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Haticegul Tuncer [1], Sevinj Hajiyeva [2], Betul Gungor Serin [1], M. Onur Atakul [1], Ali Can Gunes [1], Taylan Onat [3], Utku Akgor [4], Derman Basaran [4], Z. Selcuk Tuncer [4] and Murat Gultekin [4,*]

[1] Hacettepe University, Department of Obstetrics and Gynecology, Ankara, Turkey
[2] Hacettepe University, Faculty of Medicine, Ankara, Turkey
[3] Sincan Training and Research Hospital, Ankara, Türkiye
[4] Hacettepe University, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Ankara, Turkey
* Correspondence: mrtgultekin@yahoo.com; Tel.: +90 532 256 09 51

Abstract

Background/Objectives: Non-ablative local therapies are increasingly used in the conservative management of human papillomavirus (HPV) infection. Coriolus versicolor, an immunomodulatory medicinal mushroom, is one such approach. This study aimed to investigate the effect of a Coriolus versicolor–based vaginal gel on HPV clearance and cervical cytological outcomes. **Methods**: This retrospective cohort study included 600 women with cervical HPV infection (300 treated with a Coriolus versicolor–based vaginal gel and 300 receiving standard follow-up). Baseline and six-month follow-up assessments included HPV DNA testing and cervical cytology. **Results**: Baseline demographic characteristics, HPV genotype distribution, and cytological findings were comparable between the groups. Overall HPV clearance was significantly higher in the treatment group than in the control group (89.3% vs. 44.7%, $p < 0.001$). Complete clearance of high-risk HPV genotypes, including HPV 16 (77.0% vs. 25.4%, $p < 0.001$) and HPV 18 (73.9% vs. 18.5%, $p = 0.017$), was also significantly more frequent among treated women. Cytological normalization occurred more often in the treatment group (88.4% vs. 60.4%, $p < 0.001$). Multivariable analysis identified use of the vaginal gel as the strongest independent factor associated with HPV clearance (adjusted odds ratio [aOR] = 8.45; 95% confidence interval [CI]: 3.05–23.43; $p < 0.001$). **Conclusions**: Treatment with a Coriolus versicolor–based vaginal gel was associated with significantly higher rates of high-risk HPV clearance and cervical cytological normalization. These findings suggest that this therapy may represent an effective adjunct in the conservative management of HPV infection; however, randomized controlled trials are warranted to confirm these results.

Keywords: human papillomavirus; cervical cancer; HPV clearance; cervical cytology; coriolus versicolor; vaginal gel; non-ablative therapy

1. Introduction

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection worldwide, with the majority of sexually active individuals acquiring the virus at some point during their lifetime. Over 200 HPV genotypes have been identified, with 14 classified as high-risk types that are strongly associated with nearly all cases of cervical intraepithelial neoplasia and cervical cancer in women [1]. Most HPV infections and related low-grade cervical abnormalities resolve spontaneously without medical intervention [2]. However, some infections persist. Factors contributing to persistence include specific viral genotypes, elevated viral load, age at initial diagnosis, vaginal microbiome imbalances (dysbiosis), and immune suppression. Persistent infection with high-risk HPV types substantially increases the risk of progression from early lesions to high-grade precancerous changes and invasive cervical cancer [3,4].

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Cervical cancer remains a major cause of illness and death worldwide. Persistent infection with "high-risk" HPV types is the main cause [5]. As of 2022, cervical cancer ranked as the fourth most prevalent cancer among women globally in terms of both incidence and mortality, accounting for approximately 660,000 newly diagnosed cases and 350,000 deaths worldwide [6]. Cervical infection with high-risk genotypes, especially HPV-16 and HPV-18, leads to progression from transient infection to neoplasia and finally invasive carcinoma [5,7]. Recent global studies estimate HPV prevalence at about 11.7% for any type and 6.5% for high-risk HPV among women. These numbers show a substantial risk for disease progression [7]. Additional analyses confirm that persistent high-risk HPV infection is the main cause of cervical cancer in different regions [8].

Primary prevention through vaccination and screening has improved cervical cancer control. Still, gaps in coverage and adherence leave many women at risk [9,10]. Current guidelines promote HPV testing in "screen–triage–treat" protocols and recommend follow-up for HPV-positive women. Most algorithms focus on monitoring low-grade abnormalities. They reserve definitive therapy for confirmed higher-grade disease [9–11]. Studies show most HPV infections clear within 12 to 24 months. Some persist, especially in adults or in the presence of cofactors. This has increased interest in adjunctive strategies to speed up viral clearance and repair mucosa without affecting safety [3,12,13].

Recently, non-ablative, locally applied products have been studied. These products aim to support cervical healing, maintain a healthy vaginal environment, and modulate local immunity. They may complement standard clinical follow-up in women with high-risk HPV infection and low-grade cervical abnormalities [14]. One approach uses Coriolus versicolor (syn. Trametes versicolor), a medicinal mushroom. Its protein-bound polysaccharides (PSK/PSP) helps to enhance local immunity by affecting both innate and adaptive responses. These include the local activation of dendritic cells and macrophages, as well as cytokines involved in antiviral and antitumor actions [15–17]. This provides a basis for testing Coriolus versicolor–based vaginal gels as local aids to improve clearance of HPV and restore epithelial integrity.

