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Effectiveness of Glycyrrhizinic Acid Compared to Trichloroacetic Acid in Condyloma Acuminata Treatment: A Literature Review

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KEY WORDS
Glycyrrhizinic Acid, Trichloroacetic Acid, Efficacy, Condyloma Acuminata.

ABSTRACT
Condyloma acuminata (CA), caused by low-risk HPV types 6 and 11, remains a widespread sexually transmitted infection that requires effective, safe, and patient-compliant treatment options. Conventional therapy using trichloroacetic acid (TCA) is effective but often results in discomfort and recurrence, thus prompting exploration of alternative treatments. This study aims to compare the effectiveness of glycyrrhizinic acid (GA), a novel self-applied antiviral and anti-inflammatory agent, with TCA in managing CA. A systematic literature review was conducted using PRISMA guidelines. Articles published between 2005 and 2025 were sourced from PubMed, ScienceDirect, and Google Scholar. Seven studies met the inclusion criteria and were analyzed qualitatively. The results show that both GA and TCA offer similar levels of efficacy in wart removal. However, due to its antiviral properties, GA demonstrated advantages in reducing side effects, improving patient compliance, and possibly lowering recurrence rates. GA was also preferred due to its self-application, offering convenience in outpatient settings. While promising, GA requires further research involving larger clinical trials and cost-effectiveness analysis. These findings support the potential of GA as a more patient-centered treatment option for immunocompetent individuals with CA.

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INTRODUCTION

Human papillomavirus (HPV) is known as the most common etiology of sexually transmitted diseases (STDs) in the world (Hirth, 2019). Condyloma acuminata is a benign neoplasm in the genital tract, caused by HPV types 6 and 11 infection. It is manifested by the appearance of warts in the vulvar, pubic, and anorectal regions, but can occur in other areas (Andriani, 2018; Csuk et al., 2012; Hutagalung & Wiraguna, 2021; Yenny & Hidayah, 2013). Condyloma acuminata in HIV patients tends to be more extensive than in the healthy population; they are also more resistant to therapy and have more recurrences (Damayanti & Susetiati, 2021). Nearly 80% of the world`s population is exposed to HPV, with the probability of infection exceeding 80% for women and 90% for males (Sindhuja et al., 2022).

Various modalities of therapy have been developed for the treatment of condyloma acuminata. Based on Asian Guidelines for condyloma acuminatum, the preferred treatment modality is based on the number and size of warts, and efficacy of the available therapies. Few small lesions are suggested to be treated with imiquimod 5% cream, 5-fluorouracil, and Polyphenon ointment. Surgery, cryotherapy, and podophyllotoxin application could be used for the treatment of a few larger lesions. For multiple lesions, combination therapies are recommended (Chauhan et al., 2018; Kaçar et al., 2012; Lynde et al., 2013; Mahajan et al., 2014; Tsao & Yin, 2015).

One of the most conventional therapies for condyloma acuminata is trichloroacetic acid (TCA). TCA has been widely used for the treatment of HPV lesions in gynecology. TCA produces denaturation, precipitation, and destruction of lesions via chemical coagulation of the affected tissue (Lorduy, 2018).

Although it is known to be effective in treating condyloma acuminata, its mechanism of action gives several adverse reactions (burning sensation, irritation, itching, pain, peeling, etc) that may cause discomfort (Recanati et al., 2018) .

Recently, novel therapeutic agents have been developed and shown to manage condyloma acuminata effectively. Glycyrrhizinic acid is one of the natural agents that shows promising results. Glycyrrhizinic acid is a natural triterpene saponin found in the root and rhizomes of plant species of the genus Glycyrrhiza (Glycyrrhiza glabra, G. uralensis, etc.), popularly known as liquorice. Several studies show its antiviral and anti-inflammatory properties, as well as fewer adverse effects (Bravo et al., 2023). However, further studies are still needed to explore its efficacy in managing condyloma acuminata. Therefore, this review aims to compare the effectiveness of Glycyrrhizinic acid and TCA in managing condyloma acuminata.

