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Effect of Coriolus Versicolor-based Vaginal Gel on Clearance of Human Papillomavirus and Cervical Dysplasia - A scoping review

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Abstract

Background: Cervical cancer, primarily caused by sexually transmitted high-risk Human Papillomavirus (HPV) infections, remains a major global health challenge. Despite significant advances in HPV vaccination and cervical cancer screening strategies, effective and non-invasive treatment options for HPV infections and cervical dysplasia. are still lacking. Current management strategies of cervical dysplasia vary from the “wait and see” strategy to surgical interventions. This scoping review aimed to map the existing evidence on the efficacy and safety of Coriolus Versicolor-based vaginal gel as a novel and effective non-invasive treatment of HPV infection and mild cervical dysplasia.

Methods: A comprehensive scoping review was performed using systematic searches in PubMed, Embase, EBSCOhost, Ovid, CNKI and SciELOdatabases. The literature search covered publications up to August 2025. Two reviewers independently screened possible studies, following the PRISMA guidelines for scoping reviews. Only human experimental randomized controlled trial (RCT) and observational cohort studies published in English, Norwegian, Swedish or Danish were considered.

Results: A total of 127 articles were screened, and five studies met the inclusion criteria: one RCT (n=91), one sub-analysis of this RCT (n=41), and three cohort studies (n=183, 192, 21). Treatment with CV-based vaginal gel was associated with improved HPV clearance and regression of cervical dysplastic lesions, with regression rates of 76.1–84.9% in treated women compared 40.8–64.5% in

untreated controls. Positive effects were also observed in women with hrHPV and in postmenopausal women. No serious adverse events were reported.

Conclusion: This scoping review suggests that CV based vaginal gel shows promising but preliminary efficacy and safety in promoting regression of cervical dysplastic lesions and HPV clearance. Larger, long-term multinational RCT studies with standardized outcomes definitions are needed to confirm these preliminary findings and to establish the therapeutic role of the CV based vaginal gel in clinical practice.

Keywords: HPV, cervical dysplasia, Coriolus Versicolor-based vaginal gel, cervical cancer

Introduction

Cervical cancer is the fourth most common cause of cancers worldwide, with an estimated 600000 new cases and 340000 deaths worldwide (1). Almost all cancer cases are caused by a pre-existing infection with HPV which is a widespread sexually transmitted virus. It is estimated that approximately 80% of sexually active people experience an HPV infection at some point in their life and some may even be infected in more than one occasion (2, 3). Currently, more than 200 types of HPV have been identified (4), with certain genotypes of HPV showing an increased risk of persistence and being classified as high-risk HPV (hrHPV), especially HPV-16 and HPV-18 are known as oncogenic genotypes leading to premalignant cervical dysplastic lesions accounting for approximately 70% of all cervical cancer cases (1, 5-7). Some HPV infections are transient and cleared or suppressed by cell-mediated immunity and about 70% will regress spontaneously within one year and 90% after two years (8, 9). In 10-20% of the infected women, the infection remain persistent (10) and may progress to cervical intraepithelial neoplasia (CIN), potentially advancing to cervical cancer if left untreated (11). The severity of the cervical dysplastic lesions is classified either by using the CIN classification or WHO terminology. In the CIN classification CIN1 indicates mild dysplasia, CIN2 represents moderate dysplasia and CIN3 represents severe dysplasia. According to WHO terminology, CIN1 includes Atypical Squamosa Cells of Undetermined Significance (ASCUS) and Low-Grade Squamosa Intraepithelial Lesion (LSIL), while CIN2 and CIN3 include High-grade Squamous Intraepithelial Lesion (HSIL). Studies have estimated that without treatment 16% of CIN2 lesions will progress to CIN3 or worse and

12% of CIN3 lesions will progress to cervical cancer (12, 13). In immunocompetent women progression to invasive cervical cancer typically occurs 10 to 20 years after primary infection (14). Studies (6) have shown that some risk-factors such as smoking, multiparity, long-term use of contraceptives and immunosuppression can double or triple the risk of precancer among women infected with an oncogenic HPV. Risk-factors for persistent infection and cervical cancer, other than the HPV subtype, have not been identified, and it is unknown why or when the infections are cleared, or when it remains persistent (6, 15).

Despite progress due to HPV vaccination, a global burden of HPV infection and cervical dysplasia persists. In recent decades considerable efforts have focused on developing effective screening strategies, HPV-detecting tools, and implementing HPV vaccines worldwide to prevent HPV and HPV induced cervical cancers (6, 16). However, there is still a gap in the discovery of effective and less-invasive treatments for cervical HPV infections and consequently cervical dysplasia. Nowadays the conventional treatment of HPV and cervical dysplasia includes wait and see strategy and follow-up after 6-12 months dependent on the dysplasia grade. However, for CIN2+ cases a surgical excision of the cervix is considered depending on the woman´s desire for fertility. This surgical intervention is combined with risk of pre-term birth, abortion, infection and cervical agglutination (17). CIN2 can also, in some cases, be treated with the wait and see approach due to a high rate (50%) of spontaneous regression (12). This is combined with a long follow up period including HPV testing, cytology, and colposcopy every 6 months. In addition