Early clinical evidence is emerging. The PALOMA trial, a prospective, randomized, multicenter, open-label study with an observation-only control arm, demonstrated that a Coriolus versicolor–based vaginal gel (Papilocare, Procare Health, Spain) improved normalization of HPV-related low-grade cervical lesions. The gel formulation includes hyaluronic acid, Asian centella, aloe vera, and alpha-glucan oligosaccharide which possess tissue-regenerative and vaginal microbiota-protective properties. Additionally, Coriolus versicolor, Azadirachta indica, and carboxymethyl-β-glucan, present in Papilocare, are established ingredients that have demonstrated efficacy in clearing HPV-related cervical lesions. Papilocare vaginal gel primarily helps prevent virus-induced cervical lesions. It does this by promoting the re-epithelialization of the cervical transformation zone. Additionally, the gel supports normalization of virus-associated intraepithelial abnormalities, alleviates vaginal dryness, restores the integrity of the cervical-vaginal mucosa, reestablishes balanced vaginal microbiota, and enhances overall vaginal health. Papilocare led to higher HPV clearance versus control over six months [18]. Observational data from real-world use, such as PAPILOBS, indicate this multi-ingredient gel can achieve lesion regression and meaningful HPV clearance. These findings hold in routine practice, even in older women who often do not clear HPV spontaneously [19]. Sub-analyses in women aged ≥40 years show similar benefits and good safety, supporting validity across ages [20]. These studies do have limits: open-label designs, assessment bias, and different endpoints. Still, their results support further rigorous evaluation in real-world groups relevant to clinical decisions [18–20].

This retrospective cohort study looks at women with cervical HPV infection in routine care. It measures the effectiveness of a Coriolus versicolor–based vaginal gel when added to standard follow-up. Specifically, it checks HPV clearance, cytologic and colposcopic results, and safety across subgroups. Findings are discussed in the context of current screening advice and new literature on non-ablative, immune-modulatory cervical therapies.

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2. Materials and Methods

2.1. Study Design & Participants

This study was designed as a retrospective cohort study based on previously recorded clinical data. The study period extended from January 2023 to August 2025, and the research was conducted in the Department of Obstetrics and Gynecology at Hacettepe University Hospital, a tertiary referral center. Patient demographic and clinical data were obtained from archived medical records, including patient follow-up files, hospital archive records, hospital procedural databases, and comprehensive medical information files encompassing follow-up data from other healthcare centers.

A total of 600 patients were included in the study and divided into two groups. The Papilocare group consisted of 300 patients who received a Coriolus versicolor–based vaginal gel, while the control group included 300 patients who did not receive any systemic or topic pharmacological treatment and were managed with standard clinical follow-up without pharmacological intervention.

All participants underwent HPV DNA testing and cervical cytologic examination at baseline and at six months. Cervical cytology samples were collected using a Cervix-Brush® cervical sampling device, which was inserted into the cervical canal and rotated 360 degrees to obtain epithelial cells from both the ectocervix and endocervix. Immediately after sampling, the brush head was rinsed into a vial containing liquid-based cytology preservative solution (CY-PREP® Pap Test Dual Filtration Cytology Preparation system). Cytological evaluation was performed according to standard laboratory protocols, and results were reported using the Bethesda System [21].

For HPV testing, cervical specimens were collected using a sterile Copan eSwab® collection and preservation system. After collection, the swab was placed into the transport medium and stored at room temperature until further processing. Cervical cells were subsequently suspended in PreservCyt solution (Hologic, Marlborough, MA, USA) and stored at room temperature until analysis. DNA extraction was performed using an eMAG automated extractor (bioMérieux, Marcy l'Etoile, France), with samples resuspended in 1 mL of buffer according to the manufacturer's instructions. HPV DNA detection and genotyping were conducted using the Anyplex™ II HPV28 real-time PCR assay (Seegene, Seoul, South Korea).

For methodological analysis, HPV genotypes were categorized into five groups: HPV 16, HPV 18, other high-risk HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), intermediate-risk HPV types (HPV 26, 53, and 66), and low-risk HPV types (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81).

Participants in the Papilocare group were instructed to apply the Coriolus versicolor–based vaginal gel according to the manufacturer's recommendations. The treatment regimen consisted of one vaginal cannula administered daily for 21 consecutive days during the first month, followed by application on alternate days in the subsequent months. A high-dose regimen was defined as daily administration during the first three months of treatment. Some patients received this high-dose regimen for three consecutive months (corresponding to the use of three boxes), whereas others continued the same regimen for a total of six months (corresponding to the use of six boxes), thereby completing an overall treatment duration of six months. All patients receiving Papilocare were analyzed within the same treatment group regardless of treatment duration. Participants in the control group did not receive any topical or systemic treatment during follow-up.