Condyloma acuminata (CA), or genital warts, is a significant manifestation of human papillomavirus (HPV) infection, predominantly caused by low-risk HPV types 6 and 11. The lesions are often benign but can cause substantial physical discomfort, emotional distress, and social stigma. In immunocompromised individuals, including those with HIV, CA tends to be more extensive, persistent, and difficult to treat, which underlines the need for effective and well-tolerated therapeutic options. Globally, CA represents one of the most common sexually transmitted infections, with up to 80% of the population exposed to HPV at some point in their lives. This prevalence creates an ongoing demand for safe, accessible, and patient-compliant treatments.

Current therapeutic options for CA include topical agents, surgical procedures, and immunomodulatory therapies. Treatment choice often depends on wart size, number, location, and patient preference. Trichloroacetic acid (TCA), a physician-applied caustic agent, remains a widely used and cost-effective standard treatment. It acts through chemical coagulation, leading to tissue necrosis. Despite its effectiveness, TCA is associated with adverse effects such as pain, burning, and local irritation, which may reduce patient compliance and necessitate multiple clinical visits.

Glycyrrhizinic acid (GA), derived from licorice root, is a novel therapeutic option with antiviral, anti-inflammatory, and immunomodulatory properties. It presents a self-applied alternative that has shown promise in the treatment of CA. Preliminary studies suggest that GA may achieve comparable efficacy to conventional agents while offering advantages in terms of fewer side effects, ease of use, and improved patient adherence. Furthermore, GA may act beyond wart removal by targeting the underlying viral infection, potentially reducing recurrence rates, which is a limitation in many conventional therapies.

The pharmacological mechanisms of GA include inhibition of viral gene expression, modulation of immune responses, and suppression of inflammatory mediators. These properties make it a unique candidate among CA treatments, especially in the context of home-based care and in regions with limited access to specialist services. Given its potential for enhancing treatment compliance and reducing healthcare burdens, GA merits closer comparison with established treatments like TCA in terms of both clinical outcomes and patient experience.

Despite its potential, glycyrrhizinic acid has yet to be widely accepted as a first-line agent due to limited comparative studies and a lack of long-term efficacy data. Most existing literature focuses on case reports, in vitro analyses, or trials with small sample sizes. Therefore, synthesizing available data into a systematic literature review allows for a more comprehensive evaluation of its effectiveness and limitations. Such a review is critical to understanding where GA fits within the broader landscape of CA management.

In light of the growing interest in patient-centered care and minimally invasive therapies, this review seeks to provide clinicians with an evidence-based comparison between glycyrrhizinic acid and

trichloroacetic acid. By focusing on clinical efficacy, recurrence rate, safety profile, and patient compliance, this study contributes to informed decision-making in the management of condyloma acuminata. It also identifies knowledge gaps for future research, including the need for standardized protocols and broader trials evaluating glycyrrhizinic acid across diverse patient populations.

Condyloma acuminata, or genital warts, remains a significant public health issue globally, especially among sexually active populations. It is caused primarily by low-risk strains of the human papillomavirus (HPV) such as types 6 and 11. While not life-threatening, the condition can result in psychological distress, discomfort, and complications in immunocompromised individuals, such as those with HIV. The standard treatment approaches often focus on physical removal of warts through chemical agents, surgical excision, or immunotherapy. However, these treatments' high recurrence rates and adverse effects remain a problem, impacting patient satisfaction and compliance.

Trichloroacetic acid (TCA) has long been a preferred conventional treatment due to its affordability and efficacy. However, its side effects—burning, pain, irritation, and the need for professional application—limit its practicality for long-term and self-managed care. Glycyrrhizinic acid (GA), a natural compound with antiviral and anti-inflammatory properties, has emerged as a potentially superior alternative. Nonetheless, its effectiveness, safety, recurrence rate, and patient convenience compared to TCA have not been widely or systematically analyzed, leading to uncertainty about its standing in standard clinical protocols.