the risk of developing invasive cancer after treatment of CIN2 or CIN3 with cervical excision is still five times higher when compared to the general population, also indicating a long follow-up period for these women (18). In addition, studies indicate that after clearance of an HPV infection there is still a high risk of re-infection with the same type of HPV. This necessity for repeated screening, long period of follow-up and the risk of re-infection makes the management and treatment of HPV-infections and cervical dysplasia costly for society. Additionally, studies have also shown that the wait and see approach and the risk of reinfection or progression to severe dysplasia often result in anxiety, distress and lower quality of life in relation to the fear of progression to cervical cancer for the woman (19, 20). The absence of an effective treatment, the potential consequences for infected women, and the risk of invasive cervical cancer without intervention highlight the urgent necessity of finding an alternative treatment. This alternative treatment could not only treat HPV infections but also enhance the quality of life for the affected women and reduce the long-term risk of developing cancer.

Recent studies have introduced a new approach using a multi-ingredient vaginal gel containing the medical mushroom Coriolus Versicolor (CV). CV has been used medically and approved for over 30 years in China and Japan, although its use in Western countries is relatively unknown (21). Studies have reported that CV possesses many physiological activities, such as promoting immune function and providing antimicrobial, antitumor and anti-inflammatory effects. The polysaccharopeptide found in CV is identified as the major bioactive component with immunomodulatory function (22, 23). By

modulating immune response, CV may facilitate the clearance of HPV-infected cells through the activation of natural killer (NK) cells and cytotoxic T lymphocytes, which are essential for recognizing and eliminating viral infections or dysplastic epithelial cells (24). Its mechanisms of action also include inducing apoptosis through increased release of Tumor Necrosis Factor (TNF)-α and regulating cytokines such as Transforming Growth Factor (TGF)-β, which carries both pro- and anti-inflammatory effects (24, 25). Studies have also shown increase in Lactobacilli (Lactobacillus Crisplantus) and a decrease in bacteria such as Gardnerella Vaginalis following application of CV based vaginal gel (26).

The first CV-based vaginal gel, Papilocare®, was launched by ProCare Health in 2016 as a non-prescription medicine (27). Papilocare®, combines CV with additional ingredients that support HPV clearance and regression of cervical dysplastic lesions. It includes moisturizing (Hyaluronic acid), tissue reparation (NEEM, Aloe vera, Centella Asiatica) and microbiota-balancing (BIOECOCIA) properties (28). Recent studies have reported promising results, suggesting that CV-based vaginal gel may be an effective treatment for HPV infection and cervical dysplasia (28-32).

The purpose of this scoping review was to assess the current state of research on the efficacy of the CV-based vaginal gel for the clearance of vaginal HPV infection and the repair of cervical dysplastic lesions. This review focuses on exploring evidence that supports the use of CV-based vaginal gel as a new treatment approach.

Method

Search strategy

Study searches were made on PubMed, Embase, EBSCOhost, Ovid, CNKI and SciELO. The search string was made in PubMed and then translated to additional databases. The search string for PubMed database: ((Vaginal gel) OR ("Vaginal Creams, Foams, and Jellies"[Mesh]) OR (coriolus versicolor gel)) AND (((HPV) OR (Human papillomavirus) OR (HPV infection) OR ("Papillomaviridae"[Mesh]) OR (HPV induced cervical lesions)) OR ((((Cervical dysplasia) OR (Cervical lesion) OR (cervical epithelization)) OR (Cervical intraepithelial neoplasia)) OR ("Uterine Cervical Dysplasia"[Mesh]))). The literature search covered publications up to August 2025 and was supervised by a librarian in the Library of Health Studies at Aarhus University.

Inclusion and exclusion criteria

Studies regarding the effects of CV-based vaginal treatment on either vaginal HPV infection, cervical lesions, cervical dysplasia or both were included. Articles regarding other types of vaginal gel treatments were excluded. Only human experimental randomized and observational studies written in English, Norwegian, Swedish or Danish were included. There was no restriction on the date of publication.

Screening of articles and data extraction

The screening process was performed according to the PRISMA guidelines (33). Initially, all paper titles and abstracts were independently reviewed by 2 authors, and those not meeting the inclusion criteria were excluded. The full