All participants were advised to use condoms during sexual intercourse and to avoid vaginal douching or the use of vaginal deodorants throughout the study period. Based on retrospective follow-up records, only patients who adhered to these recommendations were included in the Papilocare group.

Diagnostic and therapeutic procedures, including colposcopy, directed cervical biopsy, and excisional interventions such as the loop electrosurgical excision procedure (LEEP), were undertaken

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according to clinical indications and in compliance with established cervical cancer screening and management guidelines [22].

Overall HPV clearance was defined as the occurrence of either total or partial clearance. Total clearance was defined as a negative HPV DNA test result or the complete disappearance of all baseline HPV genotypes detected at enrollment. Partial clearance Partial clearance was defined as the disappearance of at least one HPV genotype.

Smear clearance was defined using the same classification as HPV clearance. Overall smear clearance was defined as the occurrence of either total or partial clearance. Total smear clearance was defined as the complete resolution of the baseline cytological abnormality with a return to normal cervical cytology. Partial smear clearance was defined as regression from the baseline cervical lesion to a lower-grade cervical lesion.

Demographic, clinical, and behavioral data collected included participants' age, educational level, Papilocare use and number of treatment boxes, pregnancy and parity history, menstrual regularity, oral contraceptive use, presence of chronic diseases, smoking status, HPV vaccination status, immunosuppression status, age at menarche, age at first sexual intercourse, baseline HPV genotype, and history of loop electrosurgical excision procedure.

Patients were eligible for inclusion if they had a positive HPV DNA test result and cervical cytology findings of normal cytology, atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical glandular cells (AGC).

Patients were excluded from the study if they had evidence of sexually transmitted infections or symptomatic vulvovaginal infections, immunodeficiency disorders or autoimmune diseases, were receiving immunosuppressive therapy at the time of evaluation, were pregnant, had undergone total hysterectomy, or had a history of gynecologic malignancy.

2.2. Ethics

The study received approval from the Ministry of Health Local Ethics Committee (Approval No: SEAH-BAEK 2025-151) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Patient data were obtained from Hacettepe University Hospital, where written informed consent for the use of clinical data for scientific research purposes is routinely obtained from both outpatients and inpatients at the time of clinical evaluation.

2.3. Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize demographic, clinical, virological, and cytological characteristics of the study population. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate, while categorical variables were presented as frequencies and percentages.

Comparisons between the Papilocare and control groups for continuous variables were conducted using the Mann–Whitney U test, as data did not consistently meet normal distribution assumptions. Categorical variables, including HPV genotype distribution, cytological categories, and clearance outcomes, were compared using the Chi-square test. Fisher's exact test was applied when expected cell counts were less than five.

HPV and cytological clearance outcomes were analyzed as complete, partial, and no clearance, as well as overall clearance (defined as the combination of complete and partial clearance). Group differences in clearance rates were assessed using Chi-square tests.

To identify factors independently associated with overall HPV clearance, univariate and multivariable binary logistic regression analyses were performed. Variables included in the regression models were selected based on clinical relevance and prior evidence and comprised use of the Coriolus versicolor–based vaginal gel (yes/no), number of Papilocare treatment boxes (<3, ≥3),

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age (<30, 30–45, >45 years), pregnancy history (yes/no), menstrual status (regular, irregular, menopausal), oral contraceptive use (yes/no), presence of chronic diseases (yes/no), smoking status (current smoker/non-smoker), HPV vaccination status (vaccinated/unvaccinated), immunosuppression status (yes/no), age at menarche (≤15, >15 years), age at first sexual intercourse (≤18, >18 years), baseline HPV type (HPV 16/18/high-risk vs other types), history of loop electrosurgical excision procedure (yes/no), and educational level (below university vs university and above). Results were reported as odds ratios (ORs) and adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs).

All statistical tests were two-sided, and a p value of <0.05 was considered statistically significant.

3. Results

3.1. Study Population and Baseline Characteristics

A total of 600 women with HPV infection were included in this retrospective analysis, comprising 300 women in the Papilocare group and 300 women in the control group. The mean age was 37.24 ± 9.56 years in the Papilocare group and 38.09 ± 9.58 years in the control group, with no statistically significant difference between groups (p=0.279). Baseline demographic characteristics were comparable, indicating adequate group homogeneity (Table 1).

Table 1. Distribution of age, HPV genotype positivity and Pap smear cytology between study groups 1.

