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The Vaginal Microbiome Modulates High-Risk HPV Persistence: Mechanisms, Biomarkers, and Therapeutic Opportunities

Fu Shuhua[1], Li Quantong[2], Chen Yuan[2] and You Hailing[2]*

[1]*Beijing University of Chinese Medicine, China*

[2]*Shenzhen Hospital of Beijing University of Chinese Medicine, Shenzhen, 518172, Guangdong, China*

***Corresponding author:** You Hailing, Shenzhen Hospital of Beijing University of Chinese Medicine, Shenzhen, 518172, Guangdong, China

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ABSTRACT

Background: Persistent infection with high-risk human papillomavirus (HR-HPV) is the necessary cause of cervical cancer (CC). The vaginal microbiome, particularly dysbiosis, is increasingly recognized as a critical co-factor, yet a systematic understanding of its bidirectional mechanistic interplay with HPV, especially regarding early infection events, remains incomplete.

Objective: This review synthesizes current evidence to elucidate the bidirectional mechanisms between the vaginal microbiome and HR-HPV persistence, with a focus on novel insights into viral entry modulation. It further proposes a microbiome-informed framework for clinical management.

Main Findings: We delineate a vicious cycle: vaginal dysbiosis (depleted lactobacilli, elevated pH) promotes HPV persistence by disrupting epithelial barriers, inducing immune dysfunction, and creating a pro-inflammatory milieu. Conversely, HPV oncoproteins (E6/E7) exacerbate dysbiosis by damaging epithelium, suppressing interferon responses, and reprogramming host metabolism. Notably, we highlight emerging evidence that microbial metabolites may interfere with HPV endosomal uncoating—a novel early checkpoint. Clinical studies support this interplay, showing dysbiosis correlates with increased HPV acquisition and reduced clearance.

Conclusion: The microbiome-HPV axis offers actionable therapeutic targets. Integrating vaginal microbiome profiling into risk stratification for HPV-positive women, alongside microbiome-targeted therapies (e.g., probiotics, immunomodulation, TCM), represents a promising precision prevention strategy complementary to vaccination and screening.

Keywords: HR-HPV; Vaginal Microbiome; Dysbiosis; Cervical Carcinogenesis; Probiotics

Abbreviations: HR-HPV: High-Risk Human Papillomavirus; CC: Cervical Cancer; CSTs: Community State Types; TCM: Traditional Chinese Medicine

Introduction

Cervical cancer (CC) remains a leading cause of cancer-related mortality among women worldwide, with persistent high-risk human papillomavirus (HR-HPV) infection identified as the central etiological agent in over 90% of cases [1]. While prophylactic vaccination and systematic screening have substantially reduced CC incidence in many regions, a significant proportion of women continue to develop persistent HR-HPV infections and subsequent cervical intraepithelial neoplasia. This clinical reality underscores the critical role of co-factors—beyond viral presence alone—in determining the trajectory from transient infection to viral persistence and ultimately carcinogenesis. Among these co-factors, the vaginal microbiome has garnered increasing attention as a key modulator of cervical health and disease [2,3]. Under physiological conditions, the vaginal ecosystem is dominated by Lactobacillus species, which maintain a protective

environment through acid production, antimicrobial secretion, and immune regulation [4]. In contrast, dysbiosis—characterized by a decline in lactobacilli, increased microbial diversity, elevated pH, and overgrowth of anaerobic bacteria—is frequently observed in women with persistent HR-HPV infection and higher-grade cervical lesions [5-7]. This association suggests that the vaginal microbiome may not merely be a passive bystander but an active participant in the natural history of HPV infection. Several comprehensive reviews have summarized the epidemiological associations between vaginal microbiome composition and HPV infection status [8].

However, a critical gap remains in systematically elucidating the bidirectional mechanistic dialogue between the microbiome and the virus, particularly the potential impact of microbial metabolites on the earliest stages of HPV infection, including viral entry and uncoating [9,10]. Furthermore, a translational perspective that links these mechanistic insights to stratified clinical management strategies is needed to bridge the gap between bench research and bedside application. This review therefore addresses these gaps through the following specific objectives:

1. To synthesize current evidence on how vaginal dysbiosis promotes HR-HPV persistence through multifaceted mechanisms including physical barrier disruption, immune suppression, and metabolic alteration [11-17].
2. To elucidate how HR-HPV infection actively remodels the vaginal microenvironment to favor its own persistence, creating a self-reinforcing cycle [18-22].
3. To explore the novel concept of microbiome-virus entry crosstalk as a potential early checkpoint in the infection process [23,24].
4. To propose an integrated, microbiome-informed framework for cervical cancer prevention and therapy, discussing promising strategies ranging from probiotics and immunomodulation, to metabolic intervention and traditional Chinese medicine (TCM) [25,26].

