update. *J Appl Microbiol* 2020;129(2):175–85.