		Papilocare (n=300)	**Control (n=300)**	**p-value**
Age (years), mean ± SD				0.279
		37.24 ± 9.56	38.09 ± 9.58	
Age group (years)				0.612
	<30	70 (23.3%)	64 (21.3%)	
	30-45	173 (57.7%)	169 (56.3%)	
	>45	57 (19.0%)	67 (22.4%)	
HPV Positivity by Genotype				**p-value**
				0.124
HPV 16		113 (37.7%)	118 (39.3%)	
HPV 18		23 (7.7%)	27 (9.0%)	
Other High-risk HPV Types		112 (37.3%)	100 (33.3%)	
Intermediate-risk HPV Types		17 (5.7%)	31 (10.3%)	
Low-risk HPV Types		35 (11.6%)	24 (8.0%)	
		Papilocare (n=260)	**Control (n=271)**	**p-value**
Pap Smear Cytology				0.171
Normal Cytology		125 (48.1%)	140 (51.7%)	
ASC-US		49 (18.8%)	54 (19.9%)	
ASC-H		17 (6.5%)	15 (5.5%)	
LSIL		31 (11.9%)	40 (14.8%)	
HSIL		38 (14.6%)	22 (8.1%)	

Data are presented as mean ± standard deviation or n (%), as appropriate. Percentages are calculated based on valid cases. Patients may have more than one HPV genotype.

The distribution of HPV genotypes at baseline did not differ significantly between the two groups (p=0.124). HPV 16 was the most prevalent genotype, detected in 37.7% of women in the Papilocare group and 39.3% of controls. HPV 18 positivity was observed in 7.7% and 9.0% of participants, respectively. Other high-risk HPV types accounted for 37.3% of infections in the Papilocare group and 33.3% in the control group. Intermediate-risk and low-risk HPV types were similarly distributed between groups (Table 1).

Baseline cytological evaluation was available for 260 women in the Papilocare group and 271 in the control group. Normal cytology was present in approximately half of the participants in both

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groups (48.1% vs. 51.7%). The frequencies of ASC-US, ASC-H, LSIL, and HSIL were comparable, with no statistically significant differences observed at baseline (p=0.171) (Table 1).

3.2. HPV Clearance Outcomes

Clearance analyses demonstrated significantly higher rates of HPV elimination in the Papilocare group compared with controls. For HPV 16, complete clearance was achieved in 77.0% of treated women, with an additional 14.2% showing partial clearance, resulting in an overall clearance rate of 91.2%. In contrast, the control group demonstrated complete and partial clearance rates of 25.4% and 16.1%, respectively, corresponding to an overall clearance rate of 41.5% (p<0.001) (Table 2).

Table 2. HPV and Cytology Clearance According to Study Groups (Complete/Partial/ Overall).

	CLEARANCE								
	Papilocare (n=300)				Control (n=300)				
HPV Genotype	**Complete**	**Partial**	**Overall**	**No**	**Complete**	**Partial**	**Overall**	**No**	**p-value**
HPV 16	87 (77.0%)	16 (14.2%)	103 (91.2%)	10 (8.8%)	30 (25.4%)	19 (16.1%)	49 (41.5%)	69 (58.5%)	
HPV 18	17 (73.9%)	4 (17.4%)	21 (91.3%)	2 (8.7%)	5 (18.5%)	7 (25.9%)	12 (44.4%)	15 (55.6%)	
Other High-risk HPV Types	86 (76.8%)	14 (12.5%)	100 (89.3%)	12 (10.7%)	25 (25.0%)	21 (21.0%)	46 (46.0%)	54 (54.0%)	
Intermediate-risk HPV Types	13 (76.5%)	2 (11.8%)	15 (88.2%)	2 (11.8%)	6 (25.0%)	4 (16.7%)	10 (41.7%)	14 (58.3%)	
Low-risk HPV types	22 (62.9%)	7 (20.0%)	29 (82.9%)	6 (17.1%)	7 (22.6%)	8 (25.8%)	15 (48.4%)	16 (51.6%)	
Total	225 (75.0%)	43 (14.3%)	268 (89.3%)	32 (10.7%)	73 (24.3%)	59 (19.7%)	132 (44.0%)	168 (56.0%)	<0.001
Pap Smear Cytology									
	Papilocare (n=135)				Control (n=131)				
	Complete	**Partial**	**Overall**	**No**	**Complete**	**Partial**	**Overall**	**No**	**p-value**
ASC-US	43 (87.8%)	0 (0%)	43 (87.8%)	6 (12.2%)	30 (55.6%)	0 (0%)	30 (55.6%)	24 (44.4%)	
ASC-H	13 (76.5%)	2 (11.8%)	15 (88.3%)	2 (11.7%)	4 (26.7%)	5 (33.3%)	9 (60.0%)	6 (40.0%)	
LSIL	21 (67.7%)	7 (22.6%)	28 (90.3%)	3 (9.7%)	18 (45.0%)	8 (20.0%)	26 (65.0%)	14 (35.0%)	
HSIL	25 (65.8%)	9 (23.7%)	34 (89.5%)	4 (10.5%)	6 (27.3%)	7 (31.8%)	13 (59.1%)	9 (40.9%)	
Total	102 (75.6%)	18 (13.3%)	120 (89.9%)	15 (11.1%)	58 (44.3%)	20 (15.3%)	78 (59.5%)	53 (40.5%)	<0.001

p-values refer to comparisons of overall clearance between the Papilocare and control groups using the Chi-square test or Fisher's exact test, as appropriate.Values are presented as row percentages.

