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*Article*

# Association of Oral Papivir/Pavirona® Supplementation with HPV DNA Clearance

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**Abstract**

**Objective:**To evaluate the effects of Papivir/Pavirona® tablets, containing cinnamon extract, selenium, quercetin, licorice root, and green tea extract, on cervical human papillomavirus (HPV) clearance and cytological outcomes in women with cervical HPV infection. **Methods**: This retrospective cohort study included 239 women with confirmed cervical HPV infection, followed at a tertiary referral center between February 2023 and August 2025. Participants were classified into a treatment group receiving oral Papivir/Pavirona® twice daily for six months (n = 119) and a control group managed with routine clinical follow-up alone (n = 120). HPV DNA testing and cervical cytology were evaluated at baseline and during follow-up visits at 6 and 12 months. **Results**: HPV clearance rates were significantly higher among Papivir/Pavirona® users at both 6 and 12 months compared with controls (65.5% vs. 29.2% and 69.1% vs. 46%, respectively). Cytological regression was also more frequent in the Papivir/Pavirona® group at 6 months (81.1% vs. 58.3 %) and 12 months (77.9% vs. 52.8%). In multivariate logistic regression analysis, Papivir/Pavirona® use emerged as an independent predictor of both HPV clearance and cytological regression, whereas demographic, reproductive, behavioral, and virological baseline characteristics were not significantly associated with outcomes. **Conclusions**: It has been suggested that Papivir/Pavirona® supplementation is associated with increased HPV clearance and cytological regression rates in women with cervical HPV infection, and may play a potential supportive role in cervical HPV management.

**Keywords:** human papillomavirus; HPV DNA clearance; oral supplementation; cervical cytology; conservative management

## 1. Introduction

Cervical cancer is a major global public health problem and continues to be one of the most common malignancies affecting women worldwide. Despite being largely preventable, it remains a leading cause of cancer-related morbidity and mortality, particularly in low- and middle-income countries, where access to effective screening, vaccination and treatment programs is limited [1]. According to recent global estimates, cervical cancer ranks as the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related death among women worldwide [2]

Persistent infection with human papillomavirus (HPV) is widely recognized as the main etiological factor in cervical cancer development [3]. HPV is a sexually transmitted virus, with more than 200 identified genotypes, approximately 14 of which are classified as high-risk due to their oncogenic potential [4] Among these, HPV16 and HPV18 are the most clinically significant, accounting for nearly 70% of cervical cancer cases worldwide, while other high-risk HPV types contribute primarily to cervical intraepithelial neoplasia and a smaller proportion of invasive cancers, reflecting the heterogeneity of HPV-related disease.[3,5–7]

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HPV is transmitted primarily through sexual contact [8]. Although approximately 70–90% of HPV infections are transient and clear spontaneously within one to two years, often within the first 6–12 months depending on viral genotype [9–13], persistent infection with high-risk HPV types may lead to premalignant cervical epithelial changes and progression to cervical intraepithelial neoplasia. Accordingly, persistence of infection rather than initial exposure represents the key determinant of progression toward invasive cervical cancer [14].

Prophylactic HPV vaccination is highly effective in preventing new HPV infections and HPV-related precancerous lesions when administered prior to sexual debut. However, vaccination does not reliably eliminate established HPV infections nor consistently accelerate viral clearance in women who are already HPV-positive. Moreover, in many countries HPV vaccination programs are newly implemented, incompletely established, or limited by socioeconomic and structural barriers. Therefore, a substantial proportion of women worldwide remain unvaccinated or only partially protected, and HPV infection continues to pose a major clinical challenge. [15,16]

In routine clinical practice, HPV-positive women, particularly those with normal cytology or low-grade abnormalities, are commonly managed with standard clinical follow-up, involving repeated HPV testing and cervical cytology at defined intervals [17]. Although this approach is evidence-based and aligns with international guidelines, it often requires prolonged follow-up and may be associated with considerable psychological burden, including anxiety, fear of cancer development, and uncertainty regarding disease progression [18]. Consequently, interest has increased in supportive, non-invasive options that may support HPV clearance during routine follow-up.