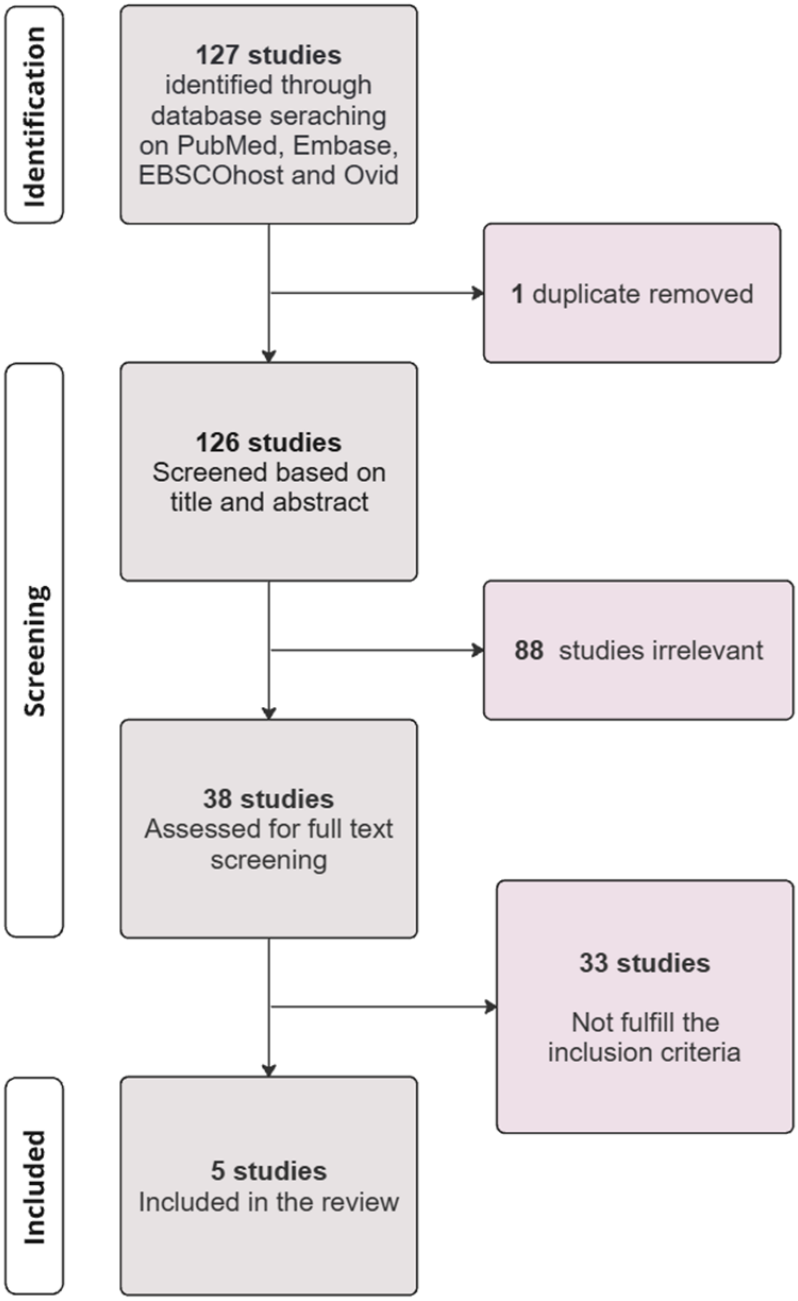
texts of the remaining papers were assessed, focusing on various factors including publication year, country, population size, study design, treatment methods, impact of CV-based vaginal gel and duration of follow-up.

This is a scoping review with the primary aim of mapping the available literature. Therefore, a decision was made not to conduct a quality assessment of the studies included.

Results

Study selection

The search yielded a total of 127 articles, 38 of which underwent full text screening, resulting in a total of five articles deemed eligible for this review (*Fig. 1).*



188

189 *Figure1. PRISMA flowchart of the study selection process showing the search results, study selection and*
190 *exclusion of studies.*

Study characteristics

Study design, study population and geography

All studies included in this review were carried out between 2016 and 2021. The study population in the included studies ranged from 21-192 women. The ages of the included women varied from 18-65 years, with median ages ranging from 30.1-41.4 years. Only one study was a randomized controlled trial (RCT) (32). A sub-analysis of this RCT was presented in another article (30). The last three articles were observational cohort studies, of which two were prospective (28, 31) and one was retrospective (29). In the RCT study (32) a total of 91 women participated, and 41 of these women were included in the sub analysis study (30). In the observational studies (28, 29, 31) the study population consisted of 192, 183 and 21 participants, respectively. Altogether, the studies provided information from 487 women, of whom 369 women received treatment with a CV-based vaginal gel, and the remaining 118 serving as untreated controls. Two studies (28, 30) performed subgroup analyses with a specific focus on examining the effects of the CV-based vaginal gel in women over 40 years old. None of the studies included a subgroup analysis exclusively for women under 40 years old. The inclusion and exclusion criteria for the studies were heterogeneous. In three studies, the included women had either a positive HPV test and/or ASCUS or LSIL (28, 30, 32). In contrast, Criscuolo et al. (29) included only women who tested positive for hrHPV and were the only study to include women with HSIL in addition to those with ASCUS and LSIL. The last study by Palcios et al. (31) included only women with normal cytology and an epithelization score

between 5 and 1, indicating mild to severe ectopy. In the PALOMA study by Serrano et al. (32) and its sub-analysis (30), women with a history of any HPV vaccination were excluded, whereas vaccinated women were included in the other three studies (28, 29, 31). In all the studies, women who were pregnant, planning to become pregnant or breastfeeding were excluded. All five studies were conducted in European countries, with four taking place in Spain (28, 30-32) and one in Italy (29). An overview of the study design, study population and geography for the included studies is presented in Table 1.

