Use of Contact Immunotherapy in the Treatment of Skin Diseases Other than Alopecia Areata

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ABSTRACT

For decades, contact immunotherapy with dinitrochlorobenzene, diphencyprone, and squaric acid dibutylester has played an important role in both clinical practice and scientific research. It is listed as the first-line treatment for extensive alopecia areata and was more recently approved for melanoma treatment as an orphan drug in the USA. Moreover, owing to the relative low cost and safety, topical immunotherapy has also been used in many infectious, neoplastic, and inflammatory dermatological diseases. It is especially valuable in vulnerable groups, for cosmetic/pain sensitive areas, or for multiple lesions. In this review, we summarize the current evidence supporting the use of contact immunotherapy for treatment of skin diseases, from articles collected from PubMed database. Owing to space limitation and already numerous studies focusing on alopecia areata, we include only skin diseases other than alopecia areata. In addition to diseases that have been reported to be treated by contact immunotherapy, the hypothesized mechanism, prognosis prediction, efficacy, and safety of these topical agents are discussed.

Keywords: Contact immunotherapy; Dinitrochlorobenzene; DNCB; Diphencyprone; Diphenylcyclopropenone; DPCP; Squaric acid dibutylester; SADBE

Key Summary Points

1. Contact immunotherapy provides a convenient, safe, and cost-effective treatment modality in clinical practice, but it is often used off-label, most commonly in alopecia areata

2. Recently, contact immunotherapy was approved for melanoma treatment in the USA as an orphan drug using diphencyprone in a gel preparation

3. Contact immunotherapy has been used in many inflammatory, infectious, and neoplastic skin diseases, but systematic reviews are limited

4. More studies are needed to elucidate the mechanism, optimal regimens, and treatment potential of contact immunotherapy
INTRODUCTION

Dinitrochlorobenzene (or dinitrochlorobenzol, DNCB), diphenylcyclopropenone (or diphenocyprone, DPCP, DCP), and squaric acid dibutylerester (SADBE) are synthetic contact allergens that have been used for decades in clinical practice for both investigation and treatment. The common features of these compounds are their ability to induce type IV hypersensitivity, thereby resulting in the resolution of skin diseases through immune modulation [1].

Recently, topical DPCP gel (Samcyprone) has been approved as an orphan drug for the treatment of cutaneous melanoma stage IIb to IV in 2015 in the USA, and trials for the treatment of warts and alopecia areata (AA) are also scheduled. These contact allergens were once used as evaluation of systemic immunity in various diseases, such as sarcoidosis [2], Chagas’ disease [3], Crohn’s disease [4], measles [5], tuberculosis [6], leprosy [7], and malignancy (head and neck cancer [8], squamous cell carcinoma [9], esophageal cancer [10], breast cancer [11], and prostate cancer [12]), to name just a few. However, their roles as diagnostic tools have waned as more specific and sophisticated methods for immunity assessment have been developed. Their roles in the treatment of skin diseases have not been systematically reviewed except in patients with alopecia areata, in which contact immunotherapy is listed as the preferred first-line treatment for extensive alopecia areata in many consensuses or guidelines [13–15]. Some studies also exist in the treatment of viral warts [16] and melanoma [17]. However, the potential applications of contact immunotherapy as alternative treatments are more extensive. The approval for topical DPCP gel as an orphan drug marked a new era in the use of contact immunotherapy. In this review, we aim to summarize the current evidence supporting the use of contact immunotherapy for treatment of skin diseases. Owing to space limitation, only skin diseases other than alopecia areata are included. Both efficacy and safety will be discussed. Although DNCB is less commonly used in clinical practice owing to its potential carcinogenicity, the reports of DNCB are still included mainly because of the shared modes of action with DPCP and SADBE, to explore the potential role of contact immunotherapy in clinical practice.

