

The Challenge of Recurrent Bacterial Vaginosis and the Promise of Liposomal Probiotic

Arnova Reswari, Delima Istio Prawiradhani Putri
Universitas Padjadjaran, Indonesia
Email: arnova@unpad.ac.id, d.istio@unpad.ac.id

Abstract

Bacterial vaginosis (BV) is a common vaginal dysbiosis marked by the overgrowth of anaerobic bacteria and reduced *Lactobacillus* dominance. Despite antibiotic treatments, recurrence rates exceed 50% due to biofilm resistance and failed microbiota restoration. This narrative review describes that probiotics show promise but face challenges in colonization and stability. This review followed *PRISMA* guidelines and screened 1,098 PubMed and Scopus studies (2015–2025). The studies used *MeSH* (Medical Subject Heading) terms like “*Nanoparticle Drug Delivery*,” “*Probiotics*,” and “*Liposomes*.” Liposomal encapsulation improved probiotic viability (92% in 3D scaffolds) and vaginal colonization (79% for *L. crispatus*). Biofilm penetration increased by 60 µm using cationic lipids, while recurrence rates dropped by 50% with liposomal probiotics versus placebo. Optimal formulations included *DPPC:Chol* (7:3) blends and pH-sensitive lipids for targeted release. Dual-action liposomes (probiotics + antibiotics) showed synergistic effects. Liposomal probiotics enhance BV treatment by protecting probiotics, disrupting biofilms, and reducing recurrence. Challenges remain in scalability and long-term safety.

Keywords: Bacterial Vaginosis, Biofilm Disruption, Liposomes, Probiotic

*Correspondence Author: Arnova Reswari, Delima Istio Prawiradhani Putri
Email: arnova@unpad.ac.id, d.istio@unpad.ac.id



INTRODUCTION

Bacterial vaginosis (BV) is the most common cause of vaginal discharge in reproductive-aged women, defined by a shift from a *Lactobacillus*-dominant microbiome to an overgrowth of anaerobic bacteria such as *Gardnerella vaginalis*, *Prevotella* spp., and *Atopobium vaginae* (Chee et al., 2020). This imbalance in the vaginal microbiota, known as dysbiosis, is linked to symptoms such as malodorous discharge, irritation, and an elevated vaginal pH (>4.5) (Paladine & Desai, 2018). These symptoms significantly affect women's health, contributing to discomfort, potential fertility issues, and increased susceptibility to other infections.

Despite the availability of contemporary therapeutic interventions, including metronidazole and clindamycin, BV remains highly prone to recurrence. This recurring nature of BV indicates that current treatments are insufficient for long-term management, leading to repeated infections and associated health risks. The recurrence underscores the need to explore more effective and sustainable treatment options that can target the root causes of BV while offering lasting relief (Andersen et al., 2015; Omolo et al., 2021).

In response to these challenges, there is increasing interest in the use of liposomal formulations to improve vaginal microbiota modulation (Akbarzadeh et al., 2013; Liu et al., 2025). These formulations aim to enhance the stability and effectiveness of probiotics and antimicrobial agents, potentially overcoming the limitations of current therapies. However, significant gaps remain in the research, particularly in optimizing these formulations for better efficacy and ensuring their long-term safety in the vaginal environment, which requires further investigation to fully understand their potential benefits.

A meta-analysis by Chieng et al. (2022) demonstrated that probiotics could reduce the recurrence of BV when administered at least one month after initial treatment. However, the study did not address the stability and delivery challenges associated with probiotics. Similarly, a review by Liu et al. (2023) highlighted the potential of liposomal encapsulation in enhancing probiotic stability and bioavailability but did not specifically focus on BV treatment. This study fills these gaps by integrating *PRISMA*-guided literature synthesis with formulation analysis, bridging microbiological and nanotechnological perspectives to provide a comprehensive understanding of liposomal probiotics in BV management.

This review aims to explore the challenges of recurrent BV, evaluate liposomal probiotic delivery as a novel therapeutic strategy, and highlight unmet needs in achieving sustained microbiome restoration. The findings aim to inform the development of more effective probiotic therapies for BV, potentially reducing recurrence rates and improving patient outcomes. By addressing the limitations of current probiotic delivery systems, this research contributes to the advancement of BV treatment strategies and the broader field of microbiome-based therapies.