The Vaginal Microbiome: From Homeostasis to Dysbiosis

A physiologically normal vaginal microenvironment represents a finely tuned ecosystem characterized by low microbial diversity with Lactobacillus species typically constituting over 70% of the bacterial population [27]. This lactobacilli-dominated state is associated with a vaginal pH between 3.8 and 4.5, maintained primarily through the production of lactic acid—a byproduct of glycogen metabolism by epithelial cells and subsequent fermentation by lactobacilli [28]. Beyond acidification, these beneficial bacteria exert protective effects through multiple mechanisms including the secretion of bacteriocins with direct antimicrobial activity, competitive exclusion of pathogens through adhesion site occupation, and modulation of local immune responses. The hydrogen peroxide (H2O2) produced by certain Lactobacillus species further contributes to pathogen suppression [29]. This collective defensive arsenal creates an environment that is inherently hostile to many pathogens, including HPV virions, which show reduced stability and infectivity under acidic conditions. The transition from this homeostatic state to dysbiosis represents a fundamental shift in the vaginal ecosystem, typically involving a marked decline in Lactobacillus abundance accompanied by increased microbial diversity and proliferation of anaerobic bacteria commonly associated with bacterial vaginosis [30,31]. Taxa such as Gardnerella vaginalis, Prevotella species, Atopobium vaginae, and Mobiluncus species frequently dominate in dysbiotic states, often forming structured biofilms that enhance their resilience and persistence.

This microbial shift is consistently correlated with elevated vaginal pH (>4.5), diminished production of protective metabolites, and altered immunological parameters. Clinically, this dysbiotic state is significantly more prevalent in women with persistent HR-HPV infection compared to those with transient infection or no infection, and its presence is associated with higher rates of progression to cervical intraepithelial neoplasia [32-35]. The correlation appears particularly strong for non-Lactobacillus dominant community state types (CSTs), especially those rich in anaerobic bacteria, suggesting that specific microbial signatures may serve as biomarkers for HPV persistence risk [36].

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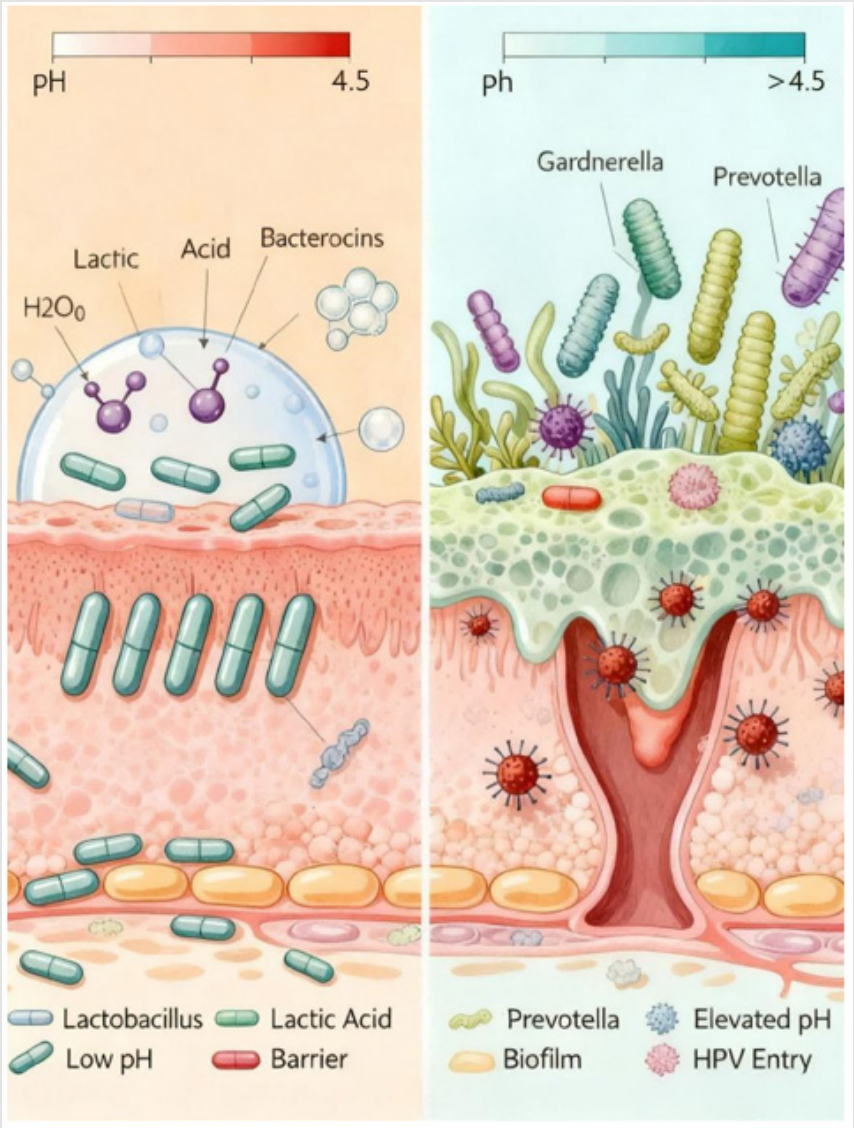