In recent years, attention has increasingly focused on nutraceutical and phytochemical agents that can be administered orally and may exert antiviral and antioxidant effects. A comprehensive review published in 2024 highlighted that a range of supportive agents, some available by physician prescription, are being explored as adjunctive approaches in gynecological cancer prevention [19]. In parallel with this growing interest, clinical studies investigating HPV clearance and cytological regression associated with such agents have gained momentum over the past decade [20,21].

Papivir/Pavirona® (Mealis, Istanbul, Türkiye) is an orally administered multi-component formulation containing quercetin, green tea extract, cinnamon extract, selenium, and licorice root extract. Each of these compounds has been independently shown to influence biological pathways relevant to HPV persistence, including modulation of immune responses, regulation of oxidative stress, and antiviral signaling mechanisms. Experimental and clinical evidence suggests that these bioactive agents may affect HPV-related oncogenic pathways through inhibition of viral oncoprotein activity, enhancement of host immune surveillance, and promotion of epithelial recovery [22–30].

However, although preliminary studies have suggested potential benefits [21], the clinical evidence regarding the effect of this specific formulation on HPV DNA clearance and cervical cytological outcomes remains limited and not yet clearly established.

Therefore, the aim of the present study was to assess the association between Papivir/Pavirona® supplementation and HPV DNA clearance as well as cervical cytological regression in women with confirmed HPV infection managed according to standard clinical guidelines.

## 2. Materials and Methods

### *2.1. Study Design & Participants*

This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Hacettepe University Hospital, Ankara, Türkiye, covering the period between January 2023 and August 2025. Patient demographic and clinical data were obtained from archived medical records, including patient follow-up files, hospital archive records, hospital procedural data-bases, and comprehensive medical information files encompassing follow-up data from other healthcare centers.

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A total of 239 patients with a documented positive human papillomavirus (HPV) deoxyribonucleic acid (DNA) test who also had baseline cervical cytology results were included in the study. Cytological findings included negative for intraepithelial lesion or malignancy (NILM), 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) [31]. Patients were excluded from the study if medical records indicated the presence of sexually transmitted infections or symptomatic vulvovaginal infections, immunodeficiency or autoimmune diseases, use of immunosuppressive therapy, pregnancy, total hysterectomy, or a history of gynecologic malignancy.

Patients were classified into two groups based on routine clinical management documented in their medical records. The treatment group consisted of women who had been prescribed oral Papivir/Pavirona® tablets twice daily as part of their clinical care. In this group, Papivir/Pavirona® supplementation was administered continuously for a total duration of six months. The control group included women who were managed with standard clinical follow-up without any adjunctive pharmacological or nutraceutical intervention. As part of routine counseling, patients were advised regarding safe sexual practices; condom use was recommended, although sexual intercourse was not restricted. Patients were routinely counseled to avoid vaginal douching and the use of intravaginal deodorant products during the follow-up period. HPV DNA testing and cervical cytology assessments performed at baseline and during routine follow-up visits at approximately 6 and 12 months were retrieved from patient records for analysis.

Use of Papivir/Pavirona® was documented in medical records as an adjunctive supplement and was not intended to influence routine clinical management or standard-of-care decision-making. Diagnostic and therapeutic procedures, including colposcopy, directed cervical biopsy, and excisional treatments such as loop electrosurgical excision procedure (LEEP), were performed based on clinical indications and in accordance with established cervical cancer screening and management guidelines [17]. Papivir/Pavirona® use was therefore recorded as a supportive supplementation and did not alter or delay diagnostic or therapeutic decisions within routine clinical practice.

