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Review Article

Investigation of the Effect of Complementary Medicine on Infection and Cancer in Human Papillomavirus (HPV): A Systematic Review

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Abstract

Introduction: Human papillomavirus (HPV) is one of the most common viruses transmitted sexually and found among men and women in both developing and developed countries. Alternative treatment options, such as the use of medicinal plants and complementary medicine, have been welcomed by researchers due to their low side effects. The present study was conducted with the aim of reviewing and comparing complementary medicine methods for HPV infection and cancer.

Materials and Methods: A systematic review was conducted on English and Farsi documents published during the years 2004 to 2024 in PubMed/Medline, ScienceDirect, Web of Science, and Google Scholar databases. The screening process was performed by two independent authors, and the selected articles were reviewed for inclusion and exclusion criteria.

Results: In total, 210 relevant studies were searched in 2004–2024, and after evaluating full texts of articles, 25 articles were opted in accordance with the eligibility criteria with keywords "complementary medicine, medicinal plants, HPV infection and cancer," and finally, 20 full-text articles were reviewed systematically. Green tea, enriched with polyphenols and sinecatechins, and therapeutic compounds from Shiitake and Ganoderma mushrooms, represent among the most effective substances utilized in complementary medicine for the treatment and prevention of genital warts. The synergistic effects of these bioactive components have demonstrated significant potential in reducing the incidence and recurrence of this condition, highlighting their relevance in integrative therapeutic approaches.

Conclusion: Complementary medicine can have a positive effect on infections and cancers caused by HPV. These drugs can be effective in preventing cancer caused by inhibiting abnormal growth and stabilizing the genome of cells. However, there is a need for more research and clinical trials to confirm these effects and prove the effectiveness of complementary medicines in this field.

INTRODUCTION

Visible external anogenital warts (EGW, *condylomata acuminate*) are nonmalignant squamous cell tumors caused by infections of the human papillomavirus (HPV) (1). The HPV is one of the most common viruses transmitted sexually and is found among men and women in both developing and developed countries. This virus is small and non-enveloped, containing double-stranded DNA, and is known as an etiologic factor for cervical cancer, the second most common neoplasia among women worldwide (2). The virus can be divided into two categories: low-risk types and high-risk types. In most cases, low-risk HPV infections resolve spontaneously due to human immune defense, taking HPV types 1, 2, 3, and 4 as examples. In very few cases, the infection persists and causes warts, benign papilloma, precancerous lesions, and even cancer. High-risk types, HPV 16 and 18 included, are known as definite biological carcinogens for cancers related to the cervix, vulva, vagina, penis, anus, and oropharynx. The HPV infection was associated with 4.8% of cancers in 2008 globally, 86.9% of cases being cervical cancer (3). The incidence of oropharyngeal cancer (OPC) is increasing in the United States despite decreasing rates of smoking- and alcohol-related OPC. This issue is driven by the rapidly increasing incidence of OPC caused by HPV, marking a striking shift in the epidemiology of OPC in Western countries. The OPC incidence is five-fold higher in males than females, and projections indicate that the number of annual OPCs diagnosed in the United States will increase by nearly 50% between 2018 and 2045 despite HPV vaccination (4). The HPV cause 90% of cervical and anal, 70% of vaginal and vulvar, and 60% of penile cancers. In the United States, the prevalence of HPV infection is 42% in men and 39% in women (5,6,7). Worldwide, HPV is the second most common cancer-causing infectious agent after Helicobacter pylori. Approximately 5% of cancers are associated with high-risk HPV. During their lifetimes, 80% of the population will encounter HPV infection, but the majority of those will clear the infection without clinical symptoms. On the other hand, nearly all cervical cancer cases are associated with HPV infection (6).

Therapies for EGW include patient-administered topical treatments, such as imiquimod (5% cream) and podophyllotoxin (0.15% cream or 0.5% solution), and physician-administered therapies, such as cryotherapy, curettage and electrodesiccation, laser surgery, podophyllin resin, and trichloroacetic acid treatment. These therapies are associated with painful side effects, mainly erythema, ulcerations, and possible tissue destruction and scarring (1). Current treatment options are often unsatisfactory and associated with many side effects. The use of medicinal plants as an alternative treatment method has attracted the attention of researchers due to the lack of side effects (8). In various studies, the effect of Chinese (3) and green tea complementary (1,8,9,10,11) and fungal compounds and medicinal mushrooms (6) on HPV has been investigated. Considering the importance and benefits of using complementary medicine methods and considering the negative results in this field, this study was conducted with the aim of investigating the effect of complementary medicine on HPV infection and cancer.