With the increasing global prevalence of HPV infections and the demand for safe, accessible, and patient-centered treatments, the need for an effective, minimally invasive, and low-recurrence therapy for condyloma acuminata is urgent. Especially in low-resource or high-burden settings, a self-applied, low-side-effect treatment such as glycyrrhizinic acid could significantly improve healthcare delivery and patient compliance. This urgency is compounded by the limitations of conventional treatments like TCA, which, despite being effective, often cause pain and require multiple clinical visits.

Previous studies have confirmed the effectiveness of TCA in removing condyloma acuminata lesions. For example, Taner et al. (2007) showed a complete response to TCA treatment in 100% of patients by week 5, although recurrence was noted in 17.6% within a year. Similarly, Recanati et al. (2018) observed that while TCA achieved lesion clearance, it caused more scarring and pain compared to cantharidin.

On the other hand, early studies on glycyrrhizinic acid, such as those by Valencia et al. (2011) and Hana et al. (2005), reported promising efficacy, including complete lesion regression with minimal side effects. Gomez et al. (2012) found that GA, combined with oral immunostimulants, had an efficacy rate of 87.5%, outperforming podophyllin in terms of side effects and patient comfort.

While TCA's efficacy is established, it is often associated with discomfort and requires professional administration. In contrast, GA shows potential as a self-applied alternative with both antiviral activity and improved tolerability, although fewer studies have explored its long-term effectiveness, cost efficiency, or recurrence rates compared to traditional methods.

Despite encouraging early findings, there is limited comparative research that evaluates glycyrrhizinic acid and trichloroacetic acid side-by-side using standardized clinical outcomes. Specifically, data on recurrence rates, safety profiles, cost-effectiveness, and patient satisfaction with GA remain sparse. Additionally, most studies on GA involve small sample sizes or are observational in design, which limits their generalizability. This review seeks to address this gap by systematically synthesizing the best available evidence.

This study offers a novel perspective by directly comparing two widely used yet clinically distinct treatment agents—TCA and GA—across four essential criteria: efficacy, safety, recurrence, and user-friendliness. By applying a systematic review method aligned with PRISMA guidelines and

utilizing data from diverse clinical settings, this research provides a more comprehensive picture of how GA could be integrated into modern condyloma acuminata management.

The objective of this study is to systematically compare the effectiveness of glycyrrhizinic acid and trichloroacetic acid in the treatment of condyloma acuminata, focusing on four key indicators: clinical efficacy, recurrence rates, adverse effects, and patient convenience. The ultimate goal is to provide clinicians with evidence-based insights to guide therapeutic decision-making for genital warts.

This research benefits the medical community by offering an evidence-based evaluation of a potentially superior, self-administered topical treatment for condyloma acuminata. It provides critical insights for dermatologists, gynecologists, and public health policymakers in selecting treatments that are not only clinically effective but also safer and more accessible. Additionally, it encourages future research into the broader use of glycyrrhizinic acid in immunocompromised populations and supports the development of patient-centered care strategies in sexually transmitted infection management.

METHODS

The research used a systematic literature review method based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The researchers used structured keyword combinations to collect relevant articles published between 2005 and 2025 from databases such as PubMed, ScienceDirect, and Google Scholar. Inclusion criteria were applied to English-language, open-access, full-text journal articles focused on condyloma acuminata treatments using glycyrrhizinic acid and trichloroacetic acid. After screening, seven articles were selected for qualitative synthesis. Data extraction focused on population characteristics, treatment modalities, comparative outcomes (efficacy, safety, recurrence), and study design. The findings were summarized thematically to compare both treatments across standardized clinical endpoints, providing an evidence-based foundation for evaluating their respective effectiveness and patient compliance.

The review process was carried out based on the PRISMA protocol. The inclusion criteria for articles reviewed by researchers include: (1) English journals; (2)Published in 2005-2025; (3) Open-access. The exclusion criteria used by researchers include: (1) the topic of the article is not relevant to the study objectives; (2) the article is not a full text; (3) the article is the result of proceedings or conferences.

