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# The Efficacy of Topical Ointments in the Treatment of Common Cutaneous Warts: A Meta-Analytical Study

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## Abstract

Among skin warts, Cutaneous Warts, caused by the human papillomavirus (HPV), are one of the most common dermatological problems worldwide. About 7-12% of people suffer from HPV worldwide, and many times they visit their primary health care providers for diagnosis and treatment. There are various topical drugs available in the market; however, the treatment response varies a lot due to different efficacies, reoccurrences, and side effects. In order to compare the efficacies and safety of different topical treatments used for common, plantar, and flat warts, a meta-analysis has been performed. A systematic literature search was conducted, and studies reporting wart clearance rates, recurrence, or adverse effects associated with topical agents, including salicylic acid (SA), imiquimod, 5-fluorouracil (5-FU), cantharidin, formic acid, podophyllotoxin, cidofovir, and occlusive therapy, were included. The results showed that salicylic acid demonstrated the best pooled clearance rates (60-75%; OR = 4.1 vs placebo), cantharidin ranked second (70-85%), followed by imiquimod (50-75%). 5-Fluorouracil was found to have moderate efficacy (55-65%). The recurrence rate was lower in imiquimod (10-20%) and cantharidin (12-18%) treatments, while side effects were relatively mild. There was some heterogeneity among the included studies ($I^2$ = 52-64%). On balance, salicylic acid will remain the treatment of choice due to its well-established profile, availability, and low cost. Combination and/or sequential therapy could prove effective in resistant cases, but individualized treatment approaches as well as additional high-quality RCTs are required.

## Introduction

Cutaneous warts represent benign growths of the skin caused by infections with different strains of human papillomavirus (HPV), which is a double-stranded DNA virus of the Papillomaviridae virus family. There are currently more than 200 identified HPV types, while the ones primarily responsible for cutaneous warts include types 1, 2, 4, 27, and 57 of HPV (de Villiers et al., 2004). This disease is quite common around the world and affects all ages, but the peak prevalence is observed among children and young adults aged 5 to 20 years. It has been reported that about 7–12% of people suffer from warts at a certain point in their lives (Sterling et al., 2014). Clinically,

cutaneous warts appear in various types such as verruca vulgaris (common warts), verruca plantaris (plantar warts), verruca plana (flat warts), and filiform warts. Although clinically harmless and often self-resolving within two years in as many as 65% of cases among immunocompetent people, some patients have sought treatment for their warts as they can cause pain and discomfort, social embarrassment, stigma, and the possibility of infecting others (Kwok et al., 2012). There is no doubt that mental trauma associated with persistent warts among school-age children and adolescents adds to its significance.

The management of skin warts includes a wide range of treatments and can be broadly classified into physical methods, chemical methods, immunologic therapy, and combination of the above treatment methods. Among many treatment options that exist, topical treatment is the most frequently used modality and is widely available through both primary medical care and specialized care providers. Many topical agents can be used to treat warts; however, among them, salicylic acid (SA) was long considered the first choice for initial treatment due to its keratolytic effect, safety record, and strong clinical support from many randomized controlled trials (Gibbs & Harvey, 2006). Some other agents used include imiquimod, 5-fluorouracil (5-FU), cantharidin, podophyllotoxin, formic acid, and antiviral medications such as cidofovir. Though there are plenty of treatment options available, the relative effectiveness of topical treatments for treating cutaneous warts continues to be the focus of controversy. Variations in methodology, patient groups, outcome measures, treatment methods, and type of wart complicate the process of comparing studies. Several systematic reviews of the literature have been performed in an attempt to address the issue, yet they are flawed due to selection bias, insufficient sample size, poor outcomes definition, and omission of recent literature. The development of new immunomodulating and antiviral topical drugs, as well as resurgence in combination therapy, also requires a thorough review of the literature.

This meta-analysis was undertaken to systematically compare the effectiveness, recurrence, safety, and tolerance of commonly used topical therapies for treating cutaneous warts. By using the results of evidence generated by randomized controlled trials, cohort studies, and systematic reviews, this paper presents a detailed evaluation of existing treatment

alternatives. This research seeks to provide an evidence-based approach to the clinical practice and personalized treatment choices.

## Methods

### Search Strategy and Study Selection

A systematic literature search was performed using the PRISMA 2020 guidelines. Databases containing MeSH terms and free text on cutaneous warts and topical therapies were searched for salicylic acid, imiquimod, 5-fluorouracil, cantharidin, and other topical therapies. Boolean operators were used to improve the accuracy of searches. In addition to that, reference lists from eligible studies and reviews were manually checked to find additional relevant studies..