METHODS

A systematic review was conducted from 2004 to 2024 in English and Farsi in four databases, including PubMed/Medline, ScienceDirect, Web of Science, and Google Scholar. All relevant articles were evaluated to find eligible articles, the titles or abstracts of which examine complementary medicine and herbal treatments for HPV infection and cancer. Moreover, the reference lists of relevant articles were searched and used in the review process. The screening process of the articles was conducted by two independent authors. The selected articles were reviewed in terms of inclusion and exclusion criteria.

Data Extraction

After considering all databases based on our keywords, the proper records were entered into EndNote X8 (Thomson Reuters, New York, USA), and the duplicate records were removed. The titles and abstracts of the searched articles were reviewed and screened for eligibility. Then, a full review of the related articles was conducted based on titles and abstracts for the final selection of articles. The methodological quality of the selected articles was assessed using the STROBE checklist for observational studies and the CONSORT checklist for clinical trials. For each article, some information, including authors, objectives, place, sample size, statistical analysis, medical error variables, and the main results, were extracted. Each article was assessed independently by two authors, and then the data were extracted independently. Another author was considered an arbiter to resolve any disagreements.

Inclusion Criteria

The inclusion criteria were the studies that have investigated the effects of complementary medicine and medicinal plants on HPV infection and cancer. All studies were published during 2004-2024 in English and Farsi languages.

Exclusion Criteria

The exclusion criteria included randomized and qualitative studies, as well as reviews of clinical trials and all studies published in conference proceedings. Additionally, studies with unclear results or incomprehensible analyses, along with those exhibiting bias or inconsistencies that could affect the selection or interpretation of information, were also excluded.

Search Strategy

Four databases, including PubMed/Medline, Google Scholar, Web Science, and ScienceDirect, were searched to find eligible articles. Keywords and search strategies include complementary medicine and medicinal plants, HPV infection, cancer, and genital warts. Descriptive data, including the author, purpose, location of the study, sample size, variables of complementary medicine and medicinal plants and HPV infection and cancer, statistical analysis, and main results, were extracted.

RESULTS

The process of searching is presented in Figure 1. In total, 210 relevant files from four different databases and their resources were searched during the initial search. After removing duplicate versions in the Endnote software, 32 articles remained for screening based on titles and abstracts. In the evaluation of the full texts of the articles, one complete text was removed, leaving 25 articles that met the eligibility criteria for the systematic review. After removing four articles, a total of 20 full-text articles were ultimately reviewed. According to the studies that were analyzed, complementary medicine improves clinical index in the treatment of cervical cancer and genital warts as a result of its regulation in cell apoptosis, viral gene expression, cell signal transduction pathways, and body immune function. The most effective and commonly used interventions in complementary medicine, yielding significant results, were green tea and therapeutic mushrooms. According to the analyzed studies, green tea—rich in polyphenols and sinecatechins—along with therapeutic shiitake mushrooms (which contain a variety of antioxidants, B vitamins, and selenium) and Ganoderma mushrooms (which contain triterpenoids), are among the most effective substances used in complementary medicine. These agents have demonstrated significant efficacy in the treatment and prevention of the recurrence of genital warts. Green tea contains compounds known as polyphenols and sinecatechins, which are effective in strengthening the immune system, inhibiting the cell cycle in cancer, and reducing external lesions of genital warts as well as their recurrence. Shiitake mushrooms contain vitamin D, fiber, zinc, copper, magnesium, B vitamins (B5, B6, B9, B12, B2, and B3), and selenium, and for this reason, they increase immunity and reduce inflammation. Shiitake mushroom has a unique chemical substance in its structure known as active hexose correlated compound (AHCC). It is important to note that AHCC is a mixture of amino acids, polysaccharides, and other minerals that significantly enhance the body's immune system, preparing it to combat various viral diseases. Ganoderma mushrooms contain ganoderic acid (a triterpenoid) with a molecular structure similar to steroid hormones. By strengthening the immune system, this mushroom can exert beneficial effects on the HPV virus and can be effectively used as a therapeutic supplement alongside shiitake mushrooms.