Table 1. PICO Criteria

PICOS framework	Inclusion Criteria	Exclusion Criteria
Population	Genital HPV infection or Condyloma acuminata patients	Other wart types population
Intervention	Glycyrrhizinic acid Trichloroacetic Acid	There were no exclusion criteria
Control	Preintervention results, other topical agents	Non-pharmacological therapy
Outcome	Efficacy, recurrence rate, safety	There were no exclusion criteria
Study design	Randomized control trial, cross-sectional, cohort, observational studies, retrospective study	Case-control, literature review

Articles were identified from databases including PubMed, Science Direct, and Google Scholar. Researchers used a combination of keywords from Boolean operators, namely ("glycyrrhizinic acid"

OR “licorice” OR “liquorice” AND “condyloma acuminata” OR “genital warts” OR “genital HPV infection”) and ("Trichloroacetic acid" OR “TCA” AND “condyloma acuminata” OR “genital warts” OR “genital HPV infection”). Article eligibility checks were carried out based on the established PICO criteria (Table 1).

The final stage of this study was data extraction. The extracted data included the author's name and year of publication, the number and characteristics of participants, the type of intervention and its comparator, and the measurement of outcomes in both groups. Data were collected manually from selected articles and arranged in tables. A qualitative synthesis was then carried out.

