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Phytotherapy for Bacterial Vaginosis with Piper Betle: from Mechanism to Safety

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Abstract
Background: Bacterial vaginosis (BV) is a prevalent vaginal dysbiosis characterized by depletion of Lactobacillus and overgrowth of anaerobic bacteria, commonly including Gardnerella vaginalis. Clinical management is complicated by high recurrence rates, which are closely linked to polymicrobial biofilm persistence and the limited microbiome selectivity of conventional antimicrobials. This narrative review aimed to synthesize current evidence on the phytotherapeutic potential of Piper betle in BV, focusing on antimicrobial and anti-biofilm mechanisms, modulation of vaginal microbiome ecology, and safety and standardization considerations relevant to translational development and recurrence prevention. **Methods:** An exploratory literature search (2015–2025) was conducted using PubMed/MEDLINE, ScienceDirect, and Google Scholar, complemented by manual reference screening, and last searched on 30 September 2025. **Results:** Findings across in vitro studies, observational reports, and mechanistic literature indicate that P. betle extracts and key phenolic constituents, particularly hydroxychavicol and eugenol, exhibit antibacterial activity against BV-associated taxa and anti-virulence effects consistent with biofilm weakening and interference with quorum-sensing–regulated behaviors. Importantly, several studies suggest comparatively limited inhibitory effects on Lactobacillus spp., supporting the plausibility of a microbiome-sparing profile that may facilitate restoration of vaginal eubiosis. Nevertheless, the evidence base is constrained by heterogeneous methodologies, predominance of preclinical models, and substantial variability in phytochemical composition across preparations. **Conclusion:** Overall, P. betle emerges as a biologically plausible adjunctive or preventive candidate for preventing BV recurrence, warranting standardized formulations, marker-based quality control, and rigorous clinical evaluation with recurrence-focused endpoints.

Keywords: antimicrobial effect; bacterial vaginosis; phenolic constituent; Piper betle

Introduction

Bacterial vaginosis (BV) is a prevalent form of vaginal dysbiosis among women of reproductive age, arising from disruption of the normal vaginal microbiota (Bradshaw & Brotman, 2015; Abbe & Mitchell, 2023). Under eubiotic conditions, *Lactobacillus* spp. dominate and sustain an acidic vaginal milieu through the production of lactic acid, hydrogen peroxide, and bacteriocins, thereby suppressing the growth and virulence of BV-associated anaerobes (Bradshaw & Brotman, 2015). When this protective state is perturbed, depletion of *Lactobacillus* facilitates overgrowth of anaerobic taxa such as *Gardnerella vaginalis*, *Atopobium vaginae*, and *Mobiluncus* spp., leading to a polymicrobial shift characteristic of BV (Muzny & Sobel, 2022; Abbe & Mitchell,

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2023). This transition commonly elevates vaginal pH above 4.5 and increases production of volatile amines, which clinically manifests as a "thin greyish-white discharge" accompanied by a characteristic "fishy odor" (Watkins et al., 2025).

The clinical importance of BV is underscored by its high prevalence and its links to reproductive morbidity. Global estimates suggest BV affects approximately 23%–29% of women of reproductive age, with prevalence reaching up to 50% in certain high-risk populations, contributing substantially to the global gynaecologic and obstetric burden (Abbe & Mitchell, 2023). Beyond symptomatic discomfort, BV has been consistently associated with pelvic inflammatory disease, heightened risk of acquiring HIV and other sexually transmitted infections, and adverse pregnancy outcomes if untreated (Abbe & Mitchell, 2023). Recent global guidance similarly emphasizes BV as a very common cause of vaginal discharge and highlights its association with increased STI/HIV risk and pregnancy-related complications (World Health Organization, 2025).