DISCUSSION

Polyphenols derived from green tea, particularly *epigallocatechin-3-gallate* (EGCG), have been demonstrated to possess anticarcinogenic and chemo-preventive effects both in vitro and in vivo (12). Green tea polyphenols (EGCG and *poly E*) can inhibit the proliferation of HPV-immortalized and HPV-positive cancer cells through cell cycle arrest at the G0/G1 phase (13). Green tea extracts in the form of ointment and capsules are effective for treating cervical lesions, suggesting that green tea extracts can be a potential therapy regimen for patients with HPV-infected cervical lesions (14). Green tea catechins may modulate the immune system by disrupting the proinflammatory cascade via antioxidant Effects, altering cell signaling (e.g., nuclear factor-kB) cytokines, and/or proinflammatory mediators (e.g., C-reactive protein [CRP]). Sinecatechin treatment modulates and down-regulates genes involved in the pro-inflammatory response to HPV infection. The strong experimental evidence for the antitumor, antiviral, and immunomodulatory effects of green tea catechins on HPV-positive cells and tumors supports an underlying mechanism for green tea and protection against genital cancers. Green tea catechins have antiviral and immunomodulation properties in addition to their antitumor effects. It is hypothesized that green tea catechins may protect against HPV-related cancers via mechanisms related to all three properties. Green tea catechins can enhance cell-mediated immunity, which is important when considering them as chemo-preventive agents for HPV-associated gynecologic cancers (15, 18). Sinecatechin ointment from green tea, along with cold therapy courses, is effective and acceptable in eliminating EGW and preventing their recurrence (16, 17, 18). Study data indicate that polyphenols in green tea reduce the risk of recurrence and are superior to cryotherapy in this context. Treatment with

polyphenols present in green tea is devoid of side effects, whereas cryotherapy, laser treatment, curettage, and trichloroacetic acid can be painful, destroy tissue, and lead to significant complications such as scarring, erosion, wounds, and infections (19, 20, 21).

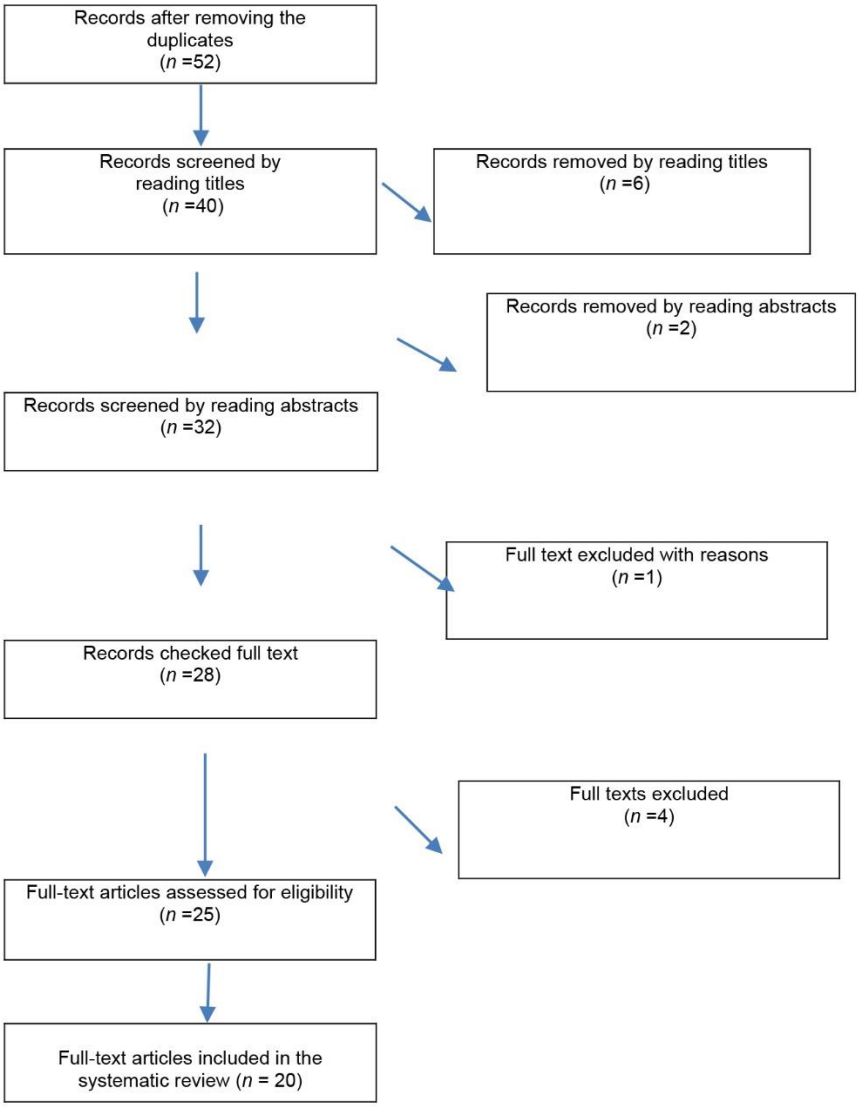

Figure 1. Flowchart of the selection of articles for the review process.