Note: provides a visual summary of this spectrum, contrasting the healthy, Lactobacillus-dominant state with the dysbiotic, pathogen-rich state that favors HPV persistence.

Figure 1: The Spectrum of Vaginal Microecology: From Homeostasis to Dysbiosis.

Mechanisms of Bidirectional Interaction

How Vaginal Dysbiosis Promotes HR-HPV Persistence: Vaginal dysbiosis facilitates HR-HPV persistence through a convergence of mechanisms that collectively compromise the host's defensive capabilities. The reduction in lactic acid production by diminished lactobacilli populations leads to elevated vaginal pH, which directly enhances HPV virion stability and epithelial accessibility by preserving the conformational integrity of viral capsid proteins [13]. Simultaneously, the loss of direct antimicrobial factors such as hydrogen peroxide and bacteriocins reduces the microenvironment's inherent virucidal activity, allowing HPV particles to remain infectious for longer durations [14]. Beyond these chemical changes, dysbiotic bacteria actively contribute to epithelial compromise through the secretion of enzymes like sialidases and proteases that degrade the protective mucus layer and disrupt tight junction proteins, thereby creating physical portals for viral entry [16]. The immunological consequences of dysbiosis are equally profound and multifaceted. The altered microbial community drives a shift in the local cytokine milieu, typically characterized by elevated levels of pro-inflammatory cytokines including IL-6, TNF-α,

and IL-1β alongside increased anti-inflammatory IL-10 [17]. This cytokine profile skews local immunity away from the Th1-dominated response necessary for effective viral clearance toward a Th2 or regulatory T-cell response that facilitates viral persistence.