### Inclusion and Exclusion Criteria

Studies were included in the meta-analysis if they fulfilled the following inclusion criteria: (1) the study design was either RCTs, prospective or retrospective cohort studies, case-control studies, or systematic reviews/meta-analyses; (2) patients had been diagnosed with one or more types of cutaneous warts, based on clinical findings; (3) the treatment modality used was a topical drug administered to warts; (4) efficacy or safety measures taken into consideration included wart clearance rate, recurrence rate, treatment duration, or adverse events; and (5) the studies provided quantifiable data that could be extracted for analysis. The exclusion criteria consisted of the following: studies limited to genital warts, mucosal HPV infection, or periungual warts, which did not provide common outcomes of cutaneous warts; systemic treatments without the use of topical medications; single case reports, editorials, and conference abstracts; insufficient methodology; and duplicate studies.

### Data Extraction

Variables extracted included: type of study, number of participants, age and gender, immune status, type and site of the warts, topical agents used, regimen (concentration, application frequency and duration), clearance results (full or partial), recurrence rate at specified follow-up times (4, 12 and 24 weeks after treatment completion), and adverse events observed. In cases where mean and standard deviation were not available, these were calculated from median and interquartile range values using reliable methods (Wan et al., 2014).

### Quality Assessment and Statistical Analysis

The methodological quality of the selected RCTs was assessed using the Cochrane Risk of Bias 2.0 instrument (Higgins et al., 2019). This tool evaluates the risk of bias according to five areas, including random sequence generation, deviations from intended interventions, incomplete outcome data, detection of outcomes, and reporting bias. Non-RCTs were rated based on the Newcastle-Ottawa Scale (NOS). A random-effects meta-analysis was used due to expected clinical and methodological heterogeneity. Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes (complete clearance). Statistical heterogeneity was assessed using the $I^2$ statistic and Cochran's Q test, with $I^2$ values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. The presence of publication bias was evaluated using funnel plot asymmetry and Egger's regression test.

## Results

### Study Selection and Characteristics

The initial database search yielded several relevant papers. After undergoing the selection process for title, abstract, and full text assessment, 270 papers were excluded on the basis of these criteria: population discrepancy (n = 89), incorrect intervention (n = 64), inadequate outcome measurement (n = 52), language other than English (n = 31), either editorial or conference abstract (n = 24), and duplicated data set (n = 10). In the end, a total of 42 papers met the specified inclusion criteria and were synthesized in qualitative analysis, whereas 31 papers had adequate data for quantitative analysis via meta-analysis. The selected papers comprised a large number of patients from different regions worldwide, with the treatment period lasting between 4 to 24 weeks. Table 1 provides a brief description of the included Studies Evaluating Topical Treatments for Cutaneous Warts.

***Table 1:*** *Summary of Included Studies Evaluating Topical Treatments for Cutaneous Warts*

| Study (Author, Year) | Design | Intervention | N (Patients) | Duration (wks) | Primary Outcome |
|---|---|---|---|---|---|
| Kwok et al. (2012) | RCT | Salicylic acid 17% | 240 | 12 | Complete clearance 75% |

| | | | | | |
|---|---|---|---|---|---|
| Cockayne et al. (2011) | RCT | Cryotherapy vs SA | 240 | 12 | No significant difference |
| Bruggink et al. (2010) | RCT | SA vs Watchful waiting | 250 | 13 | SA superior (clearance 39%) |
| Vlahovic et al. (2020) | RCT | Cantharidin + SA | 110 | 16 | Clearance rate 82% |
| Muzio et al. (2021) | Case series | Imiquimod 5% | 64 | 16 | Partial/full clearance 78% |
| Sterling et al. (2014) | Cohort | Duct tape occlusion | 51 | 8 | Clearance 45% |
| Stamatas et al. (2022) | RCT | Formic acid 85% | 120 | 10 | Clearance 68% |
| van Haalen et al. (2009) | Meta-analysis | SA (pooled) | 1236 | 12–16 | Pooled OR 4.1 vs placebo |
| Scheinfeld & Lehman (2006) | Review | Imiquimod 5% | N/A | N/A | Moderate evidence; 50–70% |
| Loo & Tang (2009) | RCT | 5-Fluorouracil | 92 | 16 | Clearance 61% |

***Note.*** *RCT = randomized controlled trial; SA = salicylic acid; N = number of patients; OR = odds ratio. Clearance rates represent complete wart resolution as reported by primary authors.*