Although BV is not typically life-threatening, its management remains challenging, particularly due to persistence and recurrence. First-line nitroimidazole and lincosamide regimens (e.g., metronidazole and clindamycin) can be constrained by polymicrobial biofilm formation, antimicrobial resistance/tolerance, and collateral depletion of *Lactobacillus* that may delay re-establishment of eubiosis (Bradshaw & Brotman, 2015; Muzny & Sobel, 2022). Contemporary syntheses further note that recurrence after antibiotic therapy is common, frequently occurring within months and often approaching or exceeding—approximately half of treated cases over 6–12 months, reinforcing the need for strategies that improve biofilm clearance while preserving protective *Lactobacillus* communities (Abbe & Mitchell, 2023; Muzny & Sobel, 2022). These limitations have motivated interest in selective, microbiome-sparing interventions that can disrupt BV-associated biofilms while supporting restoration of protective *Lactobacillus* communities (Abbe & Mitchell, 2023; Lachyan et al., 2024).

In this context, *Piper betle* L. (betel leaf) has attracted attention for its long-standing traditional use in feminine hygiene and its reported antimicrobial and antioxidant properties (Mudayatiningsih & Suryandari, 2018; Sarma et al., 2018; Watkins et al., 2025). Its leaves are rich in phenolic constituents—most notably hydroxychavicol and eugenol—that exhibit broad antibacterial effects (Singh et al., 2018). Importantly, multiple studies indicate that *P. betle* extracts inhibit key BV-associated taxa such as *G. vaginalis* and attenuate virulence through biofilm disruption and quorum-sensing interference, with preliminary signals of microbiome selectivity that may spare *Lactobacillus* (Sarma et al., 2018; Singh et al., 2018; Jalil et al., 2022; Phensri et al., 2022). However, reported activity varies with extraction solvent, dose, and chemical standardization, underscoring the need for rigorous characterization of marker compounds and formulation (Sarma et al., 2018; Nayaka et al., 2021; Biswas et al., 2022).

Despite the growing interest in *P. betle* as a phototherapeutic option, the evidence base remains fragmented across phytochemistry, microbiology, and clinical observations, with limited integration into BV pathophysiology and contemporary treatment challenges. In particular, key uncertainties persist regarding the consistency of anti-*Gardnerella* and anti-biofilm effects across standardized preparations, the extent to which *Lactobacillus* is spared under clinically relevant exposures, and the robustness of topical safety and mucosal tolerability data (Mudayatiningsih & Suryandari, 2018; Sarma et al., 2018; Nayaka et al., 2021; Biswas et al., 2022; Rahmi & Firdausi,

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2024; Vedu et al., 2024; Fadhilah Nuraini et al., 2025). Therefore, this review synthesizes current evidence on *P. betle*'s antimicrobial mechanisms, its potential to modulate the vaginal microbiome, and its safety and standardization profile to inform translational development and strategies aimed at preventing BV recurrence (Abbe & Mitchell, 2023; World Health Organization, 2025).

Method

This study used a narrative review design to synthesize evidence on the potential role of *Piper betle* in bacterial vaginosis (BV), focusing on antimicrobial and anti-biofilm mechanisms, effects on vaginal microbiome ecology, and safety/standardization considerations. A narrative approach was chosen because the literature is heterogeneous in extract preparation, experimental models, and outcome measures; therefore, a qualitative, interpretive synthesis was considered more appropriate than quantitative pooling (Basheer, 2022; Sukhera, 2022).

An exploratory literature search covering the period 2015–2025 was conducted in PubMed/MEDLINE, ScienceDirect, and Google Scholar, supplemented by manual screening of reference lists from relevant articles. A representative search string combined BV-related terms (e.g., "bacterial vaginosis," "*Gardnerella vaginalis*," "biofilm," "quorum sensing," "*Lactobacillus,*" and "vaginal microbiome") with Piper betle-related terms (e.g., "*Piper betle*," "hydroxychavicol," "eugenol," "antimicrobial," "anti-biofilm," "mucosal safety," and "standardization"). Studies were included if they were published in English or Indonesian, evaluated *Piper betle*, its extracts, formulations, or major constituents, and reported outcomes relevant to BV-associated taxa, biofilm/QS processes, vaginal microbiome or *Lactobacillus* effects, or safety/standardization for intravaginal use. In vitro, in vivo, observational, clinical, mechanistic, and narrative sources were considered. Studies were excluded if they were published before 2015, were duplicates, non-scientific sources, unrelated to BV-relevant translational questions, lacked sufficient methodological detail, or involved mixed herbal preparations in which the contribution of *Piper betle* could not be distinguished. Records were screened by title/abstract, then by full text. Data extracted included study design, model, *Piper betle* preparation, major markers, key outcomes, safety notes, and translational relevance.