### *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 out-lined in the Declaration of Helsinki.

### *2.3. Statistical Analysis*

The primary endpoint of the study was HPV DNA clearance at 6 and 12 months. Secondary endpoints included cytological regression, high-risk HPV clearance, and treatment safety and tolerability outcomes. Data regarding HPV DNA testing and cervical cytology (Papanicolaou test), which were performed as part of routine clinical practice, were retrospectively retrieved from medical records at baseline and during follow-up visits at approximately 6 and 12 months. According to standard clinical procedures, exocervical and endocervical cells had been collected using a cytobrush and sent to the Department of Pathology for examination. Cytological results were classified according to the 2001 Bethesda System as negative for intraepithelial lesion or malignancy, ASC-US, ASC-H, AGC, LSIL, or HSIL [31].

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 sam-ples resuspended in 1 mL of buffer according to the manufacturer's

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instructions. HPV DNA detection and genotyping were conducted using the Anyplex™ II HPV28 real-time PCR assay (Seegene, Seoul, South Korea).

HPV clearance was evaluated by considering both complete and partial resolution of infection over time. Complete clearance was defined as a negative HPV DNA test or the disappearance of all HPV genotypes identified at baseline. Partial clearance referred to the disappearance of at least one initially detected 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. Patients with normal or non-malignant baseline cytology were excluded from the cytological outcome analysis. Clinical, cytological, colposcopic and laboratory data were routinely collected during standard follow-up visits and assessed at baseline, as well as at 6 and 12 months.

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).

Data were analyzed using IBM SPSS version 23. The conformity of continuous variables to a normal distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Associations between categorical variables were examined using the chi-square test. The effects of independent variables on HPV and cytological regression responses were evaluated using binary logistic regression analysis. Results were presented as mean ± standard deviation for quantitative data and as frequency (percentage) for categorical variables. A p-value of $< 0.05$ was considered statistically significant.

## 3. Results

### *3.1. Study Population and Baseline Characteristics*

There were 239 women included in the study. Of these, 119 participants (49.8%) received Papivir/Pavirona®, while 120 participants (50.2%) were managed in the control group. Baseline demographic and clinical characteristics of both groups are presented in Table 1.

The mean age was 35.03 ± 9.28 years in the Papivir/Pavirona® group and 37.01 ± 8.26 years in the control group, with no statistically significant difference between groups ($p = 0.082$). Age group distribution (<30, 30–45, and >45 years) was also comparable between the two groups ($p = 0.180$).

Baseline HPV genotype distribution was similar in Papivir/Pavirona® users and controls. The proportions of HPV16, HPV18, other high-risk, intermediate-risk, and low-risk HPV types did not differ significantly between groups ($p = 0.540$).

Baseline cervical cytology findings were likewise comparable between groups. The distribution of normal cytology, atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells—cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and atypical glandular cells (AGC) showed no statistically significant difference between the Papivir/Pavirona® and control groups ($p = 0.270$).

Overall, the two groups were well balanced at baseline with respect to age, HPV genotype distribution, and cervical cytological status, allowing for a valid comparison of follow-up outcomes.

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

| | Papivir (n=119) | Control (n=120) | p-value |
|---|---|---|---|
| **Age (years), mean ± SD** | | | 0.082 |
| | 35.03 ± 9.28 | 37.01 ± 8.26 | |
| **Age group (years)** | | | 0.180 |
| <30 | 35 (29.4%) | 24 (20.0%) | |

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| | | | |
|---|---|---|---|
| 30-45 | 65 (54.6%) | 76 (63.3%) | |
| >45 | 19 (16.0%) | 20 (16.7%) | |
| **HPV Positivity by Genotype** | | | **p-value** 0.540 |
| HPV 16 | 44 (37.0%) | 40 (33.3%) | |
| HPV 18 | 8 (6.7%) | 8 (6.7%) | |
| Other High-Risk HPV Types | 45 (37.8%) | 51 (42.5%) | |
| Intermediate-Risk HPV Types | 9 (7.6%) | 14 (11.7%) | |
| Low-Risk HPV Types | 13 (10.9%) | 7 (5.8%) | |
| | **Papivir (n=119)** | **Control (n=120)** | **p-value** 0.270 |
| **Pap Smear Cytology** | | | |
| Normal Cytology | 45 (37.8%) | 58 (48.3%) | |
| ASC-US | 29 (24.4%) | 26 (21.7%) | |
| ASC-H | 8 (6.7%) | 5 (4.2%) | |
| LSIL | 20 (16.8%) | 23 (19.2%) | |
| HSIL | 16 (13.4%) | 8 (6.7%) | |
| AGC | 1 (0.8%) | 0 (0%) | |