Traditional Chinese medicine (TCM) has been shown to improve clinical outcomes in the treatment of cervical cancer and genital warts; the mechanisms underlying its effectiveness may involve the regulation of cell apoptosis, viral gene transcription and translation, cell signal transduction pathways, and immune function (22). Detoxification therapies in TCM yield favorable results in enhancing HPV clearance rates and impacting the proportions of certain immune cells and cytokine levels. The clearance rate of wart lesions following treatment with sinecatechins is comparable to that of other topically applied drugs, such as imiquimod and podophyllotoxin, but recurrences are observed less frequently after treatment with sinecatechins. While the molecular mechanisms underlying the clinical efficacy have yet to be fully characterized, several properties are likely involved in the regression of genital warts: activation of cellular immune reactions, induction of cell cycle arrest and apoptosis, and inhibition of HPV gene expression. Polyphenols and sinecatechins work to induce apoptosis and exert anti-inflammatory actions in HPV-related diseases (23, 24, 25, 26, 27).

Medicinal mushrooms and curcumin have been used for thousands of years in the traditional medicine of many countries due to their curative and preventive effects on various diseases. Today, a number of works describe the functional components of fungi in the fight against many diseases, including cancer. In the case of cervical cancer, the beneficial effects of medicinal mushrooms on hindering the development of the disease, mainly due to cell cycle arrest and induction of apoptosis, have been proven. In the case of cervical precancerous lesions, increased HPV clearance and improved cervical cytology were demonstrated in patients applying vaginal gel

during the watchful waiting period. Medicinal mushrooms appear to be a suitable adjunct in the treatment of many types of cancer, and patients with diagnosed precancers can also benefit from their use. Some mushrooms act directly on inflammation. *Cordyceps sinensis*, a mushroom that thrives in humid temperate and tropical forests at high altitudes, contains a nucleoside compound known as cordycepin, which stimulates the production of interleukin 10, an anti-inflammatory cytokine. Mushroom β-glucans, which consist essentially of a (1, 3)-β-linked with small numbers of (1, 6)-β-linked side chains, can modulate the autoimmune mechanisms. These biological response modifiers (1,3)-β-glucans interact with the intestinal cell wall and are absorbed into the lymph fluid, where they recruit neutrophils and macrophages, trigger the production of cytokines, and stimulate immune function. The effectiveness of *Coriolus versicolor* polysaccharides is well documented. Several studies have demonstrated the effectiveness of *Coriolus versicolor* in the fight against a variety of cancers, primarily using polysaccharopeptide (PSP) and polysaccharide K (PSK), called krestin, extracted from this mushroom. They have proven to be helpful in ovarian, cervical, prostate, colon, lung, and breast cancer treatment, as well as in the fight against leukemia and other cancers. The protein extract of this mushroom can cause cell cycle arrest (28, 29,30), and also, in the case of curcumin, it seems to have solid and dose-dependent effects in inhibiting the proliferation of cancer cells (31).

CONCLUSION

In the present study, the effect of complementary medicines on infections and cancers caused by HPV was investigated. Complementary therapies can serve as adjunctive treatment methods to conventional therapies, demonstrating positive effects on infections and cancers associated with HPV. These drugs may improve symptoms, reduce inflammation, and boost the immune system. The mechanisms by which complementary medicines may reduce inflammation and inhibit the growth of cancer cells caused by HPV include: 1. Reducing inflammation: Certain complementary medicines, such as curcumin, resveratrol, and EGCG, possess anti-inflammatory properties that can help mitigate inflammation in HPV-related cancer cells and regulate inflammatory processes. 2. Inhibiting the growth of cancer cells: Antioxidant supplements, including vitamin C, vitamin E, selenium, and polyphenols, can inhibit the growth of HPV-related cancer cells by preventing DNA damage and enhancing immune function. 3. Stabilization of the genome: Some plant-derived substances exhibit anticancer properties that can help stabilize the genomes of cancer cells affected by HPV. However, it is recommended to consult a healthcare professional or nutritionist before using any complementary medicine to assess individual conditions. Ongoing research into the effectiveness and safety of complementary medicines for the prevention and treatment of HPV-related cancers is essential, as further studies and clinical trials are needed to confirm these effects and validate the efficacy of these therapies. Additionally, the use of complementary medicines should occur under medical supervision, considering the unique circumstances of each patient. A summary of the studies included in this review, based on the extracted data, is presented in Table 1.

Table 1. A summary of the included studies in this review based on the extracted data.