Treatment protocols

In three studies, the treatment regime involved application of CV-based vaginal gel daily for 21 days during the first month. This daily treatment regimen was followed by the application of one cannula of CV-based vaginal gel every other day for the next 5 months, excluding menstruation days, resulting in a total treatment period of 6 months (28, 30, 32). Afterward, patients included in these three studies received a follow-up examination at the gynecological outpatient clinic with cervical cytology, HPV testing and colposcopy (28, 30, 32). The study by Cortés et al. (28) was the only study to extend treatment by an additional 6 months for patients with persistent HPV infections, cytology abnormalities, and/or colposcopy due to insufficient initial data. In contrast, Criscuolo et al. (29) limited the treatment strategy to just 3 months, consisting of one month of daily treatment, followed by 2 months with treatment every other day. The follow-up was performed after 6 months. The duration of treatment in the smaller prospective study (n=21) by Palacios et al. (31) was limited to only 12 days with daily use of CV-based vaginal gel, and

with follow-up by colposcopy at day 12. In the study by Serrano et al. (32) women were randomized into two treatment groups: Group A received CV-based vaginal gel daily for 21 days, followed by alternate-day treatment for 5 months as mentioned above. Group B received the gel daily for an initial period of 3 months before switching to the alternate-day schedule for the remaining 3 months. Cervical cytology follow-ups were conducted after 3 and 6 months, whereas HPV testing was only performed at the 6-month visit. For the end-point analysis Group A and B were combined into a single treatment group and compared with untreated controls. The study treatment protocols, follow-up periods and end-points analysis of the included articles are summarized in Tabel 1.

Impact of CV-based vaginal gel

Repair of cervical dysplastic lesions

Three of the studies (28, 29, 32) demonstrated promising results for the CV-based vaginal gel, showing significant positive effects in repairing cervical dysplastic lesions. Repair of cervical dysplastic lesions was defined as normalization or reduction in cervical cytology findings along with concordant colposcopy images. The PALOMA study by Serrano et al. (32) reported a statistically significant improvement in the repair of cervical dysplastic lesions, with 84.9% of women treated with CV-based vaginal gel for 6 months, compared with 64.5% in the untreated control group ($p = 0.031$). Supporting these results, Cortés et al. (28) reported overall repair in 67.0% of the women after 6 months of treatment. Among women who continued treatment for an additional 6 months due to insufficient initial effects, 58.8% showed repair of

their cervical dysplastic lesions after a total of 12 months treatment. The study also conducted cervical biopsies from 91 women, corresponding to 48% of the total cohort, where 15 (16.5%) biopsies showed inflammatory HPV, 56 (61.5%) showed CIN 1 and 8 (9%) showed CIN2 or CIN3 at baseline. At follow up the study found that 15.4% of the biopsies improved from CIN1 to normal or inflammatory after 6 months of treatment, whereas 76.9% of the biopsies did not show changes in the biopsy result, and 7.2% of the biopsies had worsened from inflammatory to CIN1.

The study by Criscuolo et al. (29) focused specifically on the repair of cervical dysplastic lesions among hrHPV positive women. Results showed that 76.1% of the treated hrHPV positive women had improved colposcopy after 3 months of treatment, compared to 40.8% in the control group ($p = 0.0005$). Additionally, 60.9% of the treated women achieved full remission defined as a negative colposcopy result compared to 40.8% in the control group ($p = 0.05$). Subgroup analysis of hrHPV positive women performed by Cortés et al. (28) and Serrano et al. (32) showed repair of cervical dysplastic lesions after treatment with CV-based vaginal gel in 76% and 87.8% of the women, respectively.

Cervical Reepithelization

Cervical reepithelization after treatment with CV-based vaginal gel was evaluated in two of the studies (31, 32). The degree of reepithelization was evaluated by colposcopy and rated with a 5-point Likert scale, where 5 was no ectopy and 1 was severe ectopy and bleeding. Palacios et al. (31) found that the mean score of re-epithelization increased from 3.09 at baseline to 4.42

after 6 months of treatment, with an overall improvement of epithelization in 95.3% of the women. In the larger study by Serrano et al. (32), the reepithelization mean score increased from 4.2 to 4.5 after 6 months in the treatment group, whereas the mean score increased from 3.9 to 4.1 in the untreated control group.

HPV Clearance

Four studies (28-30, 32) evaluated the impact of CV-based vaginal gel on HPV clearance, which was defined as either a negative HPV test result, the disappearance of all baseline-detected HPV-genotypes or partial clearance with the removal of at least one single HPV genotype. Cortés et al. (28) reported a positive effect of treatment, with HPV clearance rates of 58.7% among patients treated for 6 months and 52.1% among those continuing treatment for 12 months. A subgroup analysis by Cortés et al. (28) further confirmed this positive effect in hrHPV positive women, with a clearance rate of 70.6% in this group. In contrast, Serrano et al. (32) did not find statistically significant results overall, as 59.6% of treated women experienced HPV clearance, versus 41.9% in the untreated group ($p = 0.118$). However, a significant effect was observed in Group B (treatment daily for 3 months followed by alternate-day treatment for another 3 months), with 75.9% achieving HPV clearance compared with 41.9% in the control group ($p = 0.008$).