Result and Discussion

Antimicrobial and anti-virulence mechanisms

Bacterial vaginosis (BV) is shaped by ecological, structural, and metabolic interactions within the vaginal microbiome (Bradshaw & Brotman, 2015; Abbe & Mitchell, 2023; Lachyan et al., 2024). A key obstacle to durable symptom resolution is the ability of BV-associated anaerobes—particularly *Gardnerella vaginalis*—to persist in structured communities that reduce antimicrobial penetration and promote chronic dysbiosis (Bradshaw & Brotman, 2015; Muzny & Sobel, 2022; Lachyan et al., 2024). Within this framework, the antimicrobial profile of *Piper betle* is of interest because selected studies have reported inhibitory activity against BV-associated taxa such as *G. vaginalis* and *Atopobium vaginae*, with hydroxychavicol frequently discussed as a putative contributor (Sarma et al., 2018; Singh et al., 2018; Jalil et al., 2022). Mechanistic explanations proposed across the literature include membrane perturbation, oxidative stress-associated intracellular damage, and interference with bacterial growth processes, which may plausibly reduce pathogen fitness under BV-like conditions (Singh et al., 2018; Nayaka et al., 2021; Biswas et al., 2022). However, because most

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mechanistic evidence derives from heterogeneous in vitro systems that differ in strain selection, exposure time, and extract composition, these mechanistic interpretations should be regarded as supportive rather than definitive for BV pathophysiology.

Beyond direct growth inhibition, anti-biofilm and quorum-sensing (QS) interference have been highlighted in selected studies as potentially relevant "anti-persistence" features. In some in vitro studies, *P. betle* extracts have been reported to inhibit early biofilm formation and may also weaken established biofilm matrices, which—if reproduced in BV-relevant models—could increase the susceptibility of embedded cells to host defences and antimicrobials (Sarma et al., 2018; Jalil et al., 2022). QS interference has also been proposed as a mechanism by which *P. betle* may attenuate coordinated virulence behaviours and community organization (Sarma et al., 2018). Importantly, evidence for QS and biofilm inhibition has largely been demonstrated in non-BV model systems, supporting the biological plausibility of anti-virulence activity but not establishing BV-specific clinical efficacy (Sikdar et al., 2024). Taken together, the available evidence suggests that *P. betle* may have multi-pronged antimicrobial and anti-virulence potential, while underscoring the need for BV-targeted validation using polymicrobial biofilm and mucosal models.

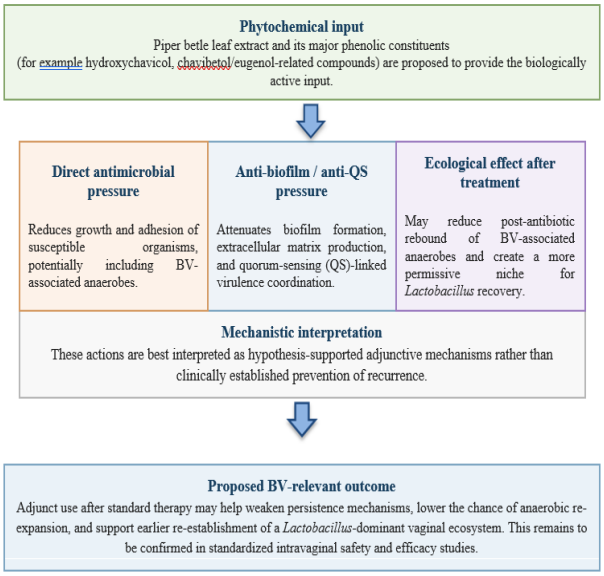

Figure 1. Proposed adjunctive mechanism of Piper betle in bacterial vaginosis (BV), including putative antimicrobial, anti-biofilm, and anti-quorum-sensing effects, together with the possible support of post-treatment restoration of a Lactobacillus-dominant vaginal microbiome. The scheme is intended as a mechanistic summary derived from selected in vitro and supportive literature, rather than as evidence of established clinical efficacy (Lade et al., 2014; Kusuma et al., 2017; Krzyżek, 2019; Abbe & Mitchell, 2023, 2023; Jantorn et al., 2023; Gao et al., 2024; Nuno et al, 2024; Kim et al., 2025).