Similarly, for HPV 18, complete clearance was achieved in 73.9% of treated women, with an additional 17.4% showing partial clearance, resulting in an overall clearance rate of 91.3%. In contrast, the control group demonstrated complete and partial clearance rates of 18.5% and 25.9%, respectively, corresponding to an overall clearance rate of 44.4% (p = 0.017). Among other high-risk HPV types, complete clearance was observed in 76.8% of treated women, with an additional 12.5% demonstrating partial clearance, yielding an overall clearance rate of 89.3% ; in the control group, the corresponding overall clearance rate was 46.0% (p < 0.001). Comparable trends favoring Papilocare were observed for intermediate-risk (88.2% vs. 41.7%) and low-risk HPV types (82.9% vs. 48.4%) (Table 2).

When complete and partial responses were combined, overall HPV clearance was achieved in 89.3% of women in the Papilocare group, compared with 44.7% in the control group, representing a statistically significant difference (p<0.001) (Table 2).

3.3. Cytological Clearance Outcomes

Among women with abnormal baseline cytology, Papilocare treatment was associated with significantly higher rates of cytological normalization. For ASC-US lesions, overall clearance was observed in 87.8% of treated women, compared with 55.6% in the control group. ASC-H lesions demonstrated overall clearance rates of 88.3% in the Papilocare group and 60.0% among controls (Table 2).

For LSIL, overall clearance occurred in 90.3% of women treated with Papilocare versus 65.0% in the control group. HSIL clearance rates were also higher in the Papilocare group (89.5%) compared with controls (59.1%) (Table 2).

Overall smear clearance, combining complete and partial responses, was achieved in 89.9% of women in the Papilocare group compared with 59.5% in the control group, with the difference reaching statistical significance (p<0.001) (Table 2).

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HPV DNA detection and smear analyses revealed a statistically significant difference in clearance rates between the Papilocare and control groups (p<0.001). This significant difference persisted across both complete and partial clearance conditions, as well as in the overall analysis (Table 2).

Of the patients with a diagnosis of HSIL, LSIL, or ASC-H who underwent loop electrosurgical excision procedure 73 belonged to the Papilocare group and 46 to the control group. In the Papilocare group, LEEP was performed in 12 of 24 patients (50.0%) with ASC-H, 25 of 41 patients (61.0%) with LSIL, and 36 of 54 patients (66.7%) with HSIL. In the control group, LEEP was applied in 12 of 24 patients (50.0%) with ASC-H, 16 of 41 patients (39.0%) with LSIL, and 18 of 54 patients (33.3%) with HSIL. Histopathological examination of LEEP specimens revealed cervicitis in 12 patients (63.2%) in the Papilocare group and 7 patients (36.8%) in the control group. CIN 1 was identified in 19 Papilocare-treated patients (65.5%) and 10 control patients (34.5%), CIN 2 in 15 (57.7%) and 11 (42.3%), and CIN 3 in 27 (60.0%) and 18 (40.0%) patients, respectively.

3.4. Multivariable Analysis

Multivariate logistic regression analysis identified use of the Coriolus versicolor–based vaginal gel as the strongest independent factor associated with overall HPV clearance in the combined cohort (adjusted OR 8.45 ; 95% CI: 3.05–23.43; p<0.001). Other demographic and clinical variables, including age, smoking status, HPV vaccination, baseline HPV risk group, and cytological category, were not independently associated with clearance after adjustment (Table 3).

Table 3. Factors Associated with HPV Clearance in the Combined Control and Papilocare Cohort (Binary Logistic Regression Analysis).

		Clearance (+), n(%)	Clearance (–), n(%)	Combined cohort			
Variable				**Univariate OR (95% CI)**	**p-value**	**Multivariate aOR (95% CI)**	**p-value**
Papilocare Use							
	No	134 (44.7%)	166 (55.3%)	Reference			
	Yes	268 (89.3%)	32 (10.7%)	0.096 (0.063–0.148)	**<0.001**	8.45 (3.05–23.43)	**<0.001**
Age (years)							
	<30	98 (73.1%)	36 (26.9%)	Reference			
	30-45	223 (65.2%)	119 (34.8%)	1.445 (0.849–2.459)	0.175		
	>45	81 (65.3%)	43 (34.7%)	0.995 (0.646–1.532)	0.981	0.81 (0.39–1.66)	0.565
Pregnancy							
	Nulliparous	130 (87.2%)	19 (12.8%)	Reference			
	Multiparous	164 (73.5%)	59 (26.5%)	2.461 (1.398–4.335)	**0.002**	0.30 (0.12–0.76)	0.013
Menstrual Status							
	Regular	196 (77.2%)	58 (22.8%)	Reference			
	Irregular	70 (88.6%)	9 (11.4%)	1.560 (0.568–4.285)	0.389		
	Menopause	13 (68.4%)	6 (31.6%)	3.590 (1.091–11.806)	**0.035**	1.26 (0.66–2.41)	0.479
Age at menarche (years)							
	≤15	225 (80.6%)	54 (19.4%)	Reference			
	>15	14 (73.7%)	5 (26.3%)	1.49 (0.51–4.31)	0.464	0.50 (0.10–2.48)	0.394
First Intercourse (years)							
	≤18	60 (88.2%)	8 (11.8%)	Reference			
	>18	209 (78.9%)	56 (21.1%)	2.010 (0.91–4.45)	0.085	0.47 (0.17–1.26)	0.131
HPV Vaccination							
	No	114 (44.9%)	140 (55.1%)	Reference			
	Yes	275 (83.6%)	54 (16.4%)	0.160 (0.109–0.234)	**<0.001**	1.41 (0.49–4.05)	0.527
Baseline HPV Group							
	Others	333 (67.5%)	160 (32.5%)	Reference			
	HPV 16,18 and Other High-Risk Types	69 (64.5%)	38 (35.5%)	1.146 (0.739–1.777)	0.542	0.59 (0.24–1.47)	0.261