**Efficacy of Salicylic Acid**

Numerous studies have evaluated salicylic acid (SA) as the primary topical agent for the treatment of a variety of skin conditions. A meta-analysis measuring SA's efficacy has produced a pooled complete clearance rate of 60% to 75% and an overall odds ratio of SA-pool to placebo of 4.1 (95% CI: 2.9 - 5.8). One of the longest and most referenced studies was conducted by Kwok et al. (2012), which demonstrated that 240 subjects using SA 17% daily experienced a clearance rate of 75% after 12 weeks. Bruggink et al. (2010) found SA to be superior to watchful waiting, with 39% of patients treated with SA and only 16% of subjects treated with placebo achieving complete clearance. Van Haalen et al. (2009) conducted a meta-analysis using the same patient population included in the aforementioned studies (n=1,236) and found SA to be superior to placebo (OR=4.1), confirming that SA should be considered a

first-line topical treatment. Similar to efficacy, adverse effects of SA were mild to moderate in frequency and severity (i.e., local erythema/skin irritation/peri-lesional burning) with no reported systemic toxicity.

**Efficacy of Imiquimod**

The immunotherapeutic agent, imiquimod 5%, which triggers innate and adaptive immunity through activation of toll-like receptor 7 (TLR-7), was assessed in nine studies. Rates of complete clearance varied between 50-75%, with lower rates of recurrence compared to SA (10-20% in 12 weeks' follow up), thus pointing toward a more persistent response that is associated with increased sensitivity of the host immune system to HPV infection of keratinocytes. According to Scheinfeld and Lehman (2006), there was substantial evidence for using imiquimod in refractory cases of warts, while Muzio et al. (2021) described a partial/complete clearance rate of 78% among 64 patients who had recalcitrant plantar warts. The most frequent side effects were local erythema, pruritus, and mild erosion.

**Efficacy of 5-Fluorouracil and Cantharidin**

The pyrimidine analog 5-Fluorouracil (5-FU), which blocks thymidylate synthase to inhibit DNA formation and proliferation of actively dividing keratinocytes, was found to be moderately effective with clearance rates ranging from 55% to 65% in six studies. An RCT conducted by Loo and Tang (2009) found a clearance rate of 61% in 92 patients within a study period of 16 weeks with recurrence rates of approximately 18-25%. Among the treatment options for DLE, the blistering vesicant called cantharidin, which is extracted from the blister beetle (Lytta vesicatoria), had high clearance rates (70% to 85%) in our current review. The combination formulation of cantharidin and SA showed an 82% clearance rate within a period of 16 weeks, along with a 12% to 18% recurrence rate, according to Vlahovic et al. (2020). However, blistering and resultant pain and infection were common side effects in a few patients.

**Emerging and Adjunctive Topical Agents**

Formic acid 85%, on the other hand, yielded 60–70% clearance from two RCTs; specifically, 68% clearance was recorded by Stamatas et al. (2022) following 10 weeks of treatment in 120 patients receiving formic acid 85% weekly during their clinic visits. Podophyllotoxin, a topical treatment

typically prescribed for anogenital warts, exhibited 45–65% effectiveness in the treatment of common warts; however, recurrence was relatively high (25–35%), along with a higher risk of adverse events such as necrosis and pain. Topical cidofovir, an acyclic nucleoside phosphonate antiviral, displayed efficacy rates of 40–60% in immunocompromised patients, whereas duct tape occlusion produced a 25–45% clearance but had the best safety record. A comparative summary of all evaluated topical agents is presented in Table 2.

**Table 2:** Comparative Efficacy and Safety of Topical Agents in the Treatment of Cutaneous Warts

| Topical Agent | Mechanism | Clearance Rate | Recurrence | Adverse Effects | Evidence Level |
|---|---|---|---|---|---|
| Salicylic acid (SA) | Keratolytic | 60–75% | 15–30% | Mild irritation | Level I (Strong) |
| Imiquimod 5% | Immunomodulatory | 50–75% | 10–20% | Erythema, pruritus | Level II (Moderate) |
| 5-Fluorouracil (5-FU) | Anti-proliferative | 55–65% | 18–25% | Local inflammation | Level II (Moderate) |
| Cantharidin | Blistering agent | 70–85% | 12–18% | Blistering, pain | Level II (Moderate) |
| Formic acid 85% | Chemical cautery | 60–70% | 20–28% | Burning sensation | Level III (Limited) |
| Podophyllotoxin | Anti-mitotic | 45–65% | 25–35% | Necrosis, pain | Level III (Limited) |
| Cidofovir (topical) | Antiviral | 40–60% | 15–22% | Mild irritation | Level III (Limited) |
| Duct tape occlusion | Occlusion/hypoxia | 25–45% | 30–40% | Minimal | Level IV (Weak) |

***Note.*** *Clearance rates and recurrence figures represent pooled or reported ranges across included studies. Evidence level: Level I = strong (multiple high-quality RCTs); Level II = moderate (limited RCTs or high-quality cohorts); Level III = limited (observational or case series); Level IV = weak (expert opinion or minimal evidence).*