Potential to modulate the vaginal microbiome (microbiome-sparing profile)

A major limitation of standard BV antibiotics is that they may reduce the pathogen burden but can also suppress beneficial *Lactobacillus* populations, thereby delaying the re-establishment of a protective, acidic vaginal environment and potentially contributing to recurrence (Bradshaw & Brotman, 2015; Abbe & Mitchell, 2023). In principle, an adjunct with relative selectivity—namely, one that reduces BV-associated anaerobes while sparing protective lactobacilli—would be mechanistically aligned with recurrence prevention. In

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selected studies and under certain conditions, *P. betle* appears to exert comparatively limited inhibitory effects on *Lactobacillus* spp. and may be less disruptive than non-specific cleansing products, thereby providing an early, but still preliminary, signal of microbiome-sparing potential (Mudayatiningsih & Suryandari, 2018; Sarma et al., 2018). One clinical observation also reported higher levels of *Lactobacillus vaginalis* among women using *P. betle*-based preparations than among those using soap or water, a finding that is broadly consistent with the wider principle that earlier restoration of *Lactobacillus* dominance may support resistance to BV recurrence (Bradshaw & Brotman, 2015; Biswas et al., 2022).

Nevertheless, the notion of "microbiome selectivity" should remain provisional. Microbiome outcomes are likely to depend strongly on formulation characteristics, including solvent system, pH, osmolality, concentration, exposure duration, and baseline community state. In addition, Lactobacillus is not a single functional entity; different species, such as *L. crispatus* and *L. iners*, may differ in both susceptibility and ecological role. Accordingly, BV-relevant confirmation would ideally include standardized testing across multiple *Lactobacillus* species and BV-associated consortia, together with readouts such as lactate production, pH stabilization, and community recovery kinetics

Safety, Tolerability, and Standardization Requirements

The translational development of *P. betle* for BV requires careful separation of traditional use signals from product-level evidence. Observational studies and local clinical reports have reported improvement in pathological vaginal discharge and suggest acceptable tolerability when *P. betle* preparations are used for feminine hygiene, although these findings arise from limited, methodologically heterogeneous settings (Rahmi & Firdausi, 2024; Nuraini et al., 2025). Reviews and ethnopharmacological syntheses likewise often describe *P. betle* as broadly tolerable for topical use, but the underlying evidence remains heterogeneous and is not consistently BV-specific (Sarma et al., 2018; Nayaka et al., 2021; Biswas et al., 2022).

Given that intravaginal application introduces unique safety constraints, including potential mucosal irritation, effects on the epithelial barrier, and unintended disruption of protective commensals, a conservative interpretation is that current evidence supports the feasibility but not yet definitive clinical safety of standardized BV-indicated products. In this context, the safety threshold for *Piper betle* with respect to *Lactobacillus* should not be interpreted as a single universally accepted concentration, but rather as the highest formulation-specific exposure that does not meaningfully reduce protective vaginal *Lactobacillus* populations, does not impair epithelial barrier integrity, and does not induce clinically relevant irritation. At present, such a threshold remains undefined in human vaginal models and clinical studies. Although in vitro evidence from red *Piper betle* extract suggests that 0.2% w/v may preserve survival of tested *Lactobacillus* isolates better than higher concentrations, the same evidence base also indicates inhibitory activity at increased doses, and these findings cannot yet be directly extrapolated to the clinically relevant vaginal ecosystem or to long-term prevention of BV recurrence (Kusuma et al., 2017) , the same body of evidence also indicates inhibitory activity at higher doses, and these findings cannot yet be directly extrapolated to the clinically relevant vaginal ecosystem or to long-term prevention of BV recurrence (Kusuma et al., 2017). Accordingly, any claim of safety should remain provisional until supported by standardized formulation studies evaluating commensal viability, epithelial compatibility, and local

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tolerability in models that more closely reflect human intravaginal use.