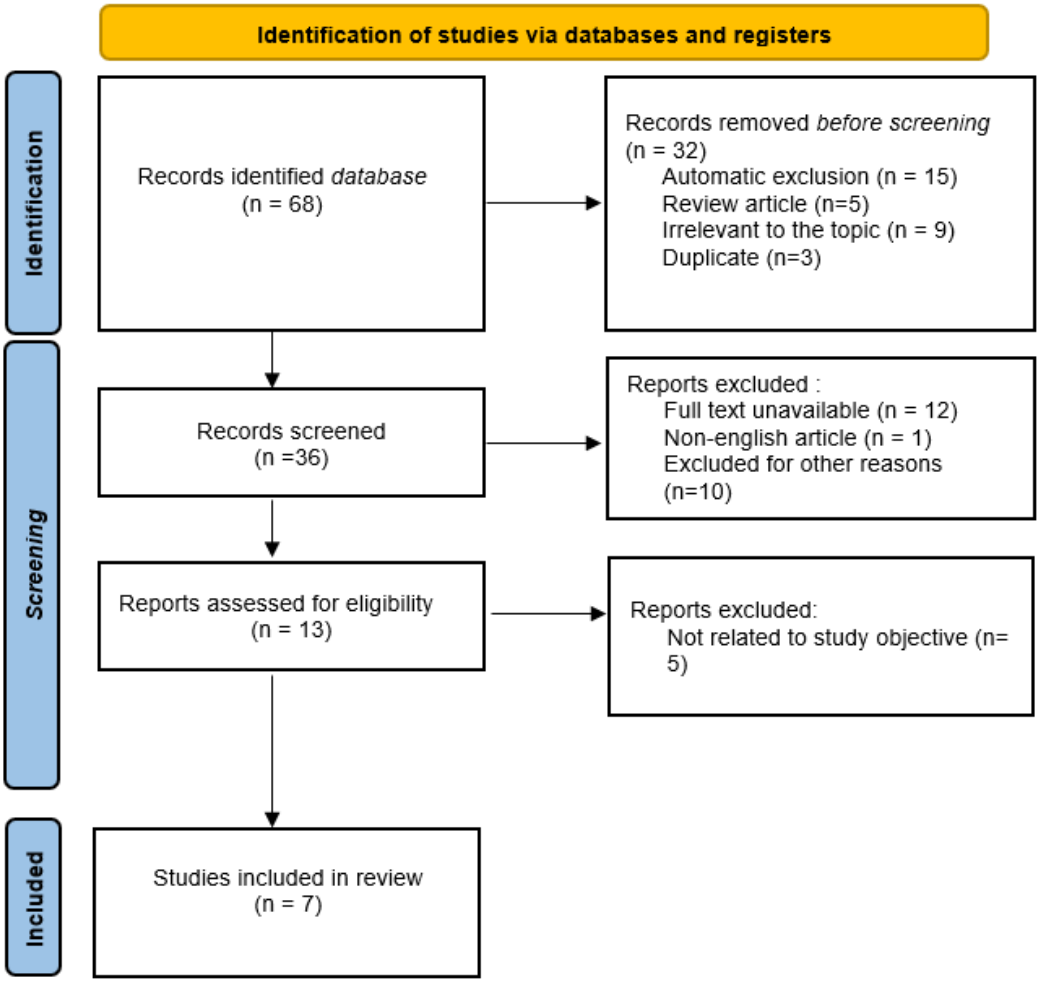

Figure 1. Article Selection Process

RESULTS AND DISCUSSION

Study selection

Based on the journal search results using keywords, 24 articles were found. After exclusion using an automated tool (n=15), review article (n=5), irrelevant to the topic (n=9), duplicate article (n=3), full articles unavailable (n=12), non-English article (n=1), not relate to study objective (n=5), and excluded for other reasons (n=10), 7 articles were obtained that were analyzed qualitatively.

Table 2. Summary of Studies

Author	Population	Intervention	Comparison	Outcome
				Efficacy
Valencia, et.al (2011)	70 HPV infection patients	Oral and spray of Glycyrrhizinic acid in 8 weeks	Pre-intervention result	• Recovery was achieved in all patients with GA, which was observed from 4 weeks of treatment initiation, but without a significant difference. Improvement in most patients (74%) was demonstrated at 12 weeks (P<0.05), and in all patients after 13 weeks (P<0.001)
Hana et.al (2005)	10 condyloma acuminata patients (5 men and 5 women)	Glycyrrhizinic acid 0,1 g in 100 ml excipient, applied 3-5x/day for 7-60 days	Pre-intervention results	• The application of Glycyrrhizinic acid on small condyloma (up to 1 mm) had an excellent effect and was well tolerated. The regression of the finding was evident within 7 up to the maximum of 14 days. In the end, the lesions were healed. • No relapses have been recorded.
Gomez, et.al (2012)	100 patients with anogenital warts	Glycyrrhizinic acid spray + oral immunostimulant for 8 weeks	Podophyllin 25% once a week for 6 weeks	• The combined Glycyrrhizinic acid spray + oral immunostimulant treatment was seen to have an 87.5% efficacy rate, which was slightly more than that of the treatment with podophyllin • There were less adverse reactions related to treatment (burning sensation, pain, itching), compared to the podophyllin group (18% vs 46%)
Anggraini et.al (2020)	72 anogenital wart patients	90% trichloroacetic acid	1% 5-fluorouracil, 5% 5-fluorouracil cream	• Evaluation at week 7 demonstrated no significant difference in the efficacy between 1% 5-FU cream and 90% TCA (p = 0.763) or between 5% 5-FU cream and 90% TCA (p = 0.274). • Subjective side-effects with 1% and 5% 5-FU were significantly milder than 90% TCA
Recanati, et.al (2018)	12 genital warts patient	Trichloroacetic acid	Cantharidin 0,7% cream	• Patients treated with TCA healed with more scarring than those treated with Cantharidin (P<0.034). • Cantharidin required significantly fewer treatments (2.21 vs 3.07) to eradicate warts (P=0.012). • Overall amount of pain experienced by patients in the cantharidin group was significantly less than that of the TCA group, both at the time of treatment (P<0.01) and at the 2-week follow-up visit (P<0.02).