Values are presented as row percentages. Univariate analyses were performed separately for Papilocare and Control groups. Multivariable analysis was performed in the combined cohort.
OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

Among women treated with Papilocare, multivariable analysis demonstrated that none of the evaluated demographic, clinical, or behavioral parameters were independently associated with overall HPV clearance. No statistically significant associations were observed for age, pregnancy history, menstrual status, age at menarche, age at first sexual intercourse, HPV vaccination status, or baseline HPV risk group. All participants in the Papilocare group received a high-dose regimen, consisting of either three or six boxes of treatment, and no dose-related differences in HPV clearance were identified.

4. Discussion

This retrospective study evaluated the effectiveness of a Coriolus versicolor-based vaginal gel in clearing high-risk HPV and improving cervical health. The gel demonstrated significantly higher

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clearance rates for HPV 16 and HPV 18, with overall clearance rates of 91.2% for HPV 16 and 91.3% for HPV 18 in the treatment group, compared with 41.5% and 44.4%, respectively, in controls ($p<0.001$; $p=0.017$) (Figure 1). Cytological and tissue assessments corroborated these findings, underscoring clear therapeutic benefits.

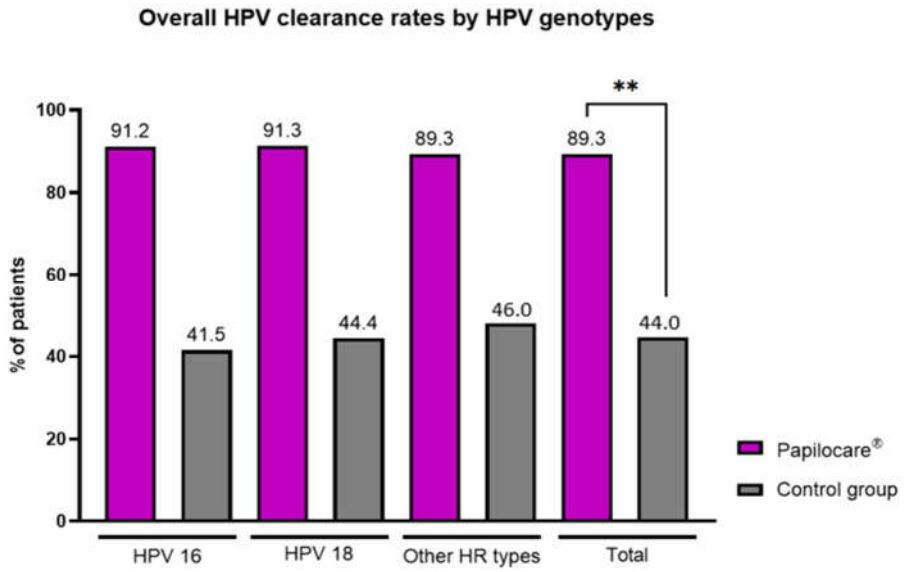

Figure 1. Overall HPV clearance rates according to HPV genotypes in the Papilocare and control groups.

These observations suggest that the Coriolus versicolor-based gel may enhance regression of HPV-related cervical abnormalities, potentially by enhancing the local immunological environment [19,20]. Coriolus versicolor contains beta-glucans and polysaccharopeptides known to stimulate innate and adaptive immune responses, including macrophage activation, cytokine production, and enhancement of natural killer cell activity [16,23]. Such mechanisms offer a plausible explanation in addition to the known mechanical barrier main effect and microbiome restauration, for the accelerated viral clearance observed in this study.