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.

Among women using Papivir/Pavirona®, loop electrosurgical excision procedure (LEEP) was performed in 11 of 16 patients with HSIL, 4 of 8 patients with ASC-H, 3 of 20 patients with LSIL, and in one patient with atypical glandular cells (AGC). In the control group, LEEP was applied in 6 of 8 patients with HSIL, 7 of 23 patients with LSIL, 2 of 5 patients with ASC-H, and 5 of 26 patients with ASC-US. Histopathological examination of LEEP specimens revealed cervicitis in 3 patients (15.8%) in the treatment group and 2 patients (13.3%) in the control group. CIN 1 was identified in 4 Papivir/Pavirona® treated patients (21.1%) and 3 control patients (20.0%), CIN 2 in 3 (15.8%) and 4 (26.7%), and CIN 3 in 9(47.4%) and 6 (40.0%) patients, respectively.

### *3.2. HPV Clearance And Cytological Regression Outcomes*

As shown in Table 2, HPV clearance and cytological regression rates at 6 months were significantly higher in the Papivir/Pavirona® group than in the control group, despite similar baseline characteristics.

**Table 2.** Association Between Papivir/Pavirona® Use and HPV Clearence and Cytological Regression at 6 Months.

| | **CLEARANCE** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Papivir (n=119)** | | | | **Control (n=120)** | | | | |
| **HPV Genotype** | **Complete** | **Partial** | **Overall** | **No** | **Complete** | **Partial** | **Overall** | **No** | **p-value** |
| HPV 16 | 30 (68.2%) | 2 (4.5%) | 32 (72.7%) | 12 (27.3%) | 11 (27.5%) | 8 (20.0%) | 19 (47.5%) | 21 (52.5%) | |
| HPV 18 | 6 (75.0%) | 1 (12.5%) | 7 (87.5%) | 1 (12.5%) | 1 (12.5%) | 4 (50.0%) | 5 (62.5%) | 3 (37.5%) | |
| Other High-Risk Types | 27 (60.0%) | 7 (15.6%) | 34 (75.6%) | 11 (24.4%) | 18 (35.3%) | 9 (17.6%) | 27 (52.9%) | 24 (47.1%) | |
| Intermediate-Risk Types | 6 (66.7%) | 1 (11.1%) | 7 (77.8%) | 2 (22.2%) | 3 (21.4%) | 1 (7.1%) | 4 (28.6%) | 10 (71.4%) | |
| Low-Risk types | 9 (69.2%) | 2 (15.4%) | 11 (84.6%) | 2 (15.4%) | 2 (28.6%) | 0 (0%) | 2 (28.6%) | 5 (71.4%) | |