Taner, et.al (2007)	51 vulvar and/or perianal genital warts	85% Trichloroacetic acid	Preintervention results	• All lesions were successfully treated by the end of the treatment period (median, 4; range, 2-5). • None of the patients had recurrence or new lesions during the 6-month follow-up period. In the second 6 months, 9 patients (17.6%) were diagnosed with recurrent lesions. • Although all the patients experienced transient burning pain during therapy, none of them discontinued the therapy. Ulceration was observed in 8 patients (15.6%). Of those patients, only 3 had permanent scarring (5.8%).
Karaca, et.al (2007)	35 condyloma acuminata patients	80% trichloroacetic acid	5-Fluoruracil	• No significant difference was detected between the groups with respect to response to additional treatment (p=0.574) • Recurrence was detected but not statistically significant (TCA= 6 patients; 5-FU= 1 patient) • In comparison to the cost per patient, the average cost was detected to be 2 USD for the trichloroacetic acid group and 20 USD for the 5-fluorouracil group.

Comparison of efficacy

Valencia et al. (2011) found a significant effect of Glycyrrhizinic acid on HPV infection. Recovery was achieved in all patients with the use of Glycyrrhizinic acid, which was observed from 4 weeks of treatment initiation, but without a significant difference. Improvement in most patients (74%) was demonstrated at 12 weeks ($P<0.05$), and in all patients after 13 weeks ($P<0.001$). A similar result was also found in Hana et. al.'s (2005) study. The application of Glycyrrhizinic acid on small condyloma had an excellent effect. The regression of the finding was evident within 7 up to the maximum of 14 days. Gomez et.al (2012) studied the efficacy of Glycyrrhizinic acid spray combined with oral immunostimulant as condyloma acuminata treatment. The results showed an 87.5% efficacy rate, which was slightly more than that of the treatment with podophyllin (Zelenkova, 2005).

As one of the most common treatment applications, TCA application shows similar effectiveness. When it is compared to cantharidin, as stated in the article by Recanati et.al (2019), patients treated with TCA healed with more scarring than those treated with Cantharidin ($P<0.034$). Patients treated with TCA also require more treatment sessions (2.21 vs 3.07) to eradicate warts ($P=0.012$).

Compared with 5-fluorouracil, two studies showed no significant difference in TCA efficacy. Anggraini et.al (2020) stated that there was no significant difference in the efficacy between 1% 5-FU cream and 90% TCA ($p = 0.763$) or between 5% 5-FU cream and 90% TCA ($p = 0.274$)[10]. Research conducted by Karaca et.al (2007) also found no significant difference between the groups with respect to response to additional treatment ($p=0.574$) (Domínguez Gómez et al., 2012).

Recurrence rate after complete therapy response

There are limited studies on the recurrence rate of condyloma acuminata after glycyrrhizinic acid treatment. Hana et al.'s (2007) study detected no relapse cases after treatment. However, there is no more detailed information about relapse evaluation, such as follow-up duration, frequency, etc.

In contrast, TCA treatment is considered to have a higher recurrence rate compared to other topical agents. Taner et.al (2007) found no recurrence or new lesions during the 6-month follow-up period. But, in the second 6 months, 9 patients (17.6%) were diagnosed with recurrent lesions (Anggraini et al., 2020)Recurrence was also detected in the Karaca et al. (2007) study, but it was not statistically significant (TCA=6 patients; 5-FU=1 patient).

Safety profile

A study conducted by Gomez et.al (2012) shows fewer adverse reactions related to treatment (burning sensation, pain, itching) in the glycyrrhizinic acid group, compared to the podophyllin group (18% vs 46%). Contrary to glycyrrhizinic acid, some studies found that TCA causes more adverse effects, compared to other topical agents. Anggraini et.al (2020) found that subjective side-effects with 1% and 5% 5-FU were significantly milder than 90% TCA. A study by Recanati et.al (2018) also stated that the overall amount of pain experienced by patients in the cantharidin group was significantly less than that of the TCA group, both at the time of treatment ($P<0.01$). In Taner et. al.'s (2007) study, ulceration was observed in 8 patients (15.6%), and 3 patients had permanent scarring (5.8%).

Discussion

Condyloma acuminatum (CA) is primarily a sexually transmitted disease (STD) marked by the development of soft, flesh-colored papules in the anorectal area, resulting from an infection with various strains of human papillomavirus (HPV). CA typically does not cause significant damage to patients; however, more severe cases can develop, which are often seen in immunocompromised patients, leading to the enlargement of warty growths that may block or disrupt the normal functioning of some anatomical regions (Taner et al., 2007). Prevalence and recurrence of CA were higher in immunocompromised patients, including HIV patients. In addition, HIV infection enhances the reactivation and expression of latent HPV infection due to its immune deficiency.