These results are consistent with previous studies evaluating vaginal products containing Coriolus versicolor. Criscuolo et al. and Serrano et al. reported significant improvements in HPV clearance and cytology normalization after six months of treatment with a Coriolus versicolor-based vaginal gel, with clearance rates exceeding those of untreated controls [18,24]. Similarly, Galvez et al. and Serrano et al. observed substantial regression of low-grade cervical lesions following daily application of a similar product, attributing this effect to enhanced epithelial repair and restoration of mucosal immunity [19,25]. In a multicentric, randomized and, prospective trial, Serrano et al. and, Cortés et al. found improved clearance of high-risk HPV genotypes and reductions in cervical inflammation after treatment with a multi-ingredient vaginal gel containing Coriolus versicolor, hyaluronic acid, and antioxidants [18,19]. The current study corroborates these findings and further strengthens the evidence base by demonstrating a robust effect specifically on HPV 16 and HPV 18, confirmed by tissue-level outcomes.

The cytological results provide further evidence of the effectiveness of the Coriolus versicolor-based vaginal gel, as clearance rates for ASC-US, ASC-H, LSIL, and HSIL were markedly higher in the treatment group than in controls ($p<0.001$). Notably, overall cytological clearance was consistently higher across all lesion categories in women treated with the gel, with clearance rates of 87.8% for ASC-US, 88.3% for ASC-H, 90.3% for LSIL, 89.5% for HSIL, compared with 55.6%, 60.0%, 65.0%, 59.1%, and no observed clearance, respectively, in the control group (Figure 2). These findings suggest that the gel facilitates both viral elimination and accelerated epithelial repair. These findings

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align with previous studies indicating that Coriolus versicolor-containing formulations promote cytological normalization enhancing tissue regeneration. Criscuolo et al. [24] observed significant regression of ASC-US and LSIL cytology following treatment, while Bordoy et al. [19] reported notable improvements in cytological abnormalities in a multicenter study of women with low-grade lesions. Bordoy et al. demonstrated that high-risk HPV-positive women treated with a Coriolus versicolor-based gel exhibited greater normalization of ASC-US and LSIL cytology than controls, attributing this effect to the balancing of the vaginal microbiota allowing the restoration of cervical microenvironmental balance [19]. These results are consistent with broader evidence that barrier-repairing agents can promote regression of cervical lesions across the Bethesda spectrum. The observed concordance between smear clearance and HPV DNA clearance in the present study further reinforces the therapeutic potential of Coriolus versicolor based vaginal gel in the non-ablative management of HPV-related cytological abnormalities.

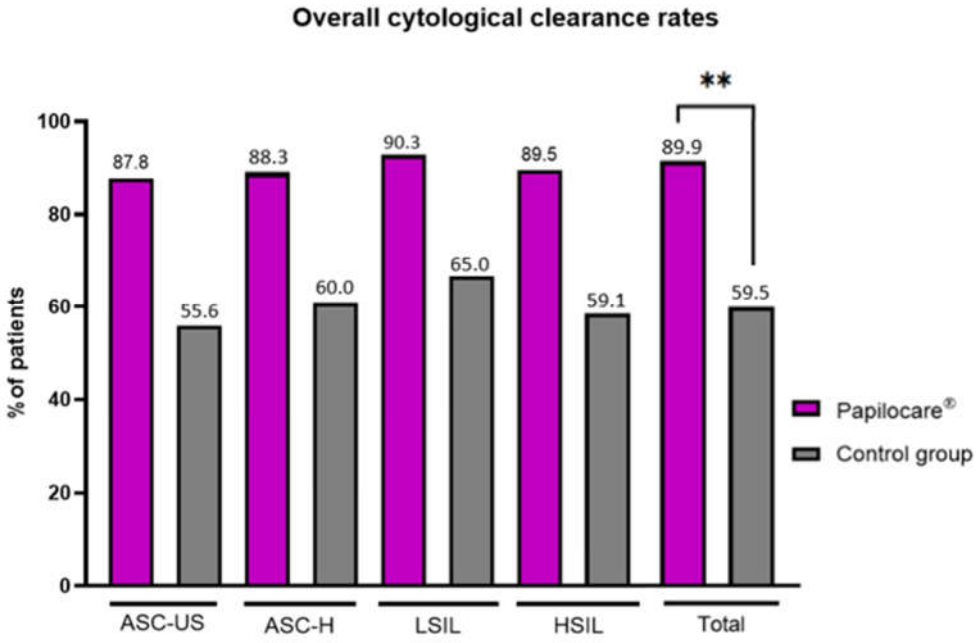

Figure 2. Overall cytological clearance rates according to baseline cervical cytology in the Papilocare and control groups.

While the retrospective design limits causal inference, the large sample size, stringent inclusion criteria, and consistency across HPV DNA, cytology, and tissue-level assessments enhance the credibility of the observed associations. The lack of significant baseline differences in key demographic variables further reduces the likelihood of confounding. Nonetheless, these findings should be interpreted in light of certain limitations. Retrospective data may be subject to incomplete documentation, and the influence of unmeasured behavioral factors, such as sexual practices or condom use, cannot be fully excluded. Additionally, although the six-month follow-up period is clinically relevant, longer-term assessments are necessary to evaluate recurrence and the durability of viral clearance.