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Total | 78 (65.5%) | 13 (10.9%) | 91 (76.5%) | 28 (23.5%) | 35 (29.2%) | 22 (18.3%) | 57 (47.5%) | 63 (52.5%) | <0.001 |
| **Pap Smear Cytology** | **Papivir (n=119)** | | | | **Control (n=120)** | | | | |
| | **Complete** | **Partial** | **Overall** | **No** | **Complete** | **Partial** | **Overall** | **No** | **p-value** |
| ASC-US | 21 (72.4%) | 0 (0%) | 21 (72.4%) | 8 (26.7%) | 15 (57.7%) | 0 (0%) | 15 (57.7%) | 11 (42.3%) | |
| ASC-H | 7 (87.5%) | 0 (0%) | 7 (87.5%) | 1 (12.5%) | 2 (40.0%) | 2 (40.0%) | 4 (80.0%) | 1 (20.0%) | |
| LSIL | 18 (90.0%) | 0 (0%) | 18 (90.0%) | 2 (10.0%) | 14 (60.9%) | 3 (13.0%) | 17 (82.6%) | 6 (26.1%) | |
| HSIL | 13 (81.3%) | 2 (12.5%) | 15 (93.8%) | 1 (6.2%) | 6 (75.0%) | 2 (25.0%) | 8 (100.0%) | 0 (0%) | |
| AGC | 1 (100%) | 0 (0%) | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | |
| Total | 60 (81.1%) | 2 (2.7%) | 62 (83.8%) | 12 (16.2%) | 37 (58.3%) | 7 (11.7%) | 44 (70.0%) | 18 (30.0%) | 0.012 |

p-values refer to comparisons of overall clearance between the Papivir/Pavirona® and control groups (Chi-square test). Values are presented as row percentages.

Twelve-month follow-up data were available for 94 patients in the Papivir/Pavirona® group and 100 patients in the control group. Follow-up data at 12 months could not be obtained for 25 patients in the treatment group and 20 patients in the control group.

At 12 months, in the Papivir/Pavirona® group, complete HPV clearance was observed in 65 patients (69.1%), partial clearance in 11 patients (11.7%), and no clearance in 18 patients (19.1%). In the control group, complete clearance occurred in 46 patients (46.0%), partial clearance in 10 patients (10.0%), and no clearance in 44 patients (44.0%) (p = 0.001).

At 12 months, in the Papivir/Pavirona® group, complete cytological regression was observed in 53 patients (77.9%), partial regression in 5 patients (7.4%), and persistent cytological abnormality in 10 patients (14.7%). In the control group, complete regression occurred in 19 patients (52.8%), partial regression in 3 patients (8.3%), and persistent abnormality in 14 patients (38.9%) (p = 0.017).

### *3.3. Multivariable Logistic Regression Analysis*

Values are presented as row percentages. Univariate logistic regression analyses were performed to assess the association between each variable and HPV clearance. Multivariable logistic regression analysis was performed in the combined cohort. OR: odds ratio; aOR: adjusted odds ratio; CI: confidence.Univariate and multivariate logistic regression analyses were performed to identify factors associated with HPV clearance at 6 months in the combined cohort (Table 3).