Focusing on the clearance of hrHPV, Criscuolo et al. (29) reported that 67.0% of hrHPV positive women treated with CV-based vaginal gel for 3 months exhibited an overall clearance of hrHPV, whereas only 37.2% of the untreated

controls (*p <0.0001*). Similarly, the study by Serrano et al. (32) reported hrHPV clearance with 62.5% in the treated women versus 40.0% in the untreated control group, although this result was not statistically significant. However, statistically significant results were observed in Group B, in which 81.8% of the women achieved clearance of hrHPV (p = 0.004). An overview of the effects of the CV-based vaginal gel on HPV-induced cervical lesions and HPV clearance is presented in Table 2.

Women aged ≥40 years

Two of the studies (28, 30) evaluated the effect of CV-based vaginal gel among women over 40 years of age, suggested a positive effect of CV-based vaginal gel in women around the postmenopausal age. A subgroup analysis by Cortés et al. (28) found that 82.4% of treated women experienced repair or normalization of their cervical dysplastic lesions. Similarly, the sub-analysis of the PALOMA study (30), reported a high repair rate of cervical dysplastic lesions among women over 40 years old, with 92.3% of treated women showing repair compared to only 50% of untreated controls (p = 0.007). Cortés et al. (28) also evaluated HPV clearance in women over 40 years old, finding an overall HPV clearance rate of 73.5%. The sub-analysis of the PALOMA study (30) found an HPV clearance rate of 61.5% among treated women compared to 50% of untreated controls (p = 0.725), though this result was not statistically significant. Similarly, the study found no statistically significant difference in the clearance of hrHPV, with a clearance rate of 66.7% in the treated group compared to 44.4% in the control group (p = 0.418). An overview of the effects of the CV-based vaginal gel on HPV-induced

cervical lesions and HPV clearance among women aged over 40 years is presented in Table 2.

Satisfaction and compliance

Perceived stress was analyzed in one study (32), whereas tolerability and satisfaction with the use of the CV-based vaginal gel were analyzed in two of the studies (28, 32). The level of stress was evaluated by a 14-item Perceived Stress Scale, where a higher score represents a greater degree of perceived stress. Serrano et al. (32) found that treatment with the CV-based vaginal gel decreased the level of stress from a mean score of 21.1 at baseline to 19.0 after 6 months of treatment compared with the control group whose stress increased from a mean score of 17.7 at baseline to 20.7 at 6-month follow-up. Furthermore, this study found that 86.5% of treated women expressed satisfaction after 6 months of use. Similarly, Cortés et al. (28), reported that 93.7% of treated women were satisfied with CV-based vaginal gel after 6 months of treatment. In both studies, there were no reports of dissatisfaction. Additionally, both studies indicated very high compliance with the product, with compliance rates of 94.2% in Cortés et al. (28) and 94.3% in Serrano et al. (32). The reasons for non-compliance were menstruation, omissions and one report of discomfort. The other three studies (29-31) included in this review did not evaluate the level of stress, compliance, or satisfaction/dissatisfaction with the product.

Side effects

Two of the included studies (28, 32) reported side effects related to CV-based

vaginal gel. In general, the product was well-tolerated, with a few cases of potential treatment-related side effects, such as vulvovaginal itching, skin rash and other infections, noted. In the PALOMA study conducted by Serrano et al.(32) 41% (n=7/17) of the reported side effects were considered directly linked to the use of the CV-based vaginal gel. In the study by Cortés et al.(28) a total of 8 side effects were reported, but only 3 of these were possibly related to the use of the vaginal gel. In both studies most of the reported side effects were classified as mild or moderate, and there were no reports of severe side effects directly associated with the treatment. The most common reported side effects include infections and vulvovaginal stinging and burning (28, 32). One case with candidiasis was reported (32). The study by Criscuolo et al. (29) reported data on adverse events, but found none, whereas the study by Palacios et al. (31) did not collect any data on adverse events.

Discussion

To the best of our knowledge, this scoping review is the first to map the existing evidence on the effectiveness and use of CV-based vaginal gel on the clearance of vaginal HPV infection and regression of cervical dysplastic lesions. This review highlights results from a limited number of recently published studies with small sample sizes, all of which show promising outcomes for CV-based vaginal gel as an effective and safe new treatment for improving HPV clearance and repairing cervical dysplastic lesions (28-32). Notably, this positive effect was also shown for women infected with hrHPV (28, 29, 32) as well as women over 40 years old (28, 30), suggesting a potential effective treatment also for women around post-menopausal age.

Importantly, no serious adverse events were reported related to the use of CV-based vaginal gel.