No	Authors	Year	Objectives	Location	Type of Study	Sample Size	Main Results
1	W-S Ahn et al.	2003	Clinical efficacy of green tea extracts (*Poly E* and EGCG) delivered as ointment or capsules in patients with HPV-infected cervical lesions	Korea	RCT	51 patients with cervical lesions were divided into four groups as compared with 39 untreated patients as a control	A component of green tea, catechin, is known to possess anti-cancer properties. Green tea extracts, available in the form of ointments and capsules, have proven effective in treating cervical lesions, suggesting that these extracts could serve as a potential therapeutic regimen for patients with HPV-infected cervical lesions. The anti-carcinogenic and anti-proliferative effects

							of green tea have been attributed to the biological properties of its polyphenolic compounds. Specifically, green tea extracts, such as *poly E* and EGCG, exhibit anti-cancer properties and may be effective chemopreventive options for preventing cervical dysplasia from progressing to more severe stages of cervical neoplasia.
2	Silvio Tatti et al.	2008	To estimate the clinical efficacy of topical sinecatechins, a defined green tea extract, in treating external genital and perianal warts.	USA	RCT	502 male and female patients aged 18 years and older, with 2–30 anogenital warts	Topical sinecatechins ointments at concentrations of 15% and 10% have proven to be effective and well-tolerated in the treatment of anogenital warts. Therapeutic success, defined as a clearance rate of at least 50% for all warts, was observed in nearly 80% of patients in both sinecatechins ointment groups, with low rates of recurrence. Green tea catechins exhibit multiple biological activities, including potent antiviral and antioxidant effects. These catechins bind to various proteins, such as enzymes involved in the generation of inflammatory mediators, proteases that promote tumor invasion, and kinases essential for tumor cell signaling, cell cycle modification, and the induction of apoptosis. These proposed immune-stimulatory, antioxidative, antiviral, and antitumor properties likely contribute to the therapeutic effects of sinecatechins ointment.
3	Jing Lin et al.	2017	The application of TCM in HPV infection and related diseases based on clinical findings.	Japan	Review	30 articles	TCM has been shown to improve clinical outcomes in the treatment of cervical cancer and genital warts, with mechanisms of effectiveness

							potentially involving the regulation of cell apoptosis, viral gene transcription and translation, cell signal transduction pathways, and immune function. Given the absence of clinically recommended pharmacological therapies for HPV-related health issues, TCM remains a viable alternative due to its efficacy, safety, and low cost. Among these therapies, *dehydrocostus lactone*, a TCM used for a wide range of diseases, has demonstrated the ability to inhibit the proliferation and invasion of HeLa (HPV 18 positive) and C33A (HPV negative) human cervical cancer cell lines. This inhibition is associated with a reduction in phospho-protein kinase B (Akt) phosphorylation in a time- and dose-dependent manner.
4	Masatoshi Yokoyama et al.	2004	To investigate the effect of the major tea polyphenol, EGCG, on cervical carcinogenesis.	---	Cell growth rate was examined after treatment in organotypic culture	---	EGCG (*epigallocatechin gallate*) prevents the carcinogenesis of cervical cancer by inducing apoptosis and inhibiting telomerase activity. Polyphenols derived from green tea, particularly EGCG, have been shown to exhibit anticarcinogenic and chemopreventive effects both in vitro and in vivo. EGCG demonstrates growth-inhibitory activities against immortalized cell lines that represent various CIN (cervical intraepithelial neoplasia) premalignant lesions in a cervical oncogenesis model.
5	Samuel Pinya et al.	2019	Conducted to determine the potential clinical uses of mushrooms: reishi	Spain	Review	52 articles	Reishi, shiitake, and maitake are three mushrooms that hold significant importance in oriental culture and are increasingly utilized

			(*Ganoderma lucidum*), shiitake (*Lentinula edodes*), and maitake (*Grifola frondosa*).				in Western countries. Among their potential therapeutic applications, Ganoderma species are noted for their anti-cancer, anti-neurodegenerative, and anti-HIV properties. Polysaccharides derived from *Lentinula edodes* (shiitake) have been reported to exhibit a variety of bioactivities, with the most extensively studied being their antitumor and immunomodulatory effects. In vitro studies have demonstrated that polysaccharide fractions from shiitake mushrooms can inhibit the proliferation of a wide range of cancer cells and induce tumor cell apoptosis. Furthermore, a randomized dietary intervention involving healthy subjects showed that regular consumption of shiitake increased ex vivo proliferation of peripheral blood mononuclear cells, enhanced the expression of activation receptors, and boosted salivary immunoglobulin A production. To fully understand their therapeutic uses, further clinical studies are necessary to establish the therapeutic potential, appropriate dosages, and practical applications of these mushrooms.
6	TG Tzellos et al.	2011	Integrate valid information to provide a basis for rational decision-making regarding the efficacy and safety of green tea extracts in the treatment of EGW.	Greece	Systematic review and meta-analysis	3 articles	The efficacy of *Polyphenon E* at concentrations of 15% and 10% is clearly indicated, particularly for the primary endpoint. Treatment with *Polyphenon E* demonstrates very low recurrence rates (RRs) and appears to have a favorable safety and tolerability profile. Future studies should

