Topical cantharidin use in dermatology: an updated review

Helana Ghali[1*] BS, Logan R Smith[1*] BA, Amanda Krenitsky[1] MD, Alexia M Joseph[1] BS, David Aung-Din[1] MD, Kerry Hennessy[1] MD, Sarah Moore[1] MD, James M Grichnik[1,2] MD PhD

*Authors contributed equally

Affiliations: [1]Department of Dermatology and Cutaneous Surgery, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA, [2]Department of Cutaneous Oncology, H Lee Moffitt Cancer Center, Tampa, Florida, USA

Corresponding Author: Amanda Krenitsky MD, Department of Dermatology and Cutaneous Surgery, University of South Florida, 13330 USF Laurel Drive, Tampa, FL 33612, Tel: 813-493-3034, Fax: 813-974-4272, Email: akrenitsky1@usf.edu

Abstract

Cantharidin, a natural toxin produced by the blister beetle, is a topical agent that induces acantholysis of the epidermis, breaking down desmosome plaques through the release of serine proteases. Cantharidin is available in three liquid forms: Ycanth (0.7%), Canthacur (0.7%), and Canthacur PS (1% cantharidin, 30% salicylic acid, 2% podophyllotoxin). Ycanth is used to treat molluscum contagiosum (MC). Canthacur is routinely used to treat a variety of dermatologic conditions including MC, plantar warts, and common warts, whereas Canthacur PS is a more potent formulation indicated for treatment of plantar warts only. The objective of this review is to highlight the efficacy, safety, and diverse use of topical cantharidin in the treatment of various skin conditions. Conditions in which treatment with topical cantharidin yielded a good-to-excellent response include MC, plantar warts, and common warts. Topical cantharidin treatment of anogenital warts yielded mixed results. None of the indications reviewed herein yielded a poor response to topical cantharidin. Overall, topical cantharidin resulted in a good-to-excellent clinical response in several conditions with mild and transient adverse events. The results of this review suggest the safe and efficacious use of topical cantharidin in the field of dermatology and highlight the potential for future use.

Keywords: cantharidin, dermatology, efficacy, warts

Introduction

Cantharidin

Cantharidin is a blistering agent derived from blister beetles (Order: Coleoptera; Family: Meloidae), [1]. Historical records indicate that cantharidin has been used in Chinese folk medicine for over 2000 years [2]. It has been used topically for the treatment of several conditions including hemorrhoids, ulcers, furuncles, and tuberculosis scrofuloderma. Cantharidin in its oral formulation was used as an abortifacient and for the treatment of rabies, cancer, edema, and abdominal masses [1-3]. Additionally, aphrodisiac use of cantharidin, or 'Spanish fly', is reported in several countries throughout history. Oral administration of cantharidin is linked to toxicity and several reports of poisonings [4-6]. Today, cantharidin-containing products that are marketed as aphrodisiacs can be purchased illegally as 'Spanish fly' [1] but are not recommended for medical use.

Cantharidin and the FDA

Cantharidin was first produced synthetically for medicinal use in 1952 [7]. Topical cantharidin was routinely used in the treatment of cutaneous warts until 1962, when the U.S. Food and Drug Administration (FDA) revoked the drug's approval secondary to a lack of efficacy data [1]. Cantharidin was subsequently placed on the FDA-approved bulk substances list in 1998, with its use restricted to physician application and in-clinic use [8].

Several preparations of topical cantharidin are currently available for treatment of cutaneous conditions: Canthacur (0.7% cantharidin), Canthacur PS (1% cantharidin/30%salicylic acid/2% podophyllotoxin), (Paladin Labs, Quebec, Canada); Cantharone Plus (1% cantharidin/30% salicylic acid/2% podophyllin BP), Cantharone (0.7% cantharidin in a film-forming vehicle of acetone, camphor, collodion, and castor oil), (Dormer

Laboratories, Rexdale, Ontario); and Cantharidin crystals, (Delasco Dermatologic Lab & Supply, Inc, Council Bluffs, Iowa) that can be mixed with flexible collodion [1,8,9]. More recently, the FDA approved topical preparation of cantharidin known as Ycanth (0.7% cantharidin), (Verrica Pharmecueticals Inc., West Chester, Pennsylvania) for use in patients two years and older with a diagnosis of molluscum contagiosum (MC), [10].

There is currently a lack of sufficient information regarding the impact of topical cantharidin on female fertility, the occurrence of major birth defects or miscarriage during pregnancy, or the potential risk to infants when the medication is used during breastfeeding. Nevertheless, due to the minimal systemic absorption of cantharidin after topical application, it is unlikely that maternal use would lead to fetal exposure to the drug [11].

Mechanism of action

Cantharidin acts as a vesicant and keratolytic. Following topical application of cantharidin, bullae form and then burst, leading to crust formation. Cantharidin is absorbed into the epidermal cell membrane lipid layers, where it activates neutral serine/threonine proteases. The activation of these proteases causes tonofilament detachment via desmosomal plaque degeneration, ultimately resulting in intraepidermal blistering and acantholysis. Because the resulting acantholysis is limited to the epidermis, scar tissue production secondary to treatment with cantharidin is uncommon [1,12].

Application technique

Cantharidin is administered by a physician in a clinical setting. Topical cantharidin solution (0.7% to 1%) is first applied to the target lesion. Following application, the treated lesion may be occluded with non-porous tape for four to 24 hours before washing off the medication with mild soap and water. Specific components of treatment—such as the use of occlusive tape, time of occlusion, treatment intervals, and pre-treatment paring—vary based on physician preference, patient characteristics, as well as the type and location of the lesion being treated. A survey conducted among members of the Society of Pediatric Dermatology focused on treatments for molluscum contagiosum (MC) and experiences with cantharidin. Seventy-five percent of respondents indicated that they do not occlude MC lesions with tape after cantharidin treatment. Twelve percent reported occasional use of tape for occlusion. Regarding the duration of time patients are advised to wait before washing off cantharidin, responses varied: 45% recommended leaving it on for 4–6 hours before washing, 26% suggested less than four hours, 7% proposed between 6–12 hours, and 11% either advised against immediate washing off or suggested waiting until the following day. Additionally, 11% left the decision to the patient, setting a maximum recommended time but advising earlier removal if blistering or pain occurred before the suggested limit [13].

Cantharidin is typically applied directly to a lesion using one of three tools: the unbroken wooden end of a cotton swab, the broken wooden end of a cotton swab, or a toothpick [8]. The solution can also be applied using a 1-ml slip-tip syringe which allows for quantification while eliminating the risk of cross-contamination [14].

Intraepidermal blistering occurs approximately 24 to 48 hours post-treatment. This lasts for approximately four to seven days and resolves without intervention. Resolution time varies and is dependent on several factors including the concentration of cantharidin solution used, whether the lesion was occluded following treatment, the duration of treatment contact before washing, and patient skin sensitivity [8,15].

Significance of review

Prior to its recent official FDA approval, topical cantharidin has been used commonly in dermatology to treat conditions including MC, plantar warts, and common warts. Topical cantharidin offers a readily available, cost effective, non-invasive treatment option for many patients. The potential benefit of topical cantharidin is limited by its respective treatment efficacies and side effect profiles. Thus, it is essential to evaluate the literature regarding its current use in dermatology to expand our knowledge about the safety and efficacy of this medication and how it compares to other standard treatments.

Discussion

Topical cantharidin in dermatology

Molluscum contagiosum

Molluscum contagiosum is a common viral skin infection caused by a DNA poxvirus most commonly affecting the pediatric population. Clinically MC presents as one or multiple white, pink, or flesh-colored, firm, dome-shaped papules [16]. Although this condition is self-limiting, it can often be chronic, lasting months to years. Additionally, lesions of MC are often symptomatic and bothersome to patients and caregivers. Topical cantharidin is routinely used as treatment for MC as it expedites recovery time and minimizes the potential for spread via child-to-child contact. The safety and efficacy of topical cantharidin in the treatment of MC is well-documented within the literature (**Table 1**).

In a retrospective chart review, Silverberg et al. assessed the efficacy of topical 0.7% cantharidin in the treatment of 300 children with non-facial MC [9]. The interval between treatments ranged from two to four weeks. After an average of 2.1 treatments, complete and partial clearance of lesions was seen in 90% and 8% of patients, respectively. Only mild side effects were noted including blistering, erythema, mild to moderate pain, burning sensation, pruritus, and post-inflammatory hypopigmentation or hyperpigmentation.

Similar efficacious results were found in a prospective case series by Ross et al. [17]. The study investigated the safety and efficacy of combination treatment with a one-time application of 0.7% cantharidin followed by 5% imiquimod applied daily in 16 pediatric patients with non-facial MC. The mean treatment duration was 5.4 weeks. Four categories of clearance were reported: 100% clearance (37.5%), 91-99% clearance (37.5%), 80-90% clearance (12.5%), and 30-50% clearance (12.5%). One patient experienced bleeding at the application site; otherwise, treatment was well-tolerated with no significant side effects.

Guzman et al. investigated the efficacy of 0.7% cantharidin (VP-102) formulation in 25 patients with MC in an open-label pilot trial [18]. After 12 weeks of treatment, a significant decrease in lesion counts was noted (23.0±15.6 to 6.8±11.7, P<0.0001). Complete clearance of MC lesions occurred in 44% of patients. Blistering was the most common adverse event (87%). In a similar prospective, randomized, double-blind, placebo-controlled pilot trial by Guzman et al., 94 patients were randomized to receive cantharidin±occlusive tape, versus placebo±occlusive tape [19]. Complete clearance was observed in 41.7% of patients in the cantharidin plus occlusion group, versus 30.4% in the group treated with cantharidin without occlusion. The placebo groups demonstrated 8.0% and 13.6% complete clearance with and without occlusion, respectively. The cantharidin treatment groups had an average complete clearance rate of 36.2% compared to 10.6% in the placebo treatment groups (P=0.0065). No statistically significant therapeutic benefits were seen with the use of occlusion in either cantharidin or placebo-treated groups. No patient-reported side effects were noted. This larger study further emphasized the safety and efficacy of cantharidin treatment of MC.

In a recent randomized trial, Eichenfield et al., 2020 demonstrated the efficacy of VP-102 (a drug device containing shelf-stable 0.7% cantharidin) in the treatment of 528 patients with MC. Patients in two identical trials (referred to as CAMP-1 and CAMP-2) were randomized to receive treatment with either VP-102 or placebo vehicle, with complete clearance observed in 54.0%, and 13.4% of patients, respectively (P<0.001). Mild side effects, including the development of vesicles, erythema, pruritus, pain, and scab, were noted more frequently in patients treated with either regimen of VP-102 (96.8%) than in those in the placebo groups (58.8%), [20].

In their study, Cathcart et al., 2009 examined the adverse effects associated with the use of cantharidin for non-facial MC in children [21]. Treatment was administered to 54 patients, averaging 2.2 treatment visits. Results revealed that 96% of patients showed improvement after treatment, with a notable complete clearance observed in 53.7% of patients. Additionally, parental satisfaction reached a rate of 78%. However, it should be noted that 46% of patients experienced adverse

events, including pain, pruritus, secondary infection, and temporary skin discoloration, with 9% categorizing their adverse events as severe.

Although most study outcomes suggest that cantharidin is more effective in the treatment of MC compared to placebo, Coloe Dosal et al., 2014 found no significant difference in the efficacy of cantharidin versus placebo in 29 patients with 15% and 6% of patients achieving complete clearance, respectively [22]. The cantharidin treatment group was noted to have fewer lesions per visit (32% compared to 21% for the placebo group); however, this result was not statistically significant (P=0.24) owing to the low sample size. Minimal side effects were reported.

It is important to note that cantharidin is not the only effective treatment for MC. In a prospective, randomized study, Hanna et al., 2006 compared four treatment regimens in 118 pediatric patients with MC: cantharidin 0.7%, salicylic acid 16.7% and lactic acid 16.7%, imiquimod 5%, and curettage [23]. All patients in all four treatment groups demonstrated complete clearance of MC lesions; however, a statistically significant difference in the number of treatments needed to achieve clearance was noted between the treatment arms. Clearance after one treatment was observed in 36.7%, 53.6%, 55.2%, and 80.2% of patients in the cantharidin, salicylic acid, imiquimod, and curettage treatment groups, respectively (P<0.001). The results of this study suggest that although cantharidin can treat MC, alternative treatments may offer improved efficacy in the treatment of lesions.

Two MC studies that compared topical cantharidin to a control solution observed a statistically significant difference in the percentage of patients achieving complete clearance, except for the study by Coloe Dosal et al., 2014 [19,20,22]. Studies that directly compared topical cantharidin to another topical treatment including a combination of salicylic acid and lactic acid, imiquimod, and curettage found cantharidin treatment to be the least effective of the treatment options [23]. However, owing to its high efficacy and safety, topical cantharidin treatment of MC demonstrates high rates of patient satisfaction (87-95%), [9,13,24,25].

Cantharidin continues to be a viable treatment option for MC when assessed against innovative alternatives. Khattab et al., 2020 compared the efficacy and safety of MC treatment using intralesional immunotherapy with tuberculin PPD compared to topical 0.7% cantharidin [26]. Patients clinically diagnosed with MC aged between three and 40 with a positive tuberculin test or a previous history of BCG vaccination were included in the study. Results showed that 90.0% of patients in the cantharidin group achieved complete clearance of lesions and 10.0% showed a partial response. In the PPD group, 85% of patients achieved complete clearance, whereas 15% showed a partial response. Overall, there was no significant difference in clinical response between the two groups (P=0.65); however, a statistically significant difference was detected between the groups regarding a burning sensation reported in 25% of patients in the cantharidin group and none in the PPD group. Conversely, pain at the injection site was reported by 100% of individuals in the PPD group, contrasting with no reported instances in the cantharidin group.

Plantar warts

The efficacy of cantharidin treatment for plantar warts is well-documented (**Table 2**). In a recent retrospective study by Becerro de Bengoa Vallejo et al., 144 patients with plantar warts were treated with a topical preparation containing 1% cantharidin, 5% podophylline, and 30% salicylic acid (CPS), [27]. Complete clearance was observed in 95.8% of patients after an average of 1-2 treatments with the topical preparation. No significant adverse effects were noted.

In a randomized, prospective study, Kaçar et al., 2012 demonstrated the efficacy of topical CPS in the treatment of plantar warts [28]. Following treatment application, lesions were occluded for 24 hours with nonporous dressings. Treatment was repeated every 14 days for a maximum of five sessions. Fourteen patients enrolled had complete clearance after an average of 2.7 treatments. Side effects including pain, bulla, and hyperpigmentation occurred in 21.4%, 28.6%, and 7.1% of patients, respectively.

Lopez-Lopez et al., 2015 investigated the efficacy of topical CPS formulation in the treatment of 15

patients with recalcitrant plantar warts [29]. Following topical administration of the CPS formulation, lesions were covered with a porous dressing for 24-48 hours. All patients treated had complete eradication of the lesions, with 53% of lesions resolving after only one treatment. No side effects were noted. In a subsequent observational study, Lopez-Lopez et al., 2016 expanded on their previous pilot study by treating 75 patients with recalcitrant plantar warts using the same topical CPS formulation and occlusive regimen [30]. Again, all patients demonstrated complete clearance after one (72%) or two (28%) treatments. All patients reported side effects, the most common being pain (81.3%). However, no major adverse effects were reported. Treatment was well-tolerated, with mild side effects and high patient satisfaction, which was assessed using a ten-point scale.

Ghonemy, 2017 investigated a topical solution containing 1% cantharidin, 20% podophylline resin, and 30% salicylic acid in the treatment of 15 patients with plantar warts recalcitrant to standard topical treatments [31]. Following topical application, lesions were covered with occlusive dressings for 24 hours. Treatment was repeated every 14 days for a maximum of five sessions. Complete clearance was seen in 93% of patients, with 50% of patients demonstrating clearance after one application and an additional 36% after two applications. The most frequent side effect noted was bulla formation (60%) followed by pain (26.7%) and hemorrhagic bulla (13.3%).

One study by Wu et al., 2022 investigated the use of cantharidin alone for the treatment of plantar warts [32]. In a study of 50 patients who were treated with cantharidin (0.025% cream treated daily for four weeks), 92% of patients had complete clearance at four weeks after starting treatment. However, there were no statistically significant differences in clearance with the treatment of cantharidin compared to the other two treatment legs: CO_2 laser (N=50), and liquid nitrogen cryotherapy (N=50).

Conversely, Navarro-Pérez et al., 2022 reported a case of multiple recalcitrant plantar warts that were resolved with three sessions of topical application of 1% cantharidin, 30% salicylic acid, and 5% podophyllin formulation [33]. The patient had previously failed five sessions of liquid nitrogen cryotherapy and two sessions of therapy with a 70% salicylic acid, nitric-acid–zinc complex.

Plantar warts can be resistant to treatment and often require several treatments to achieve clearance. The literature reviewed above illustrates that cantharidin can be used as an effective treatment when combined with podophyllin resin and salicylic acid.

Cutaneous warts (verruca vulgaris and facial verruca plana)

The use of topical cantharidin in the treatment of cutaneous viral warts is well-documented and dates back to the 1950s (**Table 2**), [34,35]. More recent studies have investigated its use in combination with salicylic acid and podophyllin to improve treatment efficacy. Nguyen et al., 2019 tested the treatment of cutaneous warts in adults (N= 83) and children (N=52) with a topical solution of 1% cantharidin, 2% podophyllin, and 30% salicylic acid (CPS1) followed by occlusion for 4-8 hours every 3-4 weeks [36]. Complete clearance was seen in 86.5% of children and 62.7% of adults after a median of three and four treatments, respectively. Within a three-year post-treatment follow-up period, only 10.4% of children and 19.4% of adults experienced a recurrence of lesions. The average time to recurrence was not noted in this study. Treatment was well tolerated with no serious side effects reported.

Guenthner et al., 2021 demonstrated the efficacy of 0.7% topical cantharidin solution (VP-102), in the treatment of common warts using two treatment modalities: a non-paring, two-week application interval group (cohort 1, N=21) or a paring, three-week application interval group (cohort 2, N=35), [37]. Both treatment groups applied occlusive tape for 24 hours following the application of the cantharidin treatment. After 84 days, complete clearance occurred in 19% and 51.4% of patients in cohorts one and 2, respectively. Mild side effects including application site pain, pruritus, scabbing, erythema, and vesicles were reported in 95.2% of patients in cohort one and 94.1% of patients in cohort two. This finding suggests that paring may improve the efficacy of treatment.

The use of cantharidin in the treatment of flat facial warts has also been investigated. Kartal Durmazlar et al., 2009 utilized 0.7% cantharidin solution in six pediatric and nine adult patients with facial flat warts [38]. The solution was left on for 4-6 hours following application without occlusion. Treatments were repeated every three weeks. Within 16 weeks of treatment, complete resolution of warts was noted in 100% of patients. An average of 2.6±1.2 treatment sessions were required for clearance. Only mild side effects including pain, erythema, blistering, and burning sensation were noted.

Cantharidin has also been reported to be efficacious in the treatment of digital and periungual warts. Forty patients with a total of 61 digital and 12 periungual warts underwent topical treatment using 0.7% cantharidin dissolved in acetone and collodion before occlusion of the area. After one application of cantharidin, 52.5% of digital warts and 33% of periungual warts resolved, with few requiring more than three treatments over one-week intervals. Long-term observation for over six months revealed a lasting clearance rate in about 70% of cases and mild side effects including pain [39].

Meymandi et al., 2017 evaluated the efficacy of cryotherapy combined with cantharidin versus cryotherapy with placebo in the treatment of non-facial common warts [40]. After two freeze-thaw cycles with liquid nitrogen cryotherapy, cantharidin or flexible collodion solution (placebo) was applied, and the lesions were covered with non-porous wound-tape for 24 hours. Results indicated that both groups experienced 100% clearance rates; however, the cantharidin group achieved a complete response after an average of 3.4 treatment sessions, compared to 4.7 sessions in the control group. After three treatment sessions, more than 50% of patients in the cantharidin group achieved complete clearance, versus 15% of those in the placebo group. Despite a significantly higher prevalence of hyper-pigmentation in the cantharidin group (29.1% versus 10.9%, P=0.017), the incidence of atrophic scarring was significantly lower (9.1% versus 29.1%, P=0.008), with no significant difference in recurrence rates between the two groups.

Rosenberg et al., 1977 evaluated the use of cantharidin as a self-applied, home treatment for warts [41]. The cantharidin was provided in 2.5-ml applicator bottles as a 0.7% solution in acetone-flexible collodion. Patients were directed to apply the solution daily without occluding the area until a blister formed, or the wart vanished. This method was used to treat 336 hand warts, comprised of 158 common warts and 178 subungual or paronychial warts, in 100 adult and pediatric patients. The treatment successfully removed 63% of subungual or paronychial warts and 65.1% of common warts. None of the patients reported adverse effects.

Bock et al., 1965 successfully used 0.7% cantharidin for the treatment of palpebral warts [42]. In 27 cases, the solution was carefully applied to a papilloma on the eyelid and repeated two to three times at 8 to 10-day intervals if the wart did not disappear by a week after the initial treatment. Thirteen cases were resolved with one application (48.1%); nine needed repeated applications (33.3%) and five did not respond to treatment (18.5%). Side effects were minimal with slight pruritus.

The above studies suggest that cantharidin preparations, both alone and compounded with podophyllin resin and salicylic acid, can be used to safely and effectively treat cutaneous warts. A good-to-excellent response was noted with topical cantharidin with clearance ranging from 15-100% (MC), 93-100% (plantar warts), and 19-100% (common warts), [22,23,28,31,37,38].

Anogenital warts

The use of topical cantharidin in the treatment of anogenital warts (AGW) is a recently emerging area of interest. In 2020, Ruini et al. presented a case of a patient with AGW treated with 0.7% cantharidin solution followed by eight hours of occlusion [43]. Complete resolution of all lesions was achieved after one week of treatment, with sustained results and no recurrence noted at one-month follow-up. Mild side effects including blistering, swelling, and erythema at the application sites within 24 hours of application were noted.

Conversely, Hum et al. described a patient treated with 0.7% cantharidin for AGW who experienced a

significant bullous reaction and development of large verrucoid plaques following improper post-treatment cleansing of the topical solution [44]. This extreme adverse reaction highlights the importance of adequate patient education during cantharidin treatment, particularly when used in highly sensitive areas.

Cantharidin treatment has also been assessed in comparison to trichloroacetic acid (TCA), a recognized standard therapeutic approach for AGW. Recanati et al., 2018 utilized 0.7% cantharidin or TCA in 12 patients newly diagnosed with external genital warts [45]. Patients remained in the study for up to four visits or until the wart was no longer visible. All six patients treated with cantharidin had complete clearance of their warts compared to 66% of patients treated with TCA (P=0.45), although this result was not statistically significant potentially owing to the small sample size. Cantharidin-treated patients also had less scarring than those treated with TCA (P<0.034) and required fewer treatments for wart eradication (2.21 versus 3.07, P=0.012). Additionally, fewer warts remained at the study's conclusion in the cantharidin group compared to the TCA group (0 versus 2). Patients in the cantharidin group reported significantly less pain both during treatment (P<0.01) and at the 2-week follow-up (P<0.02) compared to the control group. Overall patient satisfaction with cantharidin was significantly higher than with TCA at the end of the trial (P<0.01).

Additional larger studies are needed to determine the utility of cantharidin in the treatment of AGW. The use of topical cantharidin in the treatment of AGW yielded mixed results [43,44].

Cantharidin as an anti-cancer agent

Historically, cantharidin was used as an anticancer agent in ancient Chinese medicine [2]. More recently, its anticancer potential has been explored in the treatment of melanoma and non-melanoma skin cancer (NMSC). Modern research of the anticancer properties of cantharidin has demonstrated its ability to decrease the expression of protein phosphatase type 2A, a protein involved in cell cycle progression and apoptosis. Additionally, cantharidin reduces the expression of the proteins HSP70 and BAG3 [46-48]. HSP70 is highly expressed in cancer cells related to its multifunctional role in suppression of apoptosis, promotion of angiogenesis and metastasis, and inhibition of cellular senescence pathways [49]. BAG3 acts as an inhibitor of apoptosis [50]. Less toxic oral formulations of cantharidin derivatives are being explored to utilize its powerful antitumor and cytotoxic properties while limiting the potential for adverse reactions [51].

Ji et al., 2015 investigated in-vitro effects of cantharidin on human melanoma cells (primary site not specified) and found that cantharidin inhibited the migratory activity of A375.S2 melanoma cells via reduced expression of COX2, PI3K, NFκB p65, FAK, MMP2, MMP9, TIMP1, TIMP2, ERK1/2, VEGF, uPA, RhoA, GRB2, ROCK1, and Ras [52]. Reduced viability of the A375.S2 cells was also noted. These effects were dose-dependent with a maximum reduction of cell viability of 5μm concentration. Similarly, Hsiao et al., 2014 found that cantharidin induces morphological changes and triggers G2/M phase arrest and apoptosis in A375.S2 cells, revealing that it also promotes the generation of reactive oxygen species and calcium ions and leads to the release of cytochrome c, AIF, and EndoG [53]. Moreover, cantharidin activates caspase-dependent apoptotic pathways, evidenced by increased caspase activation and expression of apoptosis-associated proteins such as caspase-3, -8, and -9, cytochrome c, Bax, Bid, EndoG, and AIF, while inhibiting anti-apoptotic proteins Bcl-2 and Bcl-x. Additionally, Mu et al., 2018 suggest that cantharidin inhibits A375 melanoma cells via the miR-21-PTEN signaling pathway [54].

Li et al., 2017 investigated the in-vitro effects of cantharidin on A431 human skin cancer (epidermoid carcinoma) cells and found that cell viability decreased most dramatically with doses 10μm and greater [55]. Additional findings included cantharidin-induced cell cycle arrest in the G0/G1 phase secondary to decreased levels of cyclins D and E, and CDK6, increased tumor cell apoptosis, and increased activity of caspases 8, 29, and 23 (enzymes with an essential role in regulation of cell death). In-vivo mouse models used in this study also demonstrated cantharidin-induced apoptosis of tumor cells.

Three studies evaluated the in-vitro use of cantharidin formulations in the treatment of melanoma and non-melanoma skin cancer and found that cantharidin boasts several anti-cancer properties—suggesting that future development of less-toxic oral formulations of cantharidin could have beneficial applications for dermatological cancers [52,54,55]. However, significant research is still needed in-vivo and clinically before cantharidin can be considered in the treatment of melanoma and NMSC.

Cantharidin has also exhibited antitumor effects in various cancer types beyond NMSCs. In vitro studies by Rauh et al., 2007 compared the anti-tumor properties of cantharidin and curcumin using parental CCRF-CEM leukemia cells and their multidrug-resistant sub-lines CEM/ADR5000, CEM/VLB100, and CEM/E1000 [56]. The study found that cantharidin is more potent than curcumin in inhibiting tumor cell growth in both sensitive and multidrug-resistant CEM leukemia cell lines. In lung cancer growth, Zhang et al., 2017 determined that the use of a combination of cantharidin and radiotherapy was more effective in inhibiting tumor growth than using either alone by reducing the presence of CD4+ T regulatory cells and increasing CD8+ T cells and CD4+ T effector cells compared to individual treatments [57]. Cantharidin has also been shown to inhibit the expression of *S100A4* and *MACC1* genes which are involved in tumor initiation, growth, metastasis, and cancer cell motility in colorectal cancer cells [58].

Other uses

The use of topical cantharidin in various other cutaneous conditions has been increasingly explored. Hasbún et al., 2019 described a case of a pediatric patient with a 10-year history of idiopathic knuckle pads [59]. The patient was treated with one application of topical CPS (1% cantharidin, 5% podophyllotoxin, 30% salicylic acid) followed by occlusion with a non-porous patch for 48 hours. After one week, the patient experienced minimal blistering and associated pain which was easily treated with oral analgesics. After six months, all lesions had resolved with no scarring or recurrence.

Levitt et al., 2013 described two cases of porokeratosis of Mibelli treated with one application of 0.7% cantharidin solution followed by eight hours of occlusion resulting in complete resolution after one week and no recurrence after six months [60]. Both patients experienced post-inflammatory erythema at the lesion sites which was sustained at six-month follow-up; however, no serious side effects were noted. The efficacy of cantharidin in the treatment of this condition is believed to be secondary to the destruction of mutant keratinocytes with p53 overexpression. Currently, the literature regarding cantharidin treatment for anogenital warts, idiopathic knuckle pads, and porokeratosis of Mibelli is limited [43,44,59,60].

Aksoy et al., 2009 described a case of a dermatosis papulosa nigra (DPN) patient who was treated with 0.7% cantharidin solution [61]. The patient received one topical treatment without occlusion and achieved clearance of most of the facial lesions. However, the lesions recurred after four months, suggesting cantharidin may only act as an acute treatment for DPN. Poor response to cantharidin treatment was found following topical application in the treatment of DPN—although this finding was limited to a one-patient case report.

Cantharidin has also been used to treat hyperkeratosis related to friction or trauma. Akdemir et al., 2011 evaluated the efficacy of tangential excision combined with topical cantharidin, specifically using Canthacur-PS, a solution containing 1% cantharidin, 30% salicylic acid, and 5% podophyllin [62]. Treatment was administered to 72 patients, with 90.3% presenting with hyperkeratosis on the feet and 9.7% on the hands. The procedure involved scraping the affected area and applying the solution to the lesion's periphery, followed by five days of occlusion with an antibiotic dressing. Patients were followed for at least one year, with clinical examination and satisfaction queries conducted. Results indicated successful treatment in 79.2% of patients after one session, with additional sessions required for others. Recurrence was minimal at 1.4%,and no adverse effects or scarring were observed.

In 2011, Schencking and colleagues documented a case involving herpes zoster treatment with cantharidin [63]. The patient received cantharidin patches applied below the affected dermatome three times weekly for two weeks. Additionally, the patient received intravenous injections of 7.5g of ascorbic acid every other day for the same duration, alongside standard antiviral therapy. Within the initial two-week period, there was a marked decrease in pain and the occurrence of hemorrhagic skin lesions.

Cantharidin has also been studied for its effects on *Leishmania major*. Ghaffarifar, 2010 examined various concentrations of cantharidin on the viability of *L. major* in both in vitro studies and in BALB/c mice infected with the parasite [64]. Results showed that cantharidin inhibited the growth of *L. major* promastigotes in vitro, with higher concentrations leading to greater inhibition. Additionally, treatment with cantharidin reduced the number of amastigotes per macrophage in infected cultures. Topical treatment with 0.1% cantharidin ointment for two weeks proved effective in treating cutaneous leishmaniasis in infected mice.

Issues with cantharidin

Although topical cantharidin boasts a good safety profile, it is toxic when ingested. Several reports of cantharidin poisoning after ingestion to obtain aphrodisiac effects are described. To date, there are no FDA-approved indications for oral cantharidin [1,65]. However, less toxic derivatives of and delivery mechanisms for cantharidin are being investigated for use as an anti-cancer agent [1,51].

Severe reactions with topical application of cantharidin are rare, with only two reports in the literature. The first report describes a four-year-old patient who developed toxic shock syndrome and subsequently died, following the application of cantharidin topically for 20 MC lesions. The physicians in that case hypothesize that the use of occlusive tape allowed the cantharidin to spread to surrounding skin, causing large surface area blisters that allowed entry sites for *S. aureus* [65]. Additionally, the development of an extensive bullous reaction and large verrucous plaques following improper care of topical cantharidin for AGW treatment was described in one patient [44]. When applied topically by a medical professional in the appropriate clinical setting, cantharidin poses few risks to patients. However, its improper use can result in severe and painful adverse reactions, emphasizing the need for appropriate application as well as adequate patient education about proper care during the duration of cantharidin treatment.

Additional comments

Of all conditions treated with topical cantharidin, MC was the most frequently studied. Use of topical cantharidin in MC, plantar warts, and common warts demonstrated reliability and efficacy, with reduced lesion counts and sustained results.

Cantharidin has significant historical value with thousands of years of documented usage [2]. Much of its current recognized value is based on its non-scarring mechanism of action—sloughing keratinocytes while sparing destruction of the dermal-epidermal junction. Topically, cantharidin is very effective in treating MC, HPV, and potentially other benign and malignant keratinocytic disorders. Additionally, cantharidin's anti-cancer properties hint at beneficial applications for treating dermatological cancers. The future development of less-toxic oral preparations of cantharidin may expand its practical therapeutic applications.

Recent FDA approval of topical cantharidin, Ycanth, for treatment of MC in both adult and pediatric populations, will likely catalyze approval for other uses and additional cantharidin drug development.

Limitations

The most significant limitation of note in this study is the lack of large, controlled trials, and the relatively small sample sizes of the studies included limiting the generalizability of the results. Many of the studies varied in design, populations, and measured outcomes which hindered the ability for direct comparisons. For example, in the MC studies, the time between treatments varied from one to three weeks [19,22], treatment number varied from 1-5 treatments [17,22], and there were also variations in use and time of occlusion [19,22]. Although the methods of the studies were variable and introduce some difficulty in direct comparison, there is relative

homogeneity in results of the MC studies—showing topical cantharidin as an effective treatment modality for MC. Larger randomized clinical trials are needed to assess the effect of cantharidin in treating the aforementioned conditions.

Future research

There remains a demand for randomized clinical trials demonstrating the safety and efficacy of cantharidin use in dermatologic conditions. Future research could add to the current knowledge on the efficacy and safety of cantharidin for use in MC, plantar warts, and common warts. Ultimately, additional research could expand the indications of topical cantharidin in dermatology, potentially including idiopathic knuckle pads and porokeratosis of Mibelli, among other conditions. The current cutaneous applications of cantharidin are broad, with the possibility of additional applications of cantharidin yet to be explored. Thus far, cantharidin has been used for its antikeratolytic properties to treat cutaneous conditions resulting from hyperkeratosis (e.g., seborrheic keratosis). By expanding our breadth of knowledge on cantharidin's utility in dermatology, we can offer patients a potentially safe, effective, and fiscally-conservative treatment to a breadth of common cutaneous conditions.

Conclusion

This article on clinical studies aims to review the current literature on the efficacy and tolerability of cantharidin in the treatment of various dermatologic conditions. Most conditions treated elicited a good-to-excellent clinical response with only mild and transient adverse effects. Molluscum contagiosum, plantar warts, and common warts depicted the best response to topical cantharidin treatment. There remains a demand for additional studies evaluating these parameters to assess the utility of cantharidin in these conditions and additional dermatoses.

Potential conflicts of interest

James M. Grichnik MD PhD is a Consultant to Galileo Group and Canfield Scientific and serves on Skin Advisory Board for Regeneron and Dermatology Advisory Council for Melanoma Research Foundation. Clinical trial support from Novartis, Eli Lilly, Dermira, Elorac, Boehringer and Amgen.

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Table 1. *Summary of cantharidin use for the treatment of molluscum contagiosum.*

Author	Study type	Target population	N	Intervention (TOP)	Treatment interval (weeks)	CC, N (%)	CC after one treatment, N (%)	Mean number of treatments	Side effects	Additional comments
Molluscum contagiosum										
Silverberg et al. [9]	Rs	Pediatric	300	Cantharidin 0.7%	2-3	270 (90)	ND	2.1	Blistering, erythema, mild to moderate pain, burning, pruritus, hypopigmentation or hyperpigmentation	95% would repeat treatment or found treatment tolerable
Ross et al. [13]	CS, P	Pediatric	16	Cantharidin 0.7% followed by daily imiquimod 5%	ND	6 (37.5)	ND	ND	Transient burning, pain, erythema or pruritus	87.5% would repeat treatment or found treatment tolerable
Hanna et al. [18]	P, R	Pediatric	30	Group 1. cantharidin 0.7%	ND	30 (100)	11 (36.7)	1-3	Erythema, vesiculation, pruritus, burning, and pain	60% patient satisfaction
			28	Group 2. salicylic acid 16.7% and lactic acid	ND	28 (100)	15 (53.6)	1-3	ND	
			29	Group 3. imiquimod 5%	ND	29 (100)	16 (55.2)	1-3	ND	
			31	Group 4. curettage	ND	31 (100)	25 (80.6)	1-3	ND	
Guzman14]	OL	Pediatric	25	Cantharidin 0.7% (VP-102)	3	11 (44)	ND	1-4	Blistering, erythema	ND
Guzman et al. [15]	DB, PC, P, R	Pediatric	23	Cantharidin 0.7% (VP-102)	3	7 (30.4)	ND	2	None reported	ND
			24	Cantharidin 0.7% (VP-102) + occlusion		10 (41.7)				
			22	Placebo		3 (13.6)				
			25	Placebo + occlusion		2 (8)				
Eichenfield et al. [16]	PC, R	Adult	11	Cantharidin 0.7% (VP-102)	3	156 (50.3)	35 (11.3)	1-4	Vesiculation, erythema, pruritus, pain, scabbing	ND
		Pediatric	299							
		Adult	213	Vehicle (placebo)		33 (15.5)	8 (3.7)		ND	ND
		Pediatric	5							

Cathcart et al. [18]	O	Pediatric	54	Unspecified formulation of cantharidin	ND	29 (53.7)	ND	2.2	Pain, pruritus, secondary infection, and temporary skin discoloration	96% response rate, with a parental satisfaction rate of 78%. 46% experienced adverse events
Coloe Dosal et al. [19]	DB, PC, P, R	Pediatric	13	Cantharidin 0.7%	1-2	2 (15)	ND	1-5	Skin irritation, blistering, pain	ND
			16	Placebo	1-2	1 (6)	ND		Pain	ND
Khattab et al. [24]	R	Adult and Pediatric	20	Cantharidin 0.7%	2	18 (90)	ND	ND	Burning	ND

CC, complete clearance; CR, case report; CS, case series; DB, double-blinded; MC, molluscum contagiosum; ND, not documented; O, observational.; OL, open label; P, prospective; PC, placebo-controlled; R, randomized; Rs, retrospective; TOP, topical.

Table 2. *Summary of cantharidin use for the treatment of plantar and cutaneous warts.*

Author	Study type	Target Population	N	Intervention (TOP)	Treatment interval (weeks)	CC, N (%)	CC after one treatment, N (%)	Mean number of treatments	Side effects	Additional Comments
Plantar Warts										
Beccerro de Bengoa Vallejo et al. [22]	Rs	Adult and Pediatric	144	1% cantharidin, 5% podophylline, and 30% salicylic acid	ND	138 (95.8)	125 (89)	1-2	None reported	ND
Kaçar et al. [23]	P, R	Adult	14	1% cantharidin, 5% podophyllotoxin and 30% salicylic acid	2	14 (100)	2 (14)	2.71 ± 1.33	Pain, bulla, and hyperpigmentation	ND
Lopez-Lopez et al. [24]	O	Adult	15	1% cantharidin, 5% podophyllotoxin and 30% salicylic acid	4	15 (100)	8 (53)	1-2	None reported	ND
Lopez-Lopez et al. [25]	O	Adult	75	1% cantharidin, 5% podophyllotoxin and 30% salicylic acid	4	75 (100)	54 (72)	1-2	Pain, blistering, pruritus, infection (mild), irritation, bleeding	Patient satisfaction was assessed using a ten point scale where 1= "not satisfied at all" and 10= "completely satisfied." Average score= 9.13 ± 0.74
Ghonemy [26]	R, P	Adult	15	1% cantharidin, 20% podophylline resin, and 30% salicylic acid	2	14 (93)	7 (47)	1-5	Pain, bulla, hemorrhagic bulla	ND
Wu et al. [27]	R, P	Adult	50	Cantharidin 0.025%	4	46 (92)	N/A	N/A	Pain, erythema, edema, erosion	topical cantharidin cream daily for 3-4 weeks
Navarro-Pérez et al. [31]	CR	Adult	1	1% cantharidin, 30% salicylic acid, and 5% podophyllin	2	1 (100)%	N/A	3	None reported	ND
Cutaneous Warts										

Nguyen et al. [30]	Rs	Adult (unspecified)	83	1% cantharidin, 2% podophyllin, and 30% salicylic acid	2-4	52 (62.7)	ND	4	Blistering, pain, burning	Patient satisfaction ten point scale where 1= "not satisfied at all" and 10 = "completely satised." 9.0 children 8.0 adults
		Pediatric (unspecified)	52			45 (86.5)		3		
Guenthner et al. [31]	OL	Adults (common warts)	21	Cantharidin 0.7% (VP-102)	2	4 (19)	0 (0)	1-4	Pain, pruritus, scabbing, erythema, vesiculation	ND
		Pediatric (common warts)	35		3	18 (51.4)	5 (14%)			
Kartal Durmazlar et al. [32]	P	Adult (flat facial warts)	9	Cantharidin 0.7%	3	9 (100)	4 (27)	2.6 ± 1.18	Pain, erythema, blistering, and burning sensation	14/15 had complete or partial patient satisfaction
		Pediatric (flat facial warts)	6			6 (100)				
Epstein et al. [37]	O	Adult (digital warts)	61 warts	Cantharidin 0.7%	1	32 (52.5) warts	32 (52.5) warts	3	Pain	CC lasted in 70% of cases over six months
		Adult (periungual and subungual)	12 warts			9 (75) warts	4 (33) warts			
Meymandi et al. [38]	R	Adults (common warts)	55	Cantharidin 0.7% and cryotherapy	2	55 (100)	ND	3	Hyperpigmentation, pain, blistering	Following three treatment sessions, more than 50% of patients in the cantharidin group experienced CC, compared to 15% in the placebo group
			55	Cryotherapy and placebo		55 (100)		4.7	Atrophic scaring, pain, blistering	
Rosenberg et al. [39]	CS	Adult and pediatric	158 warts	Cantharidin 0.7% in acetone-flexible	ND	103 (65.1)	ND	ND	None reported	ND

		(common warts)		col-lodion; self-application						
		Adult and pediatric (subungual and paronchiyal warts)	178 warts			112 (63.0)				
Bock et al. [40]	CS	Adult (palpebral warts)	27	Cantharidin 0.7%	1	22 (81.5)	13 (48.1)	ND	Pain, blistering, and slight pruritus	No recurrences

CC, complete clearance; CR, case report; CS, case series; DB, double-blinded; MC, molluscum contagiosum; ND, not documented; O, observational.; OL, open label; P, prospective; PC, placebo-controlled; R, randomized; Rs, retrospective; TOP, topical.