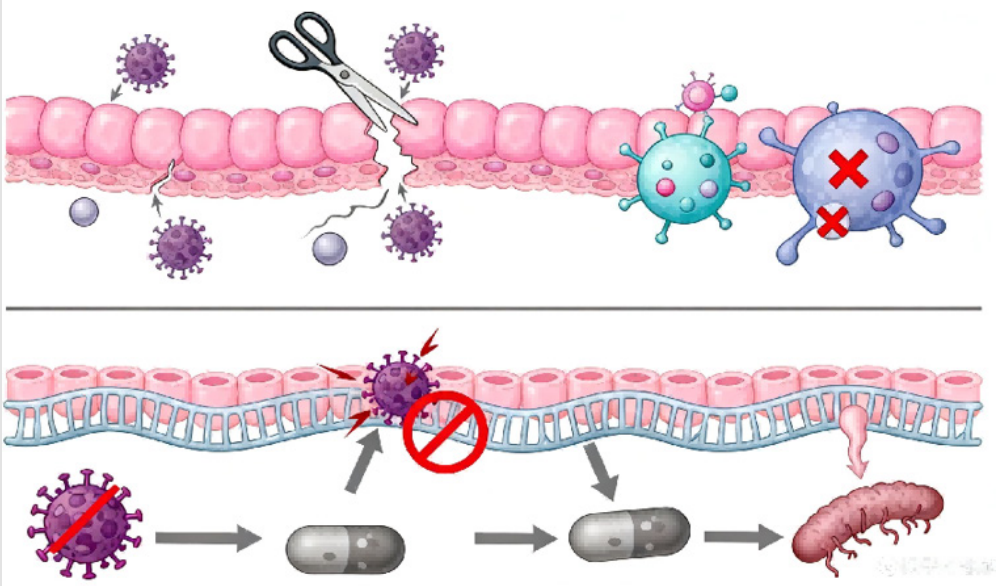
Furthermore, dysbiosis impairs mucosal immunity through reduced secretory IgA production and compromised antigen presentation capacity, dampening the adaptive immune response specifically targeting HPV-infected cells [14,15]. At the cellular level, natural killer cell and cytotoxic T-cell activities are frequently suppressed in dysbiotic environments, further enabling viral immune evasion and establishment of persistent infection. Metabolically, dysbiosis creates conditions conducive to viral persistence and genomic instability. Pathogen-derived metabolites, particularly short-chain fatty acids like butyrate produced in abundance by anaerobic bacteria, may induce direct DNA damage in epithelial cells while simultaneously modulating HPV gene expression patterns. The sustained inflammatory state characteristic of dysbiosis generates reactive oxygen species that promote mutagenesis and genomic instability, creating a microenvironment where HR-HPV oncogenes can exert their carcinogenic effects with greater potency [12]. These metabolic alterations extend beyond the epithelial cells to influence the composition of the microbial community itself, as certain metabolic byproducts selectively inhibit lactobacilli while promoting the growth of pathogenic taxa, thereby reinforcing the dysbiotic state.

How HR-HPV Infection Exacerbates Vaginal Microecological Imbalance: HR-HPV infection actively remodels the vaginal microenvironment in ways that exacerbate dysbiosis, creating a self-reinforcing cycle. The viral oncoproteins E6 and E7, expressed early in the infection cycle, directly induce epithelial damage and barrier disruption through multiple mechanisms [22]. By inhibiting epithelial differentiation programs and inducing hyperproliferation, these oncoproteins alter the architectural integrity of the cervical and vaginal epithelium. Simultaneously, they disrupt cell-cell junctions including tight junctions and adherens junctions, significantly increasing epithelial permeability and creating enhanced opportunities for bacterial adherence and colonization. This compromised barrier function not only facilitates the initial establishment of dysbiotic bacteria but also enables their deeper tissue penetration and persistence. The virus exerts profound immunosuppressive effects that extend beyond evasion of anti-viral immunity to create conditions favorable for dysbiotic overgrowth. The E6 and E7 proteins efficiently block type I interferon production and signaling, crippling a central component of innate antiviral defense while simultaneously removing a regulatory signal that helps maintain microbial homeostasis. Perhaps more significantly for microbial ecology, HPV downregulates major histocompatibility complex class I expression on infected epithelial cells, impairing antigen presentation to $CD8^+$T cells [11].

This immune evasion strategy, while primarily evolved to protect virus-infected cells from immune detection, has the collateral effect of reducing immune surveillance and control over co-colonizing bacterial pathogens, thereby permitting their uncontrolled proliferation. Metabolic reprogramming represents another critical mechanism through which HPV infection alters the vaginal niche to favor dysbiotic communities. The so-called Warburg effect—a shift toward aerobic glycolysis even in the presence of oxygen—is induced in HPV-infected cells to support the energetic and biosynthetic demands of viral replication [18]. This metabolic shift depletes local glucose reserves while accumulating lactate in the extracellular environment, creating conditions that are unfavorable for lactobacilli (which thrive in glucose-rich environments) while favoring anaerobic bacteria that can utilize alternative carbon sources [20]. Beyond these bulk nutrient changes, viral replication alters the availability of specific micronutrients and signaling molecules, further reshaping the competitive landscape of the microbial community in ways that disadvantage lactobacilli and promote pathogenic taxa [37]. Finally, HPV infection establishes a pro-inflammatory, pro-dysbiosis milieu through sustained activation of inflammatory pathways. The NF-κB pathway, frequently activated by viral proteins, drives persistent expression of pro-inflammatory cytokines including IL-6, TNF-α, and IL-1β [17]. While initially part of an anti-viral response, this chronic inflammatory state has detrimental effects on the microbial ecosystem by directly inhibiting lactobacilli growth while promoting the expansion of inflammatory-pathobiont taxa. The resulting dysbiosis then feeds back to enhance inflammation through pathogen-associated molecular patterns, creating a vicious cycle of inflammation and microbial imbalance that is difficult to break without targeted intervention.