							focus on evaluating the efficacy of green tea catechins in the treatment of internal anogenital warts, as well as conducting direct comparisons with its principal comparator, imiquimod.
7	Tomas Rokos et al.	2023	The use of medicinal mushrooms as a suitable adjunct in the treatment of various cancers or precancerous conditions, including those caused by the HPV virus.	Slovakia	Review	80 articles	Medicinal mushrooms are increasingly used in the prevention and treatment of various diseases, including as adjuncts to cancer therapy. *Coriolus versicolor*, a basidiomycete mushroom, contains glycoproteins known as PSK and PSP, which are primarily responsible for its effectiveness against a variety of cancers. Its beneficial effects stem from its ability to arrest different phases of the cell cycle, modulate immune responses, and induce apoptosis. Inhibition of proliferation has also been demonstrated in HeLa cells, while cervical cytology abnormalities improved in patients who locally applied *Coriolus versicolor*-based vaginal gel. Additionally, *Coriolus versicolor* extract, alone or in combination with another medicinal mushroom, *Ganoderma lucidum*, has been shown to enhance HPV clearance in patients who are HPV-positive, either cervical or oral.
8	Hung Q. Doan et al.	2015	Expression patterns of immune-associated genes in external genital and perianal warts treated with sinecatechins.	Texas	Gene expressi on analysis of RNA samples	18 patients with clinically diagnosed EGW	Green tea extracts, and sinecatechins in particular, have been shown to modulate various cellular processes, including apoptosis, inflammation signaling, and signal transduction pathways. Sinecatechin treatment modulates and

							downregulates genes involved in the pro-inflammatory response to HPV infection. This overall downregulation of immune regulatory genes, coupled with previous findings of the upregulation of apoptosis-associated genes in virological responders, suggests a comprehensive mechanism underlying the clearance of EGW.
9	Lesley M. Butler et al.	2011	Green and black tea in relation to gynecologic cancers	USA	Critical review	27 articles	Green tea catechins possess antiviral and immunomodulating properties in addition to their antitumor effects, which may provide protection against HPV-related cancers. Experimental evidence supports the antiviral and antitumor effects of the green tea catechin EGCG on HPV-positive cells and tumors, as well as its immunomodulatory effects in humans. The antiviral effects of EGCG are demonstrated in vitro by the downregulation of the HPV oncoproteins E6 and E7, which are essential for cervical carcinogenesis. However, observational data are needed to evaluate whether green tea reduces the risk of HPV-related cancers.
10	ChangpingZou et al.	2010	Evaluated the effects of green tea compounds (*epigallocatechin gallate* and *polyphenols E*) on immortalized cervical epithelial and cervical cancer cells	Tucson	Culture plates	1000 to 3000 cells per well in 96-well culture plates and treated on the second day with concentrations of 0, 1, 5, 10, 25, and 50 Kg/mL of EGCG or *poly E*.	The ability of green tea polyphenols (EGCG and *poly E*) to inhibit the proliferation of HPV-immortalized and HPV-positive cancer cells through cell cycle arrest at the G0/G1 phase seems to depend on the type of cervical cancer cells, specifically whether they are adeno or squamous carcinoma. Additionally, *poly E* was found to be less effective than EGCG in terms of growth

							inhibition and apoptosis. The observed cell growth inhibition is likely mediated by an upregulation of apoptotic-related genes or a downregulation of the HPV E7 oncoprotein, which triggers the pRb pathway and leads to the deregulation of cell cycle control. Future investigations will examine the in vivo effects of green tea compounds on persistent oncogenic HPV infection and low-grade cervical disease (CIN1) within the context of the currently ongoing chemoprevention trial.
11	Sara M. Meltzer et al.	2009	The activity and efficacy of green tea catechins in the management of EGW.	USA	Review	15 articles	The anti-inflammatory activity of green tea catechins can largely be attributed to their antioxidant actions. EGCG has been found to inhibit the activity of the transcription factors AP-1 and NF-kappa B, both of which mediate various inflammatory processes and can be activated by reactive oxygen species. Although Langerhans cells are often the first antigen-presenting cells to encounter infecting viruses in humans, these immune mediators are not activated by HPVs. However, catechins induce the release of several immune-stimulatory interleukins while simultaneously suppressing the release of immune-inhibitory interleukins. This process promotes the recruitment of monocytes, dendritic cells, lymphocytes, natural killer cells, and T-helper cells to enhance the immune response. *Polyphenon E* (Veregen) ointment, a botanical drug consisting of more than