The repair of cervical dysplastic lesions after treatment with CV-based vaginal gel was evaluated by cytology and colposcopy at baseline and after 6 months of treatment in four studies (28-30, 32). However, these studies included only women with ASCUS or LSIL and excluded those with HSIL because of the necessity of conization. One study by Criscuolo et al. (29) did not exclude women with HSIL but was only able to include one HSIL patient for the trial. Consequently, it is not possible to evaluate the effects of CV-based treatment on HSIL changes or compare CV-based treatment with conventional conization treatment. Overall, all studies highlight a high and significant rate in the repair of cervical dysplastic lesions when compared with untreated controls (60.8% vs 40.8%) (29) and (84.9% vs 64.5%) (32). However, the rate of repair of cervical dysplastic lesions among untreated controls was relatively high in these studies (40.8% (29) and 64.5% (32)), indicating that natural repair of cervical lesions may overestimate the effect of the CV-based vaginal gel (28-30, 32). Notably, only one of the studies (28) used cervical biopsies to grade cervical dysplasia. The use of biopsies would have allowed for a more accurate assessment of the degree of dysplasia compared to colposcopic assessment. The absence of biopsies in these studies (29-32) may therefore have led to an overestimation of the gel's efficacy, as cervical dysplasia could have been present undetected by colposcopy. Furthermore, colposcopic evaluation depends on examiners expertise, introducing a potential risk of inter-observer variability.

Another measurement of the progression or regression of cervical dysplastic lesions is the score of cervical re-epithelization, which ranges from 5 to 1. Cervical re-epithelization was evaluated in two studies (31, 32), which suggested an improvement in the re-epithelization score after treatment with CV-based vaginal gel.

In the studies included, HPV clearance was variably defined, encompassing both total and partial clearance. Of the four studies assessing HPV clearance, only one (29) reported data separately for total and partial clearance, whereas the others (28, 30-32) combined these outcomes into a single HPV clearance category. Across the four studies clearance rates ranged from 58.7% to 75.9% (28-30, 32). Two studies also reported significant hrHPV clearance rates of 70.6% and 67.0% (28, 32). In studies including untreated control groups, HPV clearance was consistently higher among women receiving CV-based vaginal gel, with HPV clearance rate of 75.9% vs. 41.9% (32) and hrHPV clearance rates of 67.0% vs 37.2% (30) and 66.7% vs 44.4% (29), suggesting a potential acceleration of HPV resolution compared with no intervention. These clearance rates exceed those reported natural HPV resolution in other studies, approximately 29% at 6 months and 41% at 18 months for HPV (34) and 43% at 6 months and 65% at 18 months for hrHPV (35) indicating that the gel may enhance or expedite HPV clearance. Notably, one study (32) found no significant HPV/hrHPV clearance at one month follow-up, but demonstrated a clear treatment effect after three months, suggesting that treatment duration may affect efficacy.

Recent research has explored complementary and alternative medicines (CAM) as a treatment for HPV related diseases. None of the studies included in this review compared CV-based vaginal gel with other treatment opportunities, limiting conclusions about its relative efficacy. A scoping review published in 2024 (36) identified several promising CAM interventions for HPV, and highlights the CV-mushroom, the phytochemical indole-3-carbinol (I3C), and the mineral selenium as the most effective interventions. However, carrageenan-based treatment and probiotics were not included in the review.

Other vaginal formulations have also shown potential, such as the antioxidative sodium selenite and carrageenan-based vaginal gel, which both showed regression of HPV-induced cervical dysplasia and improved HPV clearance (37-40). Interestingly, carrageenan-based vaginal gel has been reported to prevent HPV infection when applied before vaginal intercourse, highlighting its potential as treatment in developing countries (36, 39, 40).

The vaginal microbiome is another factor influencing HPV persistence and clearance. CV-based vaginal gel has been shown to exert moisturizing, tissue regenerating and re-epithelializing effects, while promoting restoration of a vaginal ecosystem, thereby beneficial effects on the vaginal microbiota contributing to HPV clearance and protection against reinfection are reported (29, 41). A Lactobacillus dominant microbiota is associated with higher HPV clearance and regression of cervical lesions, whereas dysbiotic anaerobes may contribute to HPV persistence and progression to cervical neoplasia (42, 43).

Supporting this, a recent RCT (44) involving 100 women with hrHPV infection found that *Lactobacillus crispatus* CHEN-01 transplantation significantly increased hrHPV clearance, reduced HPV viral load, and improved vaginal inflammation compared with the placebo-group. This also suggests the application of probiotics as an effective treatment opportunity for hrHPV. Similarly**,** Palacios et. al (31) reported an increase in Lactobacillus species in 54.5% of the women treated with CV-based vaginal gel, and a subsequent study (26), confirmed a microbiota shift toward beneficial species after treatment with CV-based vaginal gel. Together, these studies suggest that CV-based vaginal gel may help modulate the vaginal microbiome toward a more antiviral Lactobacillus rich environment, potentially enhancing HPV clearance. Future studies should include microbiome analyses to clarify these interactions and their impact on HPV related cervical diseases.

Limitations and further investigation

The review is limited by the small number of available studies, reflecting that research on CV-based vaginal gel is still relatively new and unexplored. A major limitation of the included studies was heterogeneous in design, patient populations, inclusion criteria, outcome measures and duration of treatment, which complicates and limits the robustness of conclusion.