The currently available treatments for CA mainly focus on removing the wart growths rather than eliminating the underlying viral infection. A treatment that has antiviral effects on human papillomavirus would give more success and lower recurrence rates. There is limited evidence regarding the long-term effectiveness of these treatments in eradicating genital warts or in preventing them from developing into potentially malignant lesions. As for now, there is no single therapy that has been established as the gold standard for CA treatment; instead, the choice of therapy depends on the individual characteristics of the patient (Karaca et al., 2007).

One of the alternative topical agents for CA treatment is glycyrrhizinic acid. Several studies show its efficacy in removing CA warts (Özkaya et al., 2023). Moreover, in Valencia et al. 's study, glycyrrhizinic acid also exhibits antiviral properties that are effective for eliminating HPV infection.

It is known that the antiviral effect of glycyrrhizinic acid is obtained by increasing the production of viral cyclin, which induces the selective death of virus-infected cells. GA also stimulates the production interleukin-12 in macrophages, which facilitates the development of T-helper lymphocytes in cell-mediated immune response, inhibits viral protein phosphorylation mediated by cellular kinases, and modifies the posttranslational signals essential for growth. It also promotes inhibition of prostaglandin E2 in damaged tissue, causing inflammation and increased tissue damage and inducing interferon production, which promotes the activation of macrophages and, consequently,

an increase in their phagocytic properties and destruction of microorganisms. This mechanism also promotes its anti-ulcerous and anti-inflammatory effects (Diţescu et al., 2021).

Trichloroacetic acid (TCA) is a destructive acid that causes protein coagulation and cellular necrosis. TCA is suitable for both non-keratinized (mucosal) and keratinized areas. TCA treats CA by causing chemical coagulation, protein denaturation, and cell death of tissue proteins. While TCA treatment is somewhat effective and relatively cheap, its side effects include irritation, pain, and peeling.

Although these agents show similar effectiveness in CA treatment, they have several differences. TCA must be applied by a physician approximately 4–6 times until complete alleviation of the warts. The requirement for long-term treatment and weekly visits may reduce treatment compliance. Since glycyrrhizinic acid is a self-applied treatment, it could increase patient compliance and give more favourable outcomes. Glycyrrhizinic acid application should be repeated in several weeks until the warts fully heal. Studies also show milder adverse effects after glycyrrhizinic acid treatment, which helps to maintain patient convenience and affects their treatment compliance.

There are some limitations in this systematic review. The research lacks papers that discuss the recurrence rate, safety, and cost-effectiveness of glycyrrhizinic acid as CA treatment compared to TCA. Further study is needed to compare the efficacy and safety of glycyrrhizinic acid and TCA as CA treatment.

CONCLUSION

Condyloma acuminata is a benign genital neoplasm caused by human papillomavirus (HPV) infection, and various treatment approaches have been developed to align with patient characteristics and preferences. Due to its availability and effectiveness, trichloroacetic acid (TCA) remains a widely used conventional therapy. However, glycyrrhizinic acid has emerged as a novel, minimally invasive, self-applied agent showing promising results in condyloma acuminata treatment. Its antiviral and anti-inflammatory properties assist in wart removal and contribute to viral suppression, making it a potentially superior non-surgical option compared to TCA, particularly for immunocompetent individuals. Despite these advantages, glycyrrhizinic acid may not be suitable for immunocompromised patients, limiting its generalizability in broader clinical settings. Therefore, future research should explore its efficacy in diverse patient populations, including those with compromised immune systems, and conduct large-scale, randomized controlled trials comparing long-term outcomes, recurrence rates, cost-effectiveness, and patient satisfaction between glycyrrhizinic acid and conventional agents like TCA to develop comprehensive clinical guidelines.

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