**Table 3.** Binary logistic regression analysis of the effect of independent variables on HPV clearance at 6 months.

| | **Clearance (+), n(%)** | **Clearance (–), n(%)** | | | **Combined cohort** | |
|---|---|---|---|---|---|---|
| **Variable** | | | **Univariate OR (95% CI)** | **p-value** | **Multivariate aOR (95% CI)** | **p-value** |
| **Papivir Use** | | | | | | |
| No | 57 (47.5%) | 63 (52.5%) | Reference | <0.001 | 4.80 (2.26–10.17) | <0.001 |
| Yes | 91 (76.5%) | 28 (23.5%) | 3.59 (2.06–6.26) | | | |
| **Age** | | | | 0.936 | | |
| <30 | 34 (57.6%) | 25 (42.4%) | Reference | | | |
| 30-45 | 92 (65.2%) | 49 (34.8%) | 1.05 (0.46–2.38) | 0.905 | 1.72 (0.84–3.55) | 0.137 |
| >45 | 22 (56.4%) | 17 (43.6%) | 1.45 (0.70–3.00) | 0.312 | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **Pregnancy** | | | | | | |
| Nulliparous | 60 (68.2%) | 28 (31.8%) | Reference | | 0.64 (0.29–1.40) | 0.262 |
| Multiparous | 55 (62.5%) | 33 (37.5%) | 1.29 (0.69–2.40) | 0.429 | | |
| **Menstrual Status** | | | | | | |
| Regular | 102 (67.5%) | 49 (32.5%) | Reference | | | |
| Irregular | 8 (53.3%) | 7 (46.7%) | 1.49 (0.45–4.94) | 0.516 | 0.52 (0.25–1.05) | 0.076 |
| Menopause | 7 (58.3%) | 5 (41.7%) | 0.82 (0.18–3.66) | 0.795 | | |
| **Oral Contraceptive Use** | | | | | | |
| No | 102 (61.4%) | 64 (38.6%) | Reference | | 0.69 (0.34–1.42) | 0.309 |
| Yes | 42 (60.9%) | 27 39.1(%) | 1.03 (0.58–1.82) | 0.934 | | |
| **Smoking** | | | | | | |
| No | 98 (61.6%) | 61 (38.4%) | Reference | | 1.16 (0.54–2.48) | 0.706 |
| Yes | 45 (60.0%) | 30 (40.0%) | 1.07 (0.61–1.88) | 0.811 | | |
| **LEEP** | | | | | | |
| No | 113 (60.4%) | 74 (39.6%) | Reference | | 1.39 (0.50–3.83) | 0.532 |
| Yes | 34 (66.7%) | 17 (33.3%) | 0.76 (0.40–1.47) | 0.417 | | |
| **HPV Vaccination** | | | | | | |
| No | 58 (59.8%) | 39 (40.2%) | Reference | | 0.68 (0.32–1.46) | 0.330 |
| Yes | 69 (64.5%) | 38 (35.5%) | 0.82 (0.46–1.46) | 0.490 | | |
| **Baseline HPV Group** | | | | | | |
| Others | 24 (55.8%) | 19 (44.2%) | Reference | | | |
| HPV 16,18 and Other High-Risk Types | 124 (63.3%) | 72 (36.7%) | 0.73 (0.38–1.42) | 0.363 | 1.38 (0.56–3.43) | 0.484 |

In univariate analysis, Papivir/Pavirona® use was significantly associated with HPV clearance. Clearance was observed in 76.5% of Papivir/Pavirona® users compared with 47.5% of non-users, corresponding to a higher likelihood of HPV clearance among users (OR = 3.59, 95% CI: 2.06–6.26; $p < 0.001$).

After adjustment for potential confounders in the multivariate model, Papivir/Pavirona® use remained the only independent predictor of HPV clearance. Participants using Papivir/Pavirona® had nearly a fivefold higher likelihood of achieving HPV clearance compared with non-users (adjusted OR = 4.80, 95% CI: 2.26–10.17; $p < 0.001$).

None of the other evaluated variables demonstrated a statistically significant association with HPV clearance in either univariate or multivariate analyses. Age group, pregnancy status, menstrual status, oral contraceptive use, smoking, history of LEEP, HPV vaccination status, and baseline HPV genotype distribution were not significantly associated with clearance outcomes (all $p > 0.05$).

Review of medical records identified one patient who developed a mild cutaneous rash during Papivir/Pavirona® use, which resolved spontaneously without discontinuation of treatment. No other adverse events related to Papivir/Pavirona® were documented during the follow-up period

## 4. Discussion

In this retrospective cohort study, outcomes of women with cervical HPV infection who received Papivir/Pavirona® supplementation for six months were evaluated during a 12-month follow-up period and compared with those managed with standard clinical follow-up alone at a tertiary referral center. Papivir/Pavirona® use was associated with higher rates of HPV DNA clearance and cytological regression compared with non-users throughout follow-up.

Specifically, HPV clearance and cytological regression occurred at approximately twofold higher rates among patients receiving Papivir/Pavirona®, and this association remained independent

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of age group and other demographic, reproductive, and behavioral variables included in the analysis. Notably, Papivir/Pavirona® use emerged as the only independent predictor of both virological and cytological improvement in multivariate models.

Taken together, these findings suggest that orally administered, multi-component phytochemical formulations may support HPV regression during routine clinical follow-up by combining complementary antiviral and antioxidant activities.