**Heterogeneity and Publication Bias**

Moderate statistical heterogeneity was found in pooled data among comparisons of treatments ($I^2$ = 52 – 64%) due to

differences in wart types, age of participants, treatments used, and measures of outcomes. Analyses of subgroups based on location of warts (palmar, plantar, periungual) and immunocompetence of patients yielded significant moderator variables, indicating that immunocompromised patients achieved significantly lower cure rates than immunocompetent individuals using all drugs. There was no indication of asymmetry on the funnel plot for studies evaluating SA (Egger's p-value = 0.18) but suggested possible publication bias for imiquimod studies (Egger's p = 0.04), warranting cautious interpretation of pooled estimates for this agent.

## Discussion

The results of this meta-analysis confirm the role of salicylic acid as the best studied local therapy for ordinary skin warts, as per recent recommendations of the British Association of Dermatologists and the American Academy of Dermatology (Sterling et al., 2014; Gibbs & Harvey, 2006). The action mechanism, gradual keratolysis followed by destruction of infected epidermis due to HPV infection, along with good tolerance and easy accessibility, makes it a reasonable first option in everyday practice. The pooled OR of 4.1 against placebo is clinically significant and confirms reliable efficacy in all regions and demographics of research. Imiquimod's lower recurrence rates compared to SA merit particular clinical attention. The durable responses observed with imiquimod likely reflect its immunostimulatory mechanism, which promotes the establishment of HPV-specific T-cell immunity. This distinction is clinically significant in the context of recalcitrant or recurrent warts, where conventional keratolytic treatments have failed, and may justify imiquimod's use as a second-line agent or in combination protocols. The cost of imiquimod preparations, however, represents a practical barrier in resource-limited settings.

Cantharidin has a high clearance rate (70-85%), which is encouraging, but its mechanism of inducing blisters limits its safe use on non-sensitive areas of skin; also, cantharidin may be regulated differently in different countries. For example, cantharidin is considered an off-label drug in the US , indicating that this compound requires formal regulatory approval and a uniform formulation. There is also an emerging combination strategy with cantharidin and SA, as reported by Vlahovic et al. in 2020, where further large scale clinical trials are needed to investigate this treatment option.

The heterogeneity across studies ($I^2$ =52%–64%) is anticipated in dermatology meta-analyses because of different clinical intervention types as well as diverse series of patients. The immune status significantly moderated treatment efficacy, indicating that immune profiling must be considered when making clinical decisions about therapeutic approaches to warts in patients with HIV, solid organ transplants, or cases where the use of immunosuppressive therapy occurs for prolonged periods of time. Therefore, it would be wise for clinicians treating these patients to recognize that standard first-line therapies may not work as effectively on these populations as they would otherwise, and earlier use of antiviral medications like cidofovir, or immunomodulation immunostimulatory drugs, may be necessary (Muzio et al., 2021). Methodologically, there are several issues that must be highlighted. Firstly, the wide variation in the definition of outcomes, especially the difference between the total and partial clearance of warts, is an issue in the current study. Secondly, the wide variation in the follow-up period (4 to 24 weeks) makes the comparisons on long-term relapse impossible. Thirdly, all the studies did not differentiate between the wart types to the same degree. Fourthly, publication bias, especially in relation to imiquimod, can contribute to the overestimation of efficacy in the meta-analysis. Future research should prioritize standardized outcome reporting, longer follow-up intervals, and head-to-head comparative trials between leading agents.

Further studies have also shown that the use of combination therapy with keratolytic drugs in combination with immunomodulatory agents or antiviral drugs could serve as a potent strategy for increasing clearance rates and decreasing recurrences (Stamatas et al., 2022; Vlahovic et al., 2020). Moreover, the prospect of new topical agents targeting HPV infections is an interesting area of study that may shape treatment options in the years to come.

## Conclusion

A meta-analysis conducted in the current literature review aims at integrating the best available evidence regarding the effectiveness of topical treatments in managing common skin warts. The topical use of salicylic acid is established as the standard for treating warts due to its strong efficacy profile, good safety characteristics, and widespread availability. Cantharidin and imiquimod present valid therapeutic options that are not inferior to other medications in

terms of effectiveness, with cantharidin providing the most effective results in terms of high wart clearance, while imiquimod shows the least rate of recurrence. The use of 5-fluorouracil and formic acid is less effective but presents valid options to treat certain types of warts. Clinicians should consider the type of warts, their location, patients' immune status, age, previous treatment attempts, and other factors when choosing an appropriate drug for a patient. Future research must involve long-term trials in accordance with the standard methodology.

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