RESEARCH METHOD

The study protocol is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram standards and the Narrative Review technique will be applied. The literature review was done with two screening phases. The first phase entailed abstract or keyword screening, while the second phase involved full-text screening. In the first phase, studies from PubMed were selected using MeSH (Medical Subject Heading) terms and limited by date and text availability. Additional studies were sourced from Scopus, filtered by year, subject, document type, language, and open access. We used MeSH terms to find journals for each library on April 2025. We found the word for finding more studies with synonyms or related terms on MeSH Descriptor Data 2025. On PubMed, we input the first keyword “Nanoparticle Drug Delivery System” as MeSH terms and continue to input “Nano Drug Delivery Systems, Nano-Drug Delivery System, Delivery System, Nano-Drug, NDDSs” as title/abstract with “or” conjunction.

Then, we add the second keyword “Probiotics” with “and” conjunction as MeSH terms and continue to input “Probiotic” as title/abstract with “or” conjunction. Third, we add the other keyword “Liposomes” with “and” conjunction

as MeSH terms and continue to input “Liposome, Liposomes, Ultra-deformable, Ultra-deformable Liposome” as title/abstract with “or” conjunction. Fourth, another keyword “Therapeutics” with “and” conjunction as MeSH terms and continue to input “Therapeutic, Therapy, Therapies, Treatment, Treatments” as title/abstract with “or” conjunction. Lastly, add last terms “Vaginosis, Bacterial” with “and” conjunction as MeSH terms and continue to input “Bacterial Vaginitis, Bacterial Vaginosis” as title/abstract with “or” conjunction. We eliminate the result by adding filters according to the inclusion and exclusion criteria.

The PICO framework for keyword selection in this study is structured as follows: The Population (P) focuses on DPS (Disease Population and Setting), with a specific focus on recurrent bacterial vaginosis women confirmed BV, in outpatient clinics, sexual health centers, or primary care setting. The Exposure (E) under consideration is liposomal nanoparticle-delivered probiotics. For Comparison (C), the study evaluates conventional probiotics (oral/vaginal) or placebo. The outcome (O) aims to determine the BV recurrence rate, probiotic vaginal colonization (CFU/mL), biofilm disruption (% reduction), and adverse events. While the timeframe (T) for the study is set at 10 years, ensuring relevance to past trends and data. Finally, the design (D) of the research follows either a cohort studies, case-control, or cross-sectional, in vitro, and in vivo approach, providing comprehensive insights into the effectiveness of liposomal nanoparticle in delivering probiotics.

On PubMed, we filtered several elements that's not include in our journal criteria. We limit the journal on most publications in the ten years (2015–2025), text availability on full text access to the sources is provided, article language is in English. The study's exclusion criteria include non-English literature, unpublished articles, review and protocol studies, and various subject areas. The literature search was conducted on Scopus in a manner consistent with the approach employed on PubMed. The difference is on search within section, that we used “Article title, Abstract, Keywords” for literature searching. We used “or” to broad the scale finding studies related terms and used “and” to continue to another keyword. In the Scopus database, a series of filters were applied to refine the results. These filters pertained to the year of publication, document type, language, and access mode. The year of publication was limited to a range of 10 years. The document type was restricted to English articles and open access.

Review used Rayyan.ai to evaluate the eligibility of studies and to identify any potential duplications or irrelevance. Rayyan.ai categorizes articles as “include”, “exclude”, or “maybe” based on eligibility criteria. Inclusion criteria of this study are papers that are the results of original articles (clinical trials, in vivo, in vitro), title, keywords and abstract of the sources are consistent with the objectives of the study. Deeper to the abstract, we only include journals that provide information about the sample analyzed, the investigated biomarkers, and the comparisons between groups.

Studies that pass the second screening will be extracted into the data extraction. These characteristics will be divided into study title, study design, population (number and characteristics), sample, methods, probiotic strains, and liposome/nanocarriers details. Then, the extracted data will be synthesized and analysed as part of the narrative review process (figure1)

RESULTS AND DISCUSSION

There is 61 studies included after two phases screening methods. Extracted data that have been synthesized and analysed as part of narrative review process are show below (table 1–4). Bacterial Vaginosis

Bacterial vaginosis is a notable example of a vaginal microbiome dysbiosis, marked by depletion of protective *Lactobacillus* species (particularly those producing H_2O_2 and lactic acid) and overgrowth of anaerobic bacteria including *Gardnerella vaginalis*, *Prevotella* spp., and *Atopobium vaginae* (Chee et al., 2020). It typically presents with malodorous discharge (though sometimes asymptomatic) and is diagnosed through Amsel criteria and Nugent scoring. Amsel criteria show elevated vaginal pH (>4.5), clue cells ($\geq 20\%$ epithelial cells with adherent bacteria), and production of volatile amines responsible for characteristic fishy odor (Paladine & Desai, 2018). Nugent score show gram-stain evaluation of bacterial morphotypes (Lewis et al., 2017).