SEARCHING METHODS (FIG. 1)

The PubMed, Clinicaltrials.gov, and Cochrane library databases were searched for retrieval of original articles, case reports, case series, clinical trials, systematic reviews, and narrative reviews whose full content is accessible and that were published from inception to January 2022. The articles are searched by the following terms: ((Diphenylcyclopropenone [Title/Abstract]) OR (Dinitrochlorobenzene [Title/Abstract]) OR (Squaric acid dibutylerester [Title/Abstract]) OR (DNCB [Title/Abstract]) OR (DPCP [Title/Abstract]) OR (SADBE [Title/Abstract]) OR (Diphencyprone [Title/Abstract]) OR (Dinitrochlorbenzol [Title/Abstract])) AND (humans [Filter]), and three articles from the references of identified articles were added. Here, we collected 1753 articles. Four articles that lack publications were excluded. We included articles that focused on diseases other than AA \((n = 909)\), and added 29 articles about side effects of topical immunotherapy in patients with AA \((n = 938)\). Then, articles in which the chemicals were used as prognostic markers or to evaluate systemic immunity were excluded \((n = 723)\). Articles that focused on the mechanism \((n = 11)\), and were not published in English \((n = 27)\), were also excluded. Also, eight articles regarding use of topical immunotherapy to treat AIDS were excluded owing to the lack of clinical use nowadays. Finally, 12 articles were excluded owing to duplication. A collection of 157 publications was stored and managed on EndNote X9 (Thomson Reuters, New York City, NY, USA). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.
Fig. 1 Flowchart of the search study
MECHANISM OF TOPICAL IMMUNOTHERAPY

An ideal agent for topical immunotherapy meets the following requirements: safe, reliable sensitization, absent from the environment, and not cross-reactive with other chemicals. Only DNCB, SADBE, and DPCP are currently used. It is believed that these chemicals induce type 4 hypersensitivity, and affect self-immunity in various ways, even though the precise mechanism is still speculative. For instance, some researchers found that polymorphisms in tumor necrosis factor-α and interleukin-1 receptor antagonist genes have been linked to the severity of alopecia areata, which could also influence topical immunotherapy-induced inflammation, affecting the clinical outcome [18]. Moreover, serum levels of interleukin-4 and interleukin-12 are shown to be predictive for the clinical outcome of AA, suggesting the involvement of humoral immunity [19]. As for warts, it is shown that CD4-to-CD8 ratio is reversed during immunotherapy. Furthermore, nonspecific antiviral reaction by activation of antiviral cytokines such as interleukin-2 and interferon-γ is suggested to be a mechanism for treating warts. It is also hypothesized that the agents act as a hapten to bind to an antigen associated with the viral warts, and thus help epidermal Langerhans cells or dermal dendritic cells process the complex and present to the naïve T-helper cells in the lymph nodes [1]. In melanoma, peritumoral tumor-infiltrating lymphocytes and PD-1 expression predict better response to DPCP, indicating the immune-modulating effect of the chemical agent [20].

THE RELATIONSHIP BETWEEN SENSITIZATION AND PROGNOSIS

To initiate contact immunotherapy, the patients first received the contact allergen topically at a concentration much higher than that actually used during subsequent treatment with gradual up-titration. Traditionally, a stronger inflammatory reaction was linked to a higher chance of treatment success, since the strong reaction indicates stronger stimulation of the immune system [21, 22]. However, some research did not show a correlation between the inflammatory reaction and the therapeutic results [23, 24]. Instead, it is the severity of the disease that predicts the outcome of the treatment [25–27]. The need for initial sensitization is also in doubt [26].

TOPICAL IMMUNOTHERAPY IN THE TREATMENT OF SKIN DISEASES

Infection (Table 1)

Human Papilloma Virus Infection (Table 2, Table 3)

In 1973, the first use of DNCB contact immunotherapy for resistant warts was reported with a cure rate of 91% [28]. Thereafter, numerous reports using DNCB, DPCP, and SADBE were published [1, 16, 21, 22, 24, 28–74]. Now, contact immunotherapy plays an important role in treating warts, when other options such as chemical destruction (salicylic acid and/or lactic acid topical paints) or physical destruction (liquid nitrogen cryotherapy) show unfavorable results [1]. It is a relatively painless treatment method, compared with traditional treatment modalities mentioned above that are destructive to tissues [38]. Unlike cryotherapy or salicylic acid, which impose direct destruction of the lesion including peripheral normal tissue, the “innocent bystander” hypothesis exists. The contact allergens work by enhancing systemic immunization, as shown by a higher rate of spontaneous resolution of warts to which topical agents were not applied [55, 56, 61]. Moreover, it is also safe and effective in children, with the time required for complete cure shorter than adults [31, 32, 34, 48, 49]. In immunosuppressed patients, there is a lower clearance rate, requiring a greater number of treatments over a longer time period, but contact immunotherapy still remained a useful option [36]. Duration, number of warts, and new warts adjacent to prior ones have been
shown to be negatively associated with response to therapy [69]. Some studies also found the location of the warts to influence the resolution time, with plantar and periungual warts requiring the longest time [64, 66, 69]. There is also a case report documenting a patient with epidermodysplasia verruciformis treated with SADBE successfully without recurrence [75].

Aside from monotherapy, there are also trials or case reports to combine conventional therapy with topical immunotherapy [37, 41, 69, 76]. Even though some researchers were skeptical of the effectiveness [24, 77], contact immunotherapy is still an attractive treatment option for warts for some patients.

Except for cutaneous warts, anogenital warts (condyloma acuminatum) can also be treated by DNCB [78, 79], SADBE [45], and DPCP [29, 80], offering an alternative treatment option besides local application of podophyllin resin and 5-fluorouracil (5-FU), electrodesiccation, cryotherapy, and laser therapy [78]. However, clinical trials on a larger scale are needed to prove the efficacy.

For the topical treatment of viral warts, imiquimod and sinectechins (green tea extract) are two topical immunomodulatory agents approved for the treatment of anogenital warts, but not cutaneous warts. However, no clinical study has been conducted to compare its effectiveness with that of DNCB, DPCP, or SADBE. Topical DPCP or SADBE may be more valuable for the treatment of cutaneous warts than anogenital warts.

### Leishmaniasis

Cutaneous leishmaniasis (CL) is endemic in some developing nations, and causes a considerable psychological burden on patients owing to the atrophic and disfiguring scars. The most common treatment for CL is pentavalent antimony (Sbv) compounds via a parenteral, intramuscular, or intralesional route. However, the well-recognized irreversible toxicity and the frequent laboratory monitoring needed during the treatment period complicate the usage of the compounds. In one randomized controlled pilot study, 46 patients diagnosed with CL in Iran were treated with DPCP with or without meglumine antimoniate. The intervention

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**Table 1** Reports of non-HPV infectious diseases [81–83]

| Authors          | Disease          | Participant number | Agent(s) | Sensitization protocol | Intervention protocol | DPCP concentration | Dropouts | Outcomes                                      | Study design        | OCEBM levels of evidence |
|------------------|------------------|--------------------|----------|------------------------|-----------------------|--------------------|----------|-----------------------------------------------|---------------------|-------------------------|
| Nahidi (2021)    | Leishmaniasis    | 23 (A)             | Meglumine antimoniate (Sbv) | (B) | 2% solution of DPCP to one of the lesions | 0                  | Number of injections needed to resolve the induration less in group A (5.19 ± 1.70) than in group B (9.8 ± 3.52) | 0 | Dropout 0 | Randomized controlled | Level 2               |
| Kang (2005)      | Molluscum contagiosum | 22 (children) | DPCP | 0.5% solution | 0                  | Number of DPCP injections needed to complete clearance | 4 (due to side effect) | 14 (63.6%) | Lesions gradually disappeared from eyelid to trunk and genitalia | Uncontrolled, nonprospective | Level 3 |
| Chularojanamontri (2010) | Molluscum contagiosum | 1 | DPCP | 2% solution | 0                  | Lesions gradually disappeared from eyelid to trunk and genitalia | 0 | - | Case report | Level 4 |

![Adis](https://example.com/adis.png)
| Authors            | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes | Study design | OCEBM levels of evidence |
|--------------------|--------------------|----------|------------------------|--------------|----------|----------|--------------|--------------------------|
| Bekhor (1978)      | 13                 | DNCB     | 5 drops of 2% in acetone on the upper arm | White soft paraffin containing 0.1% DNCB daily | 0         | 9 (69%)/13 cases received complete clearance | Uncontrolled, prospective | Level 3                   |
| Buckner (1978)     | 51                 | DNCB     | 0.15 ml of 2% in acetone on the upper arm | 0.05–1.0% of DNCB daily or twice daily | 16 (LOFU) | 23 (66%)/35 with total resolution, 10 (30%)/35 with partial, 2 (4%)/35 with no response | Uncontrolled, prospective | Level 3                   |
| Goihman-Yahr (1978)| 10                 | DNCB     | No                     | 2% DNCB, occluded for 2 days, every 3 weeks | 0         | All cured, and 8 (80%)/10 with healing of untreated areas | Controlled (half body), prospective | Level 3                   |
| Eriksen (1980)     | 63                 | DNCB     | 1 mg under occlusion in the right and left infrascapular region for 48 h | 0.1–10% of DNCB in acetone (43%) or DMSO (57%) weekly | 9 (CBS) + 11 (LOFU) | 34 (80%)/43 cured | Controlled (half body), nonprospective | Level 3                   |
| Sanders (1981)     | 84                 | DNCB     | 2% in acetone on upper arm | 0.1% of DNCB in Aquaphor daily | 0         | 69 (82%)/84 with complete clearing | Uncontrolled, nonprospective | Level 3                   |
| Dunagin (1982)     | 30                 | DNCB     | 0.02 ml of 2% on forearm | 0.02 ml of 2% DNCB every 2 weeks | 1 (CBS) + 5 (LOFU) | 21 (88%)/24 achieved apparent remission | Uncontrolled, nonprospective | Level 3                   |
| Authors   | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes | Study design | OCEBM levels of evidence |
|-----------|--------------------|----------|-------------------------|--------------|----------|----------|--------------|--------------------------|
| Grayson (1982) | 10 | DNCB | 0.15 ml of 0.3% in acetone on the arm | 0.1% of DNCB in Aquaphor once or twice daily | 2 (LOFU) | 6 (60%)/10 with complete remission, 2 (20%)/10 with partial remission | Uncontrolled, nonprospective | Level 3 |
| Johansson (1984) | 43 | DNCB | 0.6 mg in acetone to the back | 0.1–10% of DNCB in acetone weekly | 2 (LOFU) + 4 (due to side effect) | 19 (51%)/37 totally cured, 6 (16%)/37 with partial response, 12 (33%)/37 without response; 25 of them received follow-up after 5 years, with 3 having recurrence and 3 never having healed before | Uncontrolled, prospective | Level 3 |
| Lee (1984) | 59 | DNCB | 0.5 ml of 0.4% on right shoulder | 0.1% ointment base of DNCB applied to the left shoulder every 2–3 weeks | 0 | 46 (78%)/59 received total clearance | Uncontrolled, prospective | Level 3 |
| Naylor (1988) | 62 | DPCP | 1% in acetone on the arm for 24 h | 0.004–1% of DPCP daily | 2 (CBS) + 15 (LOFU) | 28 (62%)/45 received total clearance | Uncontrolled, nonprospective | Level 3 |
| Authors     | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes | Study design          | OCEBM levels of evidence |
|-------------|---------------------|----------|------------------------|--------------|----------|----------|------------------------|--------------------------|
| Orecchia    | 44                  | DPCP     | 2% in acetone on the forearm | 0.2–2% of DPCP weekly for at most 10 weeks | 5 (due to side effects) | 20 (51%)/39 cured completely, 17 (44%)/39 with partial response, 2 (5%)/39 without improvement | Uncontrolled, nonprospective | Level 3 |
| Shiohara    | 1                   | DNCB + interferon-γ | 1% in acetone on left arm | DNCB undocumented, intralesional injection of interferon-γ in one lesion | 0 | Complete remission of all lesions after 2 weeks | Case report | Level 4 |
| Shah        | 50                  | DNCB     | 0.1 ml of 2% acetone on the left upper arm | 0.02–0.06% of DNCB 2 days a time for 1–24 weeks | 0 | 27 (54%)/50 had regression, 23 (46%)/50 without response; 8 (16%)/50 had recurrence | Controlled (half body), nonprospective | Level 3 |
| van der Steen | 1                  | DPCP     | 2% in acetone on scalp | 0.1–2% of DPCP every other day | 0 | Lesions completely disappeared after 4 (right foot) and 7 (left foot) weeks | Case report | Level 4 |
| Iijima      | 20                  | SADBE    | 0.025 ml of 2% in acetone on medial arm for 48 h | 0.1 or 0.01% SADBE once a week or every 2 weeks | 3 (due to side effects) | 12 (70%)/17 responded well, 5 (30%)/17 with poor response | Uncontrolled, nonprospective | Level 3 |
| Authors | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes | Study design | OCEBM levels of evidence |
|---------|--------------------|----------|-------------------------|--------------|----------|----------|--------------|--------------------------|
| Larsen (1995) | 241 | DPCP | 1% in petroleum on the back of foot or forearm | 0.5 or 1 or 5% DPCP every 3 weeks | 5 (stopped treatment) + 19 (insufficient records) + 4 (spontaneous cure) + 32 (LOFU) | 154 (85%)/181 cured, 27 (15%)/181 not cured | Uncontrolled, prospective | Level 3 |
| Rampen (1996) | 134 | DPCP | 1–3% on right upper arm | 0.001–3% of DPCP once a week | 2 (CBS) + 21 (LOFU) | 49 (44%)/111 with complete remission, 18 (16%)/111 with partial remission, 44 (40%)/111 without response | Uncontrolled, nonprospective | Level 3 |
| Weisshaar (1998) | 1 | DPCP | 2% of acetone on the forehead | 0.01% of DPCP every week | 0 | Complete remission after 9 weeks | Case report | Level 4 |
| Buckley (1999) | 60 | DPCP | 2% in acetone on upper arm | 0.01–6% of DPCP every 1–4 weeks | 12 (LOFU) | 42 (88%)/48 with complete remission | Uncontrolled, nonprospective | Level 3 |
| Lee (1999) | 29 | SADBE | 1% or 2% in acetone under occlusion on the upper arm overnight | 0.5–5% of SADBE every 2–4 weeks | 3 (LOFU) | 20 (70%)/29 with total clearance, 3 (10%)/29 with partial remission, 6 (20%)/29 with no change | Uncontrolled, nonprospective | Level 3 |
| Authors         | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes | Study design | OCEBM levels of evidence |
|-----------------|---------------------|----------|------------------------|--------------|----------|----------|--------------|--------------------------|
| Haedersdal (2000) | 39                  | DPCP     | 1% in petroleum on the dorsum of the foot | 0.5–5% of DPCP every 3 weeks | 14 (LOFU) | 14 (56%)/25 registered as clear, 11 (44%)/25 unclear | Uncontrolled, nonprospective | Level 3 |
| Micali (2000)    | 568                 | SADBE    | 3% in acetone to the lesions | 0.03–3% of SADBE twice a week | 92 (LOFU) + 20 (noncompliance) + 13 (due to side effect) | 382 (86%)/443 received complete resolution, 61 (14%)/443 response partially or none | Uncontrolled, prospective | Level 3 |
| Micali (2000)    | 188 (children)      | SADBE    | 3% in acetone to the lesions | 0.03–3% of SADBE twice a week | 40 (LOFU) | 124 (84%)/148 with complete resolution, 24 (16%)/148 with no response | Uncontrolled, nonprospective | Level 3 |
| Silverberg (2000) | 61 (children)       | SADBE    | 2% in acetone on the forearm | 0.2% of SADBE 3–7 times per week | 2 (LOFU) | 34 (58%)/59 complete clearing, 11 (19%)/59 partial clearing, 14 (23%)/59 no response | Uncontrolled, nonprospective | Level 3 |
| Pollock (2002)   | 1                   | DPCP     | 2% of left upper arm | 0.001% once and 0.003% once after 2 weeks | 0 | Completely remission after 10 weeks, including untreated lesions | Case report | Level 4 |
| Authors       | Participant number | Agent(s)            | Sensitization protocol | Intervention                              | Dropouts | Outcomes                        | Study design        | OCEBM levels of evidence |
|--------------|---------------------|---------------------|------------------------|-------------------------------------------|----------|---------------------------------|----------------------|-------------------------|
| Upitis (2002)| 211                 | DPCP                | 2% in petroleum ointment to the left inner arm | 0.5–4% of DPCP every 3 weeks | 1 (CBS) + 56 (LOFU) | 135 (87.7%)/154 with complete clearance | Uncontrolled, nonprospective | Level