							85% catechins, has been approved by the FDA for the topical treatment of anogenital warts. Its established efficacy in eradicating anogenital warts is attributed to its antiviral, immunostimulatory, and antioxidant mechanisms.
12	Noriyuki Miyoshi et al.	2020	Applications of a standardized green tea catechin preparation for viral warts and HPV-related and unrelated cancers.	Japan	Review	42 articles	These findings demonstrate the excellent efficacy of Polyphenon® E/sinecatechins/Veregen (PSV) on various types of warts without significant adverse effects, encouraging the application of PSV to certain HPV-mediated diseases. Several case reports have highlighted the effects of PSV on viral warts and other HPV-related conditions. Polyphenon® E has been shown to inhibit tumor growth by targeting myeloid-derived suppressor cells and CD8+ T cells, indicating immune activation, which aligns with the infiltration of activated T cells and the upregulation of pro-inflammatory cytokines in spontaneously regressed EGW. Additionally, EGCG was found to elevate the population of CD4+ T cells without affecting the population of CD8+ T cells in the spleen.
13	Tito Fernandes et al.	2021	Mushroom nutrition as preventive healthcare in Sub-Saharan Africa.	Portugal	Review	70 articles	The use of *Coriolus versicolor* biomass supplement in women over the course of one year revealed significant efficacy in both the regression of cervical dysplasia (LSIL) and the disappearance of high-risk HPV. This dietary supplementation demonstrated a positive therapeutic impact in reversing LSIL in patients who were HPV positive, as well as in

							those with HSIL who had undergone surgery, despite an increase in high-risk HPV viral count. These findings were subsequently replicated with AHCC, a fermented extract of cultured *Lentinula edodes* mycelia, which was administered for at least six months and achieved a 60% successful elimination rate of HPV infections in women with positive PAP smears. A recent study involving 42 patients indicated that the combination of *Coriolus versicolor* biomass administration yielded positive outcomes in cases of primary or recurrent genital warts.
14	Roberta Bilenchi et al.	2018	Sinecatechins 10% ointment for the treatment of genital warts.	Italy	Case report	A 38-year-old woman with a diagnosis of condyloma acuminatum	Sinecatechins ointments are effective in the treatment of external genital and perianal warts. Although the exact mechanisms of action are currently unknown, they likely involve antiviral, pro-apoptotic, and immunomodulatory responses. The antiviral properties may result from the inhibition of activator protein transcriptional activity, which effectively downregulates the expression of HPV genes. EGCG can activate pro-apoptotic proteins, and preclinical studies suggest that polyphenols may contribute to the modulation of inflammatory processes in skin disease. The treatment is generally well tolerated, with local skin reactions such as erythema, edema, and erosion being the most commonly reported side effects. These local reactions are induced by the stimulation of the

							immune system, leading to the release of pro-inflammatory cytokines. After two weeks of treatment, complete regression of inflammation and a reduction in genital warts were observed. The lesions completely regressed within a few weeks, with no relapse noted after eight months.
15	Heidi Collins Fantasi	2012	Sinecatechins ointment 15% for the treatment of EGW.	USA	Review	8 articles	Depending on the number and size of the EGW to be treated, women can expect to use 1 to 2 tubes of sinecatechins ointment (15%) each month. Catechins also possess immune-stimulating effects, along with antiviral and anticarcinogenic properties, which may inhibit enzymes involved in the pathogenesis of HPV. These mechanisms could contribute to the resolution of EGWs. Treatment should continue until all EGWs are cleared, but no longer than 16 weeks (4 months). Application involves placing approximately 0.5 cm of ointment on the fingertip and covering the entire wart(s) with a thin layer. The treatment areas do not need to be washed prior to the next application of ointment. Patients should be reminded to wash their hands before and after applying sinecatechins ointment (15%). It is not known whether sinecatechins ointment (15%) is excreted into breast milk. This medication has not been studied in pregnant women and is classified as pregnancy category C; therefore, it should only be used during pregnancy if the benefits outweigh any

							potential risks to the fetus. Additionally, sinecatechins ointment (15%) is not recommended for individuals who are infected with HIV, are immunocompromised, or have genital herpes, as safety and efficacy in these populations have not been established.
16	EggertStockfleth et al.	2012	To update the use of sinecatechins for the treatment of *condylomata acuminata* (CA) and to describe the possible mechanisms involved in their mode of action.	Germany	Review	52 articles	The clinical studies conducted with sinecatechins 15% ointment (Veregen) demonstrated good therapeutic efficacy and safety in the treatment of genital and perianal warts, achieving complete clearance rates of over 50%. Sinecatechins not only reduced baseline warts but were also effective against newly developed warts during treatment. A potential advantage over imiquimod and podophyllotoxin is that the recurrence rate following sinecatechins treatment appeared to be lower, likely due to the distinct mode of action of the catechins in the formulation. Although not yet conclusively demonstrated, the regression of wart lesions is likely attributed to the activation of cellular immune reactions, induction of cell cycle arrest and apoptosis, and inhibition of HPV transcription. This unique combination of molecular activities may facilitate the elimination of virus-infected cells, including both clinical and subclinical lesions, providing therapeutic antiviral efficacy that is at least comparable to that of imiquimod or podophyllotoxin. Thus, sinecatechins represent