Geographical bias is another limitation as four out of the five studies (28, 30-32) were conducted in Spain and one in Italy (29), restricting generalizability of the findings to other populations. Given global differences in HPV subtypes, screening programs, and healthcare systems, additional larger multinational

studies are needed to validate the CV-based vaginal gels efficacy across broader clinical settings.

It is well known that some risk-factors can double or triple the risk of precancer among women infected with an oncogenic HPV and could therefore influence the efficacy of the treatment (6). However, not all the included studies accounted for potential confounders such as hormonal contraceptive use, number of sexual partners, immunosuppression or smoking status. All these factors could potentially affect HPV persistence and progression, thereby biasing into the reported results. Moreover, the absence of histological confirmation in most studies may have led to an overestimation of efficacy based on colposcopic findings alone.

Funding bias must also be considered as four out of five studies (28, 30-32) were sponsored by ProCare Health, the company that manufactures Papilocare®. This financial relationship may represent a potential conflict of interest, as positive results or emphasis on the product's efficacy could commercially benefit the sponsor. Additionally, some of the articles share the same authors (28, 30-32). Although overlapping authorships and inclusion period were limited, potential cohort overlapping could slightly inflate the overall effect.

Conclusion

This scoping review suggests that CV-based vaginal gel shows promising but preliminary efficacy in promoting regression of cervical dysplastic lesions and HPV clearance. Importantly, the treatment was generally well tolerated.

However, interpretation is limited number of available studies, small and regionally restricted cohorts, and the absence of biopsy validated outcomes. Larger multinational RCTs with extended follow-up, histopathology-confirmed outcomes, standardized definitions of HPV clearance, and consistent detection methods are needed to confirm the efficacy of CV-based vaginal gel and to define its role in clinical practice.

Declarations

- Ethics approval and consent to participate; Not applicable
- Consent for publication; Not applicable
- Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request
- Competing interests; Not applicable
- Funding; No funding
- Acknowledgements; Not applicable

Authors' contributions

Study idea and protocol design; PB, VMB.

Manuscript writing: IBH, MKK, PB, VMB

Comments on manuscript, review on final manuscript and approving it: IBH, MKK, PB, VMB, MT, BA, LKP

Table 1. **Overview of characteristics, treatment regime, follow-up time and endpoint analysis of the included articles**

Author, year, Country	Study design	Study population	Subpopulations	Inclusion criteria	Treatment regime	Follow up	Endpoints	Endpoint analysis
Cortés et al. (28) 2023, Spain	Prospective observational clinical study	n=192	Women aged >40 years: n= 74 hrHPV: n= 179	Women > 25 years old; HPV-positive or ASCUS or LSIL. Colposcopy image showing similar level of cervical dysplasia.	Papilocare®; one cannula every day for 21 days during the first month. Followed by one cannula alternate-day the next 5 months. Those who continued with altered cytology or colposcopy and/or persistent HPV were offered an additional 6 months.	6 months. 6 and 12 months for those who continued the treatment due to persistent HPV or altered cytology/ colposcopy.	Repair of cervical lesions Partial or total clearance of HPV and hrHPV Level of satisfaction and tolerability	Cytology Colposcopy Biopsy PCR HPV test VAS
Palacios et al. (30) 2022, Spain	Multicenter RCT. Sub-analysis.	n=41	Women aged >40 years: n= 41 hrHPV: n=31	Women from the PALOMA study aged >40 years.	Papilocare® Group A; One cannula a day for 21 consecutive days followed by 7 days with no treatment. Followed by one cannula alternate-day (except during menstrual cycle) for 5 months. Group B: One cannula a day for 21 days followed by 7 days without treatment repeated over 3 months. Followed by one cannula alternate-day /except during menstrual cycle) for 3 months. Controls: Watchful waiting	6 months	Repair of cervical lesions Partial or total clearance of HPV and hrHPV	Cytology Colposcopy PCR HPV test
Serrano et al. (32) 2021, Spain	RCT	n= 91 59 intervention group (A and B) 32 controls	hrHPV: n= 70 hrHPV 44 intervention group	Women aged 30-65 years old; positive HPV test	Papilocare® Group A; One cannula a day for 21 consecutive days followed by 7 days	6 months	Repair of cervical lesions	Cytology Colposcopy PCR HPV test