Standardization is the principal barrier to comparability and reproducibility. The phytochemical composition of *P. betle* may vary substantially across cultivars, growth conditions, harvesting methods, and extraction solvents, all of which may alter phenolic content and antimicrobial potency (Sarma et al., 2018; Biswas et al., 2022). In selected reports, ethanolic or hydroalcoholic extracts appear to exhibit stronger antibiofilm and antimicrobial effects than aqueous preparations, a pattern that may reflect greater enrichment in phenolic compounds (Sarma et al., 2018). Therefore, any translational pathway should specify the extraction protocol, batch-to-batch marker quantification (e.g., hydroxychavicol/eugenol), stability under intended storage conditions, and formulation parameters relevant to vaginal compatibility, including pH, osmolality, and excipients. Without such controls, both mechanistic and clinical claims remain difficult to generalize.

Translational implications and recurrence-prevention positioning

Because BV recurrence is closely linked to biofilm persistence and incomplete ecological recovery (Bradshaw & Brotman, 2015; Muzny & Sobel, 2022; Abbe & Mitchell, 2023; Lachyan, Khunger, and Swagatika Panda, 2024), the most defensible translational hypothesis is that *P. betle* may serve as an adjunct rather than a direct replacement for guideline-based therapy. Mechanistically, an adjunctive role would be coherent if a given preparation can weaken biofilm structure and/or virulence coordination, reduce rebound of BV-associated anaerobes after antibiotics, and support faster re-establishment of Lactobacillus dominance (Mudayatiningsih & Suryandari, 2018; Sarma et al., 2018; Singh et al., 2018; Jalil et al., 2022; Phensri et al., 2022).

On that basis, it may be hypothesized that *Piper betle*, when used after standard therapy, could help lower BV recurrence by limiting biofilm persistence and virulence signalling among BV-associated anaerobes, while potentially facilitating earlier restoration of a *Lactobacillus*-dominant vaginal ecosystem. However, this interpretation should be viewed as mechanistically grounded and hypothesis-generating, rather than as evidence of an established preventive effect (Nayaka et al., 2021).

Accordingly, the next stage of evidence most aligned with a stronger translational claim would include BV-relevant polymicrobial biofilm models, including *Gardnerella*-dominated systems, standardized extract and formulation comparisons, head-to-head testing against metronidazole or clindamycin alone versus in combination, commensal-sparing assays using representative *Lactobacillus* species, and mucosal safety readouts such as epithelial viability, inflammatory markers, and barrier integrity. Clinically, recurrence-focused endpoints, including time to recurrence, sustained eubiosis markers, and symptom relapse, would likely be more informative than short-term pathogen reduction alone. With such a pipeline, current mechanistic signals may become more informative for assessing whether *P. betle* plays a role in BV recurrence-prevention strategies.

To improve transparency of the evidence base, representative studies relevant to antimicrobial activity, anti-biofilm/anti-quorum-sensing effects, and commensal-safety considerations of Piper betle are summarized in Table 1. Because direct BV-specific studies remain limited, the table includes both BV-relevant studies and mechanistic supporting studies from non-BV models.

Table 1. Key studies on *Piper betle* relevant to bacterial vaginosis (2015–2025)