A Novel Intersection: Microbiome-Virus Entry Crosstalk: The initial stages of HPV infection represent a potential point of intersection between viral biology and microbial ecology that has received limited attention until recently. HPV entry into host cells occurs through a carefully orchestrated sequence of events beginning with binding to heparan sulfate proteoglycans on the epithelial surface, followed by conformational changes that expose secondary receptors and trigger clathrin-mediated endocytosis [9]. The internalized virions traffic through the endosomal system where acidification-dependent uncoating releases the viral genome for nuclear import and establishment of infection [10]. Emerging preclinical evidence suggests that metabolites produced by vaginal bacteria may modulate this critical entry process [24]. Certain microbial metabolites have been shown to influence endosomal pH or membrane stability in other systems, raising the possibility that they could similarly affect HPV uncoating efficiency. For instance, bacterial amines (e.g., trimethylamine) produced through amino acid fermentation can alkalinize intracellular compartments, potentially interfering with the pH-dependent uncoating step. Other metabolites might affect membrane fluidity or the activity of host factors required for successful viral entry. We hypothesize that a dysbiotic metabolite profile may lower the threshold for successful HPV infection by facilitating viral entry, a previously underexplored dimension of host-virus-microbe interaction.

This microbiome-virus entry crosstalk represents a novel mechanistic layer in the relationship between vaginal ecology and HPV outcomes. If substantiated by further research, it would suggest that microbiome composition affects not only the persistence phase of infection but potentially the very establishment of infection. From a therapeutic perspective, this early checkpoint might be particularly amenable to intervention, as strategies to maintain a lactobacilli-dominated microbiome could theoretically reduce susceptibility to initial HPV infection rather than merely addressing established persistence. Future research should prioritize elucidating whether specific microbial metabolites directly interfere with HPV entry machinery and whether this represents a viable target for preventive interventions.



Note: visually summarizes these complex bidirectional mechanisms, illustrating how dysbiosis promotes HPV persistence and how HPV, in turn, exacerbates dysbiosis.

Figure 2: Mechanisms of Bidirectional Interaction Between HR-HPV and Vaginal Microecology.

Clinical and Population Evidence Supporting the Bidirectional Interaction

The proposed bidirectional relationship between vaginal microbiome composition and HR-HPV infection is strongly supported by converging lines of clinical and epidemiological evidence. Cross-sectional studies across diverse populations have consistently demonstrated significant differences in vaginal microbiome composition between HR-HPV-positive and HPV-negative women [5-7]. Specifically, women with HR-HPV infection show markedly reduced relative abundance of Lactobacillus species, particularly the strongly protective L. crispatus, alongside increased prevalence and abundance of bacterial vaginosis-associated taxa including Gardnerella, Prevotella, and Atopobium [30,31]. These differences remain statistically significant even after controlling for potential confounders such as age, sexual behavior, and contraceptive use, suggesting an independent association between dysbiosis and HPV status [32,33]. Longitudinal cohort studies provide stronger evidence for a causal relationship by establishing temporal sequences. Women with dysbiotic vaginal microbiota at baseline have been shown to have significantly higher rates of subsequent HR-HPV acquisition compared to those with lactobacilli-dominated microbiomes [34]. More compellingly, among women already infected with HR-HPV, those with dysbiosis exhibit substantially lower rates of spontaneous viral clearance and higher rates of progression to cervical intraepithelial neoplasia over follow-up periods ranging from 6 to 36 months [35]. These observations suggest that dysbiosis not only increases susceptibility to initial infection but actively impedes the host's ability to clear established infections [36]. Interventional studies, though more limited, provide preliminary evidence that modifying the vaginal microbiome can influence HPV outcomes. Several randomized controlled trials investigating specific probiotic strains, particularly certain Lactobacillus species, have reported increased rates of HPV clearance in intervention groups compared to controls [38]. While these studies vary in design, probiotic formulation, and outcome measures, their collective findings support the therapeutic potential of microbiome modulation [39]. Importantly, post-clearance analyses frequently show that successful HPV clearance is associated with a rebound in lactobacilli dominance, further supporting the dynamic interplay between viral status and microbial

composition [40]. These observations collectively strengthen the case for a bidirectional, mutually reinforcing relationship rather than a unidirectional association [41].