			26 controls	and/or cytology with ASCUS, LSIL or AGUS together with concordant colposcopy images.	with no treatment. Followed by one cannula alternate-day (except during menstrual cycle) for 6 months. Group B: One cannula a day for 21 days followed by 7 days without treatment repeated over 3 months. Followed by one cannula alternate-day /except during menstrual cycle) for 3 months. Controls: Watchful waiting		Partial or total clearance of HPV and hrHPV Vaginal health Cervical Re-epithelization Perceived stress and satisfaction Adverse events	Bachmann Vaginal Health index 5-point Likert scale 7-point Likert scale Self-reported
Criscuolo et al.(29) ***2020, Italy***	Observational retrospective study	n=183	hrHPV: n= 183 97 intervention group 86 controls	Women aged 18-49 years old; hrHPV-positive and normal or abnormal cytology (ASCUS, LSIL or HSIL).	Papilocare®; 1 cannula every day for 21 days in the first month. Followed by 1 cannula every other day the next 2 months (except menstrual cycle) Controls: Watchful waiting	6 months	Repair of cervical lesions Partial or total clearance of hrHPV Adverse Events	Cytology Colposcopy PCR HPV-test Self-reported
Palacios et al. (31) ***2017, Spain***	Observational Prospective study	n=21		Women aged 18-45 years old; no symptoms of vaginal disease and a normal smear. Epithelization score between 4 and 1.	Coriolus Versicolor gel, Palomacare®; one cannula a day for 12 consecutive days	12 days	Epithelization of cervical mucosa Vaginal microbiota Vaginal Health	Colposcopy Ectopy epithelization score Vaginal Status Diagnostic test 5-point Likert scale Bachmann Vaginal Health index

ASCUS= atypical squamosa cells of undetermined significance. LSIL = low-grade squamous intraepithelial lesion. HSIL = High-grade squamous intraepithelial lesion. hrHPV = high-risk Human Papillomavirus

Table 2. **Overview of the effects of the CV-based vaginal gel on HPV-induced cervical lesions and HPV clearance.**

	Total sample	hrHPV	Women aged >40 years
Cortés et al. (28) 2023, Spain	**Overall repair of HPV induced cervical lesions:** 77.1% (95%CI unknown) at 6 months; 67.0% (95% CI: 60.4-73.7) at 12 months 58.8% (95% CI: 42.3-75.4) **Overall clearance of HPV;** 71.6% (95%CI unknown) at 6 months; 58.7% (95% CI: 51.7-65.8) at 12 months; 52.1% (95% CI: 38.0-66.2)	**Overall repair of hrHPV induced cervical lesions**: 76% (95%CI: 69.7-82.2) at 6 months: 66.9% (95%CI: 59.9-73.8) at 12 months: 54.8% (95%CI: 37.3-72.4%) **Overall clearance of hrHPV**: 70.6% (95%CI 63.9-77.3) at 6 months: 57.4% (95%CI: 50.1-64.7) at 12 months: 52.2% (95%CI: 37.7-80.1)	**Overall repair of HPV induced lesions**: 82.4% (95% CI: 73.8-91.1). at 6 months: 73.5% (95%CI: 63.0-84.0) at 12 months: 54.5% (95%CI: 25.1-84.0) **Overall clearance of HPV;** 75.3% (95%CI: 65.5-85.2) at 6 months: 61.1% (95%CI: 49.9-72.4) at 12 months: 57.9% (95%CI: 35.7-80.1) **Overall clearance of hrHPV**: 73.5% (95% CI: 65.5-85.2) at 6 months: 59.7% (95%CI: 48.0-71.5) at 12 months: 55.6% (95%CI: 32.6-78.5)
Palacios et al. (30) 2022, Spain			**Overall repair of HPV induced cervical lesions;** 92.3% vs. 50.0% (p=0.007) **Overall repair of hrHPV induced cervical lesions:** 90.5% vs. 33.3% (p=0.003) **Overall clearance of HPV**; 61.5% vs 50.0% (P=NS) **Overall clearance of hrHPV:** 66.7% vs 44.4% (P=NS)
Serrano et al. (32) 2021, Spain	**Overall Repair of HPV induced cervical lesions;** 84.9% vs. 64.5% (p=0.031)*	**Overall repair of hrHPV induced cervical lesions**; 87.8% vs 56.0% (p=0.003)*	

	Overall clearance of HPV; 59.6% vs 41.9% (p=0.118) Group B; 75.9% vs 41.9% (p=0.008) Group A: 39.1% vs 41.9% (P=NS)	**Overall clearance of hrHPV**; 62.5% vs 40.0% (P=NS) Group A; 38.9% vs 40.0% (P=NS) Group B: 81.8 % vs 40.0% (p=0.004)	
	Total sample	**hrHPV**	**Women aged >40 years**
Criscuolo et al.(29) 2020, Italy			**Overall Repair of HPV induced cervical lesions;** Colposcopy improvement in 76.1 vs 40.8% (p=0.0005) Colposcopy remission 60.9% vs 40.8% (p=0.05) Cytology improvement 78.5% vs 37.7% (p<0.0001) Cytology remission 70.8% vs 34.8% (<0.0001) **Overall clearance of HPV;** HPV-DNA improvement in 70.1% vs 37.2% (p<0.0001) HPV-DNA clearance in 67.0% vs 37.2% (p<0.0001)
Palacios et al. (31) 2017, Spain	**Overall improvement of mean score of cervical epithelization;** 3.09 at baseline to 4.42 at follow-up (p<0.001) **Vaginal microbiotas mean score;** 3.3 at baseline to 4.0 at follow-up (P=NS) **Vaginal health mean score;** 19.0 at baseline to 22.3 at follow-up (p=0.007)		

treatment group for the main analysis. NS = Non-significant.

**Group A and B were pooled into a single-*

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