							a safe and effective treatment option for cervical anogenital warts.
17	Elena Godoy-Gijon et al.	2017	Treatment of pediatric anogenital CA with sinecatechins ointment.	Spain	Case report	1 patient A 7-year-old girl with a 2 months history of genital warts	Condylomas completely disappeared after 9 weeks of sinecatechins topical application, with no adverse effects reported. There was no recurrence of the genital warts noted in a one-year follow-up, despite frequent relapses of the patient's atopic dermatitis. Recent studies have shown that sinecatechins modulate and downregulate genes involved in the pro-inflammatory response to HPV infection. The ointment has been approved by the FDA and EMEA for the treatment of genital warts in patients aged at least 18 years. It should be applied three times a day for up to 16 weeks or until lesion clearance, with clearance rates ranging from 45.5% to 64.9%. The treatment is generally well tolerated, with local skin reactions being the most common adverse effect. Limited data exist for pediatric use; however, a recent report documented the successful treatment of an 11-year-old boy with genital warts using 10% sinecatechins ointment. In our patient, improvement of the genital warts was evident from the first applications of the sinecatechins ointment.
18	Helmut Scho¨ fer1 et al.	2017	The existing guidelines for the treatment of external genital and perianal warts summarize the etiology, clinical features, diagnosis, and management of	Germany	Review	45 articles	Green tea sinecatechins show low RRs, as demonstrated in clinical trials, along with good tolerability, primarily resulting in mild to moderate local skin reactions. Physicians should consider initiating treatment with a physician-applied regimen for the quick

			the condition.				removal of EGW, followed by a topical immunomodulatory treatment that has proven low RRs to ensure sustained clearance and high patient acceptance. Experiences from clinical practice are encouraging; however, further clinical trials are needed to establish the benefits of this combination regimen.
19	Mei Luo et al.	2019	To explore detoxification therapy of TCM in the treatment of persistent high-risk HPV infections.	China	Systematic review and meta-analysis	17 articles	TCM has shown favorable outcomes in improving HPV clearance rates, increasing the regression rate of cervical intraepithelial neoplasia (CIN), and impacting the proportions of certain immune cells and cytokine levels. Specifically, TCM appeared to improve the HPV clearance rate, with an increased probability of clearance being 1.8-fold relative to follow-up groups and 2.6-fold compared to placebo. The regression rate of CIN was 3.6-fold higher relative to placebo and 1.8-fold compared to follow-up groups. Additionally, median HPV persistence tended to decrease with increasing follow-up time, declining from 50% (in 787 subjects) within six months after treatment to 41.5% (in 521 subjects). At 12 months, HPV persistence was observed in 31.5% of subjects (243 subjects) at 24 months. However, the pooled efficacy of TCM for persistent high-risk HPV (hr-HPV) clearance tended to decrease with increasing follow-up time. The most significant difference was noted within six

							months after the end of treatment, but this gradually approached the levels observed in the follow-up (or placebo) control groups by 24 months. The downward trend in median HPV persistence declined from 21% at six months to 10% at 24 months. Additionally, some trials with small sample sizes indicated that TCM has effects on certain immune cells and cytokine levels. It is speculated that TCM might achieve therapeutic goals by enhancing immune function over the long term.
20	Nasreen Bano et al.	2018	Differential inhibitory effects of curcumin between HPV-positive and HPV-negative oral cancer stem cells (CSCs)	India	RCT	Three cell lines, one HPV16+ve OSCC cell line, UD-SCC-2 (gift from Dr. Henning Bier, University of Dusseldorf, Germany), and two HPV–ve OSCC cell lines	Curcumin treatment at micromolar concentrations (0–50 μM) demonstrated significant differential inhibition of CSCs proliferation, orosphere formation, and miRNA-21 expression in a dose-dependent manner, with particularly pronounced effects in HPV-positive CSCs. The strong and dose-dependent inhibitory effects of curcumin on cell proliferation, stemness, and miRNA expression appear to be attributed to its chemosensitizing and anticancer properties, particularly in oral squamous cell carcinoma (OSCC) CSCs.

Ethical Considerations

Compliance with ethical guidelines

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Authors' Contributions

The authors contributed equally to the conceptualization and writing of the article. All authors approved the content of the manuscript and agreed on all aspects of the work.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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