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Study	Study type/model	Preparation/markers	BV organism/model	Main outcomes (biofilm / QS)	Safety / commensal notes
Kusuma et al., 2017	In vitro commensal-safety study	Red *P. betle* ethanolic extract; flavonoids, tannins, steroids, saponins, polyphenols	Vaginal commensal surrogates: Lactobacillus acidophilus, L. bifidus	Not a biofilm/QS study	MIC/MBC against Lactobacillus 0.625–1.25% w/v; 0.2% w/v maintained survival near normal-flora range (78.43% for L. acidophilus; 76.39% for L. bifidum). Higher concentrations were inhibitory.
Mudayatiningsih & Suryandari, 2018	Observational comparative study	*P. betle*-based vaginal cleanser vs soap vs water	Vaginal flora / pH in women of childbearing age	No direct biofilm/QS endpoint	Reported differences in Lactobacillus vaginalis normal flora and vaginal pH across cleanser groups; useful as an early clinical signal, but formulation and exposure were not standardized.
Rahmi & Firdausi, 2024	Small clinical report / practical intervention	*P. betle* decoction	Pathological vaginal discharge; not microbiologically confirmed BV	No direct biofilm/QS endpoint	Symptoms improved after one week; no formal microbiome, epithelial, or controlled safety testing was reported.
Carolin et al., 2024	Quasi-experimental clinical study	Boiled P. *betel* leaf + turmeric decoction	Pathological vaginal discharge in women of childbearing age	No direct biofilm/QS endpoint	Improvement versus control reported, but not BV-specific; combination preparation; no direct Lactobacillus or mucosal safety assessment.
Nuraini et al., 2025	Experimental in vitro vaginal secretion culture	Green *P. betle* methanolic extract, 20–30%	Bacteroides from vaginal secretion cultures, used as a BV-relevant anaerobic target	Antibacterial rather than direct biofilm/QS readout	Concentration-dependent inhibition reported; 30% categorized as sensitive. No commensal-sparing or epithelial compatibility data.
Sikdar et al., 2024	In vitro anti-virulence / anti-QS study	P. betle leaf extract; phytocompound-based mechanistic analysis	Non-BV QS models: Chromobacterium violaceum CV026 and Pseudomonas aeruginosa	QS inhibition and reduced biofilm formation; reduced violacein, EPS, pyocyanin, pyoverdine, and elastase at sub-MIC concentrations	Mechanistically supportive only; no Lactobacillus or mucosal safety testing.
Lao et al., 2023	In vitro antibacterial/antibiofilm study	P. betle ethanolic leaf extract	Non-BV biofilm model: MSSA (Staphylococcus aureus ATCC 29213)	Biofilm formation inhibition up to 71% at 0.5× MIC (1250 µg/mL); biofilm eradication lower than oxacillin	No vaginal commensal or epithelial safety assessment.
Leesombun et al., 2023	In vitro antibacterial/antibiofilm study	Ethanolic *P. betle* extract; hydroxychavicol 36.02%, allyl pyrocatechol diacetate 17.56%,	Non-BV biofilm model: Staphylococcus pseudintermedius / MRSP	Concentration-dependent antibiofilm activity; >50% inhibition at 4× MIC and 8× MIC	Useful for marker-based standardization; no Lactobacillus or mucosal safety data.

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		chavibetol 12.3%			
Ratchasong et al., 2025	Mechanistic antibacterial / nano formulation study	*P. betle* nano emulsion; HPLC showed hydroxychavicol high and eugenol lower	Non-BV model: avian pathogenic E. coli	Supports antimicrobial mechanism; hydroxychavicol is linked to disrupted cell division and elongated non-septate cells	Not a vaginal model; no commensal safety testing, but informative for mechanism and marker-based QC.

Abbreviations: BV, bacterial vaginosis; QS, quorum sensing; MIC, minimum inhibitory concentration; MRSP, methicillin-resistant Staphylococcus pseudintermedius; MSSA, methicillin-susceptible Staphylococcus aureus.
Note: Direct BV-specific evidence remains limited. Accordingly, this table includes both BV-relevant studies and mechanistic supporting studies from non-BV models when they inform antimicrobial, antibiofilm, anti-virulence, standardization, or commensal-safety interpretation.
Representative studies relevant to the antimicrobial, antibiofilm/antivirulence, and commensal-safety profile of Piper betle in the context of BV are summarized in Table

Conclusion

In summary, the available evidence suggests that *Piper betle* possesses biological activities that are mechanistically relevant to key processes implicated in the persistence and recurrence of bacterial vaginosis, including inhibition of BV-associated anaerobes, attenuation of biofilm-related persistence, and a comparatively microbiome-sparing profile under selected conditions. Collectively, these findings support the biological plausibility of *Piper betle* as an adjunctive candidate within BV management. However, the current evidence base remains limited by the predominance of preclinical studies, methodological heterogeneity, and inadequate clinical validation. Accordingly, the field now requires standardized preparations with marker-based quality control, BV-relevant translational models, and rigorously designed clinical studies with recurrence-focused endpoints before *Piper betle* can be more confidently positioned in evidence-based BV care.

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