Towards a Microbiome-Informed Clinical Management Framework

The recognition of a bidirectional interplay between the vaginal microbiome and HR-HPV infection opens promising avenues for novel preventive and therapeutic strategies. Moving beyond traditional virus-centric approaches to embrace an ecological perspective could transform clinical management paradigms for HPV-related cervical disease.

Microbiome as a Biomarker for Risk Stratification: The vaginal microbiome shows considerable potential as a biomarker for risk stratification in HPV-positive women. Current clinical management typically relies on HPV genotyping and cytology to assess progression risk, but these parameters provide incomplete prognostic information. Integrating vaginal microbiome profiling—whether through relatively simple assessments like Nugent scoring or more comprehensive methods like 16S rRNA gene sequencing—could significantly enhance risk prediction [27]. Women with HR-HPV infection and concurrent dysbiosis, particularly non-lactobacilli dominant community state types with high abundance of specific pathogenic taxa, likely represent a subgroup at substantially elevated risk for persistence and progression [32]. Identifying these high-risk individuals early would enable more intensive monitoring, earlier intervention, and potentially better outcomes through targeted management. Future research should focus on validating specific microbial signatures as predictive biomarkers and developing cost-effective, clinically feasible testing strategies suitable for implementation in diverse healthcare settings.

Therapeutic Strategies Targeting the Microbiome

Microecological Modulation: Direct modulation of the vaginal microbiome through probiotics represents the most straightforward translational application of current knowledge. Specific strains of Lactobacillus, such as L. crispatus and L. gasseri, have demonstrated efficacy in restoring vaginal acidity, producing antimicrobial compounds, and competitively excluding pathogens in clinical studies [42]. Administration routes include oral supplementation (with subsequent vaginal colonization via the rectum-vaginal pathway) and direct intravaginal application via suppositories or capsules [38]. While optimal strains, dosages, and treatment durations require further standardization, existing evidence supports the therapeutic potential of probiotics as an adjuvant strategy to enhance HPV clearance. Beyond live probiotics, prebiotics (nutrients specifically supporting lactobacilli growth) and postbiotics (direct application of beneficial microbial metabolites like lactic acid) represent complementary approaches that may offer advantages in stability and standardization.

Immunomodulation: Immunomodulatory strategies aim to reverse the immunosuppressive effects of both HPV infection and dysbiosis. Local interferon therapy has been used with mixed results, likely reflecting the complexity of cytokine networks in the cervicovaginal environment. More promising are therapeutic HPV vaccines targeting the E6 and E7 oncoproteins, which aim to stimulate cell-mediated immunity specifically against HPV-infected cells. Several vaccine candidates are in various stages of clinical development, with some showing promise in early-phase trials [39]. An intriguing possibility is combining immunomodulatory approaches with microbiome modulation, potentially creating synergistic effects by simultaneously enhancing immune recognition and reducing the inflammatory burden that suppresses protective immunity.

Metabolic Intervention: Targeting the metabolic alterations associated with both HPV infection and dysbiosis represents an innovative therapeutic frontier. Preclinical studies suggest that inhibitors of glycolysis, such as 2-deoxyglucose, can disrupt the metabolic niche supporting both viral replication and dysbiotic bacterial growth [43]. Similarly, modulators of short-chain fatty acid metabolism might mitigate the genotoxic effects of dysbiosis metabolites while restoring conditions favorable to lactobacilli. Though primarily supported by in vitro and animal studies at present, metabolic interventions offer a mechanism-based approach that addresses fundamental drivers of the vicious cycle. Their eventual clinical application would likely be as adjuvants to established therapies rather than standalone treatments.