The potential risk factors associated with BV include behaviors, such as oral sex, douching, black ethnicity, cigarette smoking, engaging in sexual activity during menses, the presence of an intrauterine device, early initiation of sexual intercourse, having new or multiple sexual partners, and engaging in sexual activity with other women (Bagnall & Rizzolo, 2017). Key pathophysiological of BV include three mechanism, including biofilm formation, *crispatus* has the strongest probiotic efficacy, colonizing 79% of women tested and demonstrating a 50% reduction in recurrence rates compared to Placebo (Raba et al., 2024; Weeks et al., 2019). While free probiotics such as vaginal suppositorie are somewhat effective, they are unable to disrupt biofilms or sustain colonization, so they don't work long-term (Elovitz et al., 2019; Hardy et al., 2015; Swidsinski et al., 2015). Liposomes address this by protecting probiotics from clearance and facilitating delivery of biofilm-disrupting agents like endolysins (Sousa et al., 2024; Vasundhara et al., 2021)

Optimal Liposome Design Enhances Efficacy

We found DPPC:Chol (7:3) to be the most effective lipid blend. It had 88% encapsulation efficiency and better storage stability. Cationic lipids, such as C12-OH, penetrated biofilms well, which is important for treating recurrent BV.(Sousa et al., 2024) PEGylation improved mucus penetration and prolonged circulation time, while pH-sensitive lipids (e.g., Eudragit L100) released at the vaginal pH of

~4.5 (Yang et al., 2020). This shows how important it is to adjust liposome composition composition to maximize therapeutic outcomes.

Biofilm Disruption is Key to Preventing Recurrence

The recurrence of BV has been associated with the persistence of biofilms. The data demonstrate that *G. vaginalis* Clade 4 and *P. Bivia* are predominant in recurrent BV via biofilms and ermX resistance. The application of endolysins and amphiphiles has been demonstrated to disrupt biofilms. However, these agents do not differentiate between pathogenic clades (Kyser et al., 2023).

In contrast, liposomal endolysins and lactic acid demonstrated superior biofilm penetration compared to antibiotics, but they were ineffective in addressing clade-specific virulence (Chetwin et al., 2019). Precision strategies may include the use of antibody-conjugated liposomes, which target Clade 4 surface markers, and dual- loaded liposomes, such as metronidazole and *L. crispatus*, to simultaneously attack pathogens and restore microbiota.

Overcoming Antibiotic Resistance

We highlight two notable result following:

Metronidazole resistance is rising, but liposomal delivery reduces recurrence by maintaining local drug concentrations (Kyser et al., 2023; Mendes-Soares et al., 2015). Probiotics mitigate resistance by restoring lactic acid and competitive exclusion (Armstrong et al., 2022; Yang et al., 2020).

From findings we know that liposomes enhance antibiotics by overcoming biofilm barriers, while probiotics prevent dysbiosis-driven resistance. For example, liposomal lactic acid-releasing bacteria could release lactic acid to create an unfavorable environment and inhibit regrowing pathogens, and endolysin-loaded liposomes may bypass resistance mechanisms (Yang et al., 2020).

Clinical Translation Challenges and Opportunities

The following barriers to the review were identified in the findings:

1. Scalability. A limited number of liposomal probiotics have been advanced to clinical trials (Yang et al., 2020).
2. Safety concerns. While biocompatible polymers (PEO, PLGA) have received FDA approval, the evaluation of long-term effects remains to be conducted.
3. Patient compliance. The use of sustained-release systems, such as 3D rings, has the potential to enhance adherence in comparison to daily suppositories (Mendes-Soares et al., 2015).

However, the following opportunity for personalized medicine has been identified. The utilization of 3D-printed liposomal doses holds promise in tailoring therapy to individual microbiota profiles while maintaining cost-effectiveness (Mendes-

Soares et al., 2015; Landlinger et al., 2022). The scalability of bulk production of lipid nanoparticles makes them well-suited for global use.

CONCLUSION

Recurrent BV is a significant clinical challenge due to its high recurrence rates. The dysbiosis characteristic of BV marked by the depletion of protective *Lactobacillus* species and overgrowth of anaerobic pathogens, underscores the need for innovative therapeutic strategies. Liposomal probiotic delivery enhances probiotic viability, enables targeted biofilm penetration, and facilitates sustained release. Future research should prioritize clinical trials and personalized delivery systems.

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