In summary, this study demonstrates that Coriolus versicolor-based vaginal gel significantly improves clearance of high-risk HPV, particularly HPV 16 and 18, and normalizes cervical cytology. This gel may serve as an effective adjunct to surveillance for women seeking non-ablative treatments. Ongoing randomized trials are required to confirm efficacy, determine optimal use, and assess long-term benefits for HPV management.

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The consistency of effects across multiple clinical endpoints reinforces the evidence supporting this non-ablative therapeutic approach. Given its favorable safety profile and ease of use, the Coriolus versicolor-based vaginal gel may represent a valuable adjunct in the management of HPV-positive women, particularly for those seeking to avoid immediate excisional procedures or those under surveillance for low-grade lesions.

Future prospective, randomized controlled trials with extended follow-up are necessary to confirm these findings, evaluate long-term viral suppression, and determine the optimal duration of therapy. As the field advances toward individualized, less invasive strategies for HPV management, immunomodulatory bioactive formulations, such as Coriolus versicolor-based vaginal gels, may meaningfully contribute to clinical practice and women's health.

4.1. Strengths and Limitations

This study has several notable strengths and limitations. A major strength is the relatively large sample size, which exceeds that of many previous real-world observational studies evaluating non-ablative interventions for HPV infection. The inclusion of 600 women enabled robust comparisons between treatment and control groups and allowed consistent evaluation across multiple HPV genotypes and cytological categories. Moreover, the concurrent assessment of HPV DNA clearance and cytological outcomes provides complementary clinical insight into treatment effects.

Several limitations should be acknowledged. The retrospective design limits causal inference and is inherently susceptible to incomplete documentation and residual confounding. In addition, the limited number of patients in certain subgroups may limit the reliability of subgroup analyses. The inability to perform fully adjusted multivariable analyses further constrains control of potential confounders. Finally, although the six-month follow-up period is clinically meaningful for assessing short-term HPV clearance, it does not allow evaluation of long-term viral persistence or recurrence.

4.1. Implications for Practice and Future Research

Despite these limitations, the findings have relevant implications for clinical practice and future research. The consistently higher rates of HPV clearance and cytological normalization observed in the Papilocare group suggest that this Coriolus versicolor–based vaginal gel may serve as a useful adjunct to surveillance strategies in women with HPV infection, particularly for those preferring conservative, non-ablative management.

These findings are consistent with prior clinical and real-world evidence supporting the role of vaginal therapies in facilitating HPV clearance and cervical epithelial repair. Given the challenges of spontaneous HPV clearance and the burden of prolonged surveillance, such interventions may help bridge the gap between observation and invasive treatment.

Future studies should prioritize prospective, randomized controlled designs with extended follow-up to confirm the durability of response and assess recurrence. Further stratified analyses by age, HPV genotype, and baseline cytological severity, as well as evaluation of combination approaches with HPV vaccination, would help refine patient selection and optimize clinical management pathways.

5. Conclusions

This retrospective cohort study demonstrates that the use of a Coriolus versicolor–based vaginal gel is significantly associated with higher rates of HPV clearance and cervical cytological normalization compared with standard clinical follow-up alone. Women treated with the vaginal gel exhibited markedly improved clearance of high-risk HPV genotypes, particularly HPV 16 and HPV 18, as well as higher normalization rates across a broad spectrum of cytological abnormalities, including ASC-US, ASC-H, LSIL, and HSIL.

The consistency of these findings across virological and cytological endpoints, together with multivariable analyses identifying Papilocare use as the strongest independent predictor of HPV

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clearance, supports the potential clinical value of this non-ablative, locally applied intervention. These results suggest that vaginal therapy may facilitate viral elimination and promote epithelial recovery in HPV-positive women, particularly those undergoing conservative management or surveillance.

Although the retrospective design and limited follow-up duration preclude definitive causal conclusions, the large sample size and comparable baseline characteristics between groups strengthen the reliability of the observed associations. Taken together, the findings indicate that Coriolus versicolor–based vaginal gel may represent a safe and effective adjunct to current HPV management strategies, especially for women seeking non-invasive therapeutic options.

Prospective, randomized controlled trials with longer follow-up are warranted to confirm these results, assess long-term durability of HPV clearance, and define the optimal role of this intervention within cervical cancer prevention and surveillance algorithms.

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Data Availability Statement: The data presented in this study are not publicly available due to ethical and privacy restrictions related to patient confidentiality. Anonymized data supporting the findings of this study are available from the corresponding author upon reasonable request and with permission from the relevant institutional ethics committee.

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Abbreviations

The following abbreviations are used in this manuscript:

HPV	Human Papillomavirus
LEEP	Loop electrosurgical excision procedure
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion
LSIL	Low-grade squamous intraepithelial lesions
HSIL	Hifgh-grade squamous intraepithelial lesions
CIN	Cervical intraepithelial neoplasia

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