Traditional Chinese Medicine (TCM): Traditional Chinese medicine approaches to persistent HR-HPV infection and cervical lesions have shown promising results in clinical studies conducted over the past five years [25]. Certain TCM formulations administered orally or as vaginal suppositories have demonstrated statistically significant improvements in HR-HPV clearance rates compared to observation alone, with some studies also reporting positive effects on regression of low-grade cervical intraepithelial neoplasia. Although the precise molecular mechanisms remain under investigation, current research suggests that TCM exerts multi-targeted effects including modulation of systemic and local cellular immunity (evidenced by increased CD4+/CD8+ T-cell ratios and enhanced NK cell activity), direct inhibition of viral replication, and synergistic improvement of the vaginal microenvironment [26]. Network pharmacology studies reveal that TCM prescriptions, such as Jinbai Heat-clearing Perscrition, may regulate multiple signaling pathways and gene networks involving in HPV-induced carcinogenesis, aligning with the complex, multifactorial nature of the host-microbe-virus interaction. This holistic, systems-level regulatory capacity positions TCM as a potentially valuable component of integrated management strategies [44].

Combined Modality Approaches: Given the complexity of the bidirectional interaction between HPV and the vaginal microbiome, single-modality interventions are unlikely to achieve optimal outcomes for all patients. The future of clinical management will likely involve

integrated protocols that simultaneously address multiple aspects of the vicious cycle. For instance, combining microbiome restoration through specific probiotics with immune activation via therapeutic vaccines or immunomodulators could target both the permissive microbial environment and the impaired immune response. Adding metabolic modulators or TCM formulations might further disrupt the self-reinforcing cycles of dysbiosis and inflammation. Crucially, such combination approaches should be tailored to individual patients based on their specific microbial profile, immune status, and clinical presentation. Future research should prioritize well-designed clinical trials that stratify participants by microbial community type and evaluate multimodal interventions against standard care.

Conclusion and Future Perspectives

A robust and growing body of evidence confirms the existence of a self-reinforcing, bidirectional relationship between vaginal dysbiosis and HR-HPV persistence, which collectively drives the process of cervical carcinogenesis. The healthy, Lactobacillus-dominant vaginal microbiome serves as a key defender against HPV through multiple complementary mechanisms including maintenance of an acidic environment, production of direct antimicrobials, competitive exclusion of pathogens, and modulation of local immunity. Conversely, dysbiosis creates a permissive environment for viral persistence through epithelial barrier disruption, immune dysfunction, chronic inflammation, and metabolic alterations—including the newly hypothesized interference with viral entry processes. The translational implications of this understanding are significant and multifaceted. First, vaginal microbiome assessment should be evaluated as a risk stratification tool in HPV-positive women, potentially identifying those at highest risk for persistence and progression who would benefit from closer monitoring and early intervention. Second, microbiome-targeted therapies, particularly probiotics with well-characterized strains and traditional Chinese medicine formulations with demonstrated efficacy, offer promising adjuvant strategies to enhance viral clearance and prevent disease progression. Third, combination approaches that simultaneously address the virus, the immune system, and the microbial ecology hold the greatest potential for breaking the vicious cycle that sustains HR-HPV persistence.

Several critical questions must guide future research directions. First, can modulating the vaginal microbiome before HPV exposure reduce acquisition risk, and if so, which interventions are most effective for primary prevention? Second, in vaccinated individuals, does microbiome health influence outcomes of "breakthrough" infections, suggesting a role for microbiome optimization even in vaccinated populations? Third, what are the optimal probiotic strains, formulations, dosing regimens, and treatment durations for maximizing HPV clearance rates? Fourth, how can traditional Chinese medicine and Western medicine be optimally integrated in clinical protocols to leverage their complementary strengths? Finally, can microbiome-based interventions be effectively delivered in resource-limited settings where the burden of cervical cancer is highest? In conclusion, moving beyond a purely virus-centric view of cervical carcinogenesis to embrace a holistic host-microbiome-virus ecosystem perspective represents a necessary evolution in our approach to cervical cancer prevention and control. Incorporating microbiome health into public health messaging, clinical risk assessment, and therapeutic strategies—alongside continued expansion of vaccination coverage and screening access—offers a comprehensive path toward reducing the global burden of HPV-related disease. As research continues to unravel the complex dialogues within the cervicovaginal ecosystem, clinicians and researchers alike must remain open to innovative approaches that address not just the pathogen, but the environment in which it thrives.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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Availability of Data and Materials

No datasets were generated or analysed during the current study. All data cited in this review are available from the corresponding publications listed in the References section.

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