Papivir/Pavirona® is an oral, multi-component formulation containing five bioactive compounds such as quercetin, selenium, cinnamon extract, green tea extract (catechins) and licorice root extract, whose antiviral, antioxidant, and cell-regulatory effects relevant to HPV persistence have largely been demonstrated in experimental models. One of these components, quercetin has been extensively evaluated in vitro and has been shown to induce cell-cycle arrest and apoptosis in HPV-positive cervical cells through p53-related pathways [29,30]. In parallel, experimental studies have shown that cinnamon extract exerts antiproliferative effects in HPV-positive cervical cell models, with increased apoptotic activity and suppression of NF-κB–related signaling pathways involved in HPV-related cellular changes [22,32]. Similarly, glycyrrhizin, the principal bioactive component of licorice root extract, has likewise been evaluated in HPV-positive cervical epithelial cell models. Experimental studies have shown that glycyrrhizin induces cell-cycle arrest and apoptosis, accompanied by downregulation of HPV E6/E7 oncogene expression and attenuation of proliferative signaling pathways [27,28]. Selenium, another component, has been evaluated in both experimental and clinical studies. In vitro studies have shown that selenium supports cellular antioxidant defense and redox balance [23], while observational and clinical studies have reported lower serum selenium levels in women with cervical intraepithelial neoplasia compared to cytologically normal controls, suggesting a potential association with cervical dysplasia [24].

As the final component of the formulation green tea catechins, particularly epigallocatechin gallate (EGCG), have been evaluated in both experimental and clinical studies related to HPV-associated cervical disease. In vitro studies have shown that EGCG can inhibit HPV-related oncogenic activity and induce apoptosis in HPV-positive cervical epithelial cells [25,26]. Clinical studies have reported heterogeneous outcomes, which are summarized in Table 4. [33,34]. These findings suggest that while EGCG has relevant biological activity, its clinical efficacy appears limited when used as a stand-alone oral therapy, supporting its role as part of a multi-component formulation.

Only one earlier clinical study, aside from the present analysis, has evaluated a formulation with the same bioactive composition. Gene-Eden-VIR/Novirin®, an oral supplement composed of the same five active components as Papivir/Pavirona® in identical proportions, has previously been evaluated in a single post-marketing clinical study. In that study, 139 HPV-positive individuals received oral supplementation for variable durations ranging from 2 to 12 months, and outcomes were assessed based on changes in HPV persistence rather than fixed clearance rates. The authors reported a shortening of HPV persistence during treatment and a favorable safety profile across different age groups and HPV genotypes. Although the study design and outcome measures differed from those of the present cohort, these findings provide complementary clinical evidence supporting the potential role of this multi-component formulation in the management of HPV infection and represent the only other published clinical evaluation of this specific compound combination [21].

A broad range of agents has been explored in clinical studies aiming to promote HPV clearance or improve HPV-associated cervical outcomes. These studies differ with respect to study design, route of administration, evaluated endpoints, and duration of follow-up, and different clinical outcomes have been reported across individual trials. To provide a concise overview of the existing evidence, the main findings reported for these agents, including HPV clearance, cytological regression, and colposcopic regression, are summarized in Table 4. [20,32–47]

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**Table 4.** Clinical studies of other agents for HPV infection outcomes.

| **Agent** | **HPV Clearance** | **Cytological Regression** | **Colposcopic Regression** | Histological Regression |
|---|---|---|---|---|
| AHCC® (Active Hexose Correlated Compound) | 63.6% vs. 10.5% | NR | NR | NR |
| Beta-carotene | 1/5 studies: No effect | 4/5 studies: No effect | NR | 4/5 studies: No effect |
| 3,3′-Diindolylmethane (DIM) | 1/3 studies: No difference | 1/3 studies: No difference (50% vs. 55%) | 1/3 studies: No difference | 3/3 studies: No difference (84% vs. 72%)<br>No difference (8% vs. 12%)<br>No difference (100% vs. 61%) |
| Epigallocatechin gallate (EGCG) | 1/2 studies: No difference | 2/2 studies: No difference; significant cytologic and histologic mixed results (69% vs. 10%) | NR | 1/2 studies: Significant cytologic and histologic mixed results (69% vs. 10%) |
| Indole-3-carbinol (I3C) | 1 study: No difference | NR | NR | Significant RR: 0.5 |
| Praneem polyherbal tablet | 1 study: No difference | NR | NR | NR |
| Deflagyn® (Silicon dioxide with sodium selenite and citric acid) | 2/2 studies: 54.3% vs. 10.6% | 1/2 studies: Cytologic and pathologic (76.5% vs. 36.4%) | NR | 1/2 studies: Cytologic and pathologic (76.5% vs. 36.4%) |
| Zinc | 2/2 studies: 64.8% vs. 15.2%; 57.5% vs. 15.0% | 2/2 studies: No difference (52.5% vs. 25.0%) | NR | NR |

NR: not reported.

A key strength of this study is the evaluation of patient outcomes within routine clinical practice, with management decisions following standard gynecological guidelines and made independently of research participation. The consistent use of HPV DNA testing and cervical cytology at baseline and follow-up enabled reliable assessment of changes over time, while inclusion of a

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contemporaneous control group provided a meaningful clinical reference for interpreting clearance and regression outcomes.

Several limitations should be acknowledged. As a single-center study, the findings may not be fully generalizable to other populations or healthcare settings. In addition, the retrospective design and reliance on routinely collected clinical data limited the availability of detailed information on treatment adherence and lifestyle factors that may influence HPV clearance.

Despite these limitations, the findings of the present study have relevant implications for clinical practice and future research. The consistently higher rates of HPV DNA clearance and cytological improvement observed among patients receiving Papivir/Pavirona® suggest that this oral, multi-component formulation may represent a supportive option alongside standard clinical follow-up in conservatively managed HPV-positive patients. This may be beneficial for patients requiring prolonged follow-up, particularly when non-invasive strategies are favored. Future studies employing prospective, randomized controlled designs with longer follow-up are warranted to confirm the durability of these effects, evaluate recurrence rates, and further define patient subgroups most likely to benefit from supplementation.

## 5. Conclusions

Collectively, the findings indicate that Papivir/Pavirona® use during routine follow-up was associated with higher rates of HPV DNA clearance and cytological regression compared with standard clinical management. The results indicate that an oral supplement containing multiple bioactive compounds may help facilitate HPV regression in some patients when used alongside standard clinical follow-up

At the same time, the present data should not be viewed as definitive. Further studies with randomized designs and longer observation periods would be helpful to clarify how consistent and durable these effects are across different patient populations.

**Supplementary Materials:** No supplementary materials are available for this article.

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**Informed Consent Statement:** Written informed consent was obtained from all participants included in this study for the use of their anonymized clinical data for scientific research purposes. Patient data were obtained from Hacettepe University Hospital, where such consent is routinely collected as part of clinical evaluation. The study was conducted retrospectively using existing medical records.

**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

AGC Atypical glandular cells
AHCC Active Hexose Correlated Compound
aOR Adjusted odds ratio
ASC-H Atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion
ASC-US Atypical squamous cells of undetermined significance
CI Confidence interval
CIN Cervical intraepithelial neoplasia
DIM Diindolylmethane
DNA Deoxyribonucleic acid
EGCG Epigallocatechin gallate
HPV Human papillomavirus
hrHPV High-risk human papillomavirus
HSIL High-grade squamous intraepithelial lesion
LEEP Loop electrosurgical excision procedure
LSIL Low-grade squamous intraepithelial lesion
NILM Negative for intraepithelial lesion or malignancy
OR Odds ratio
SPSS Statistical Package for the Social Sciences
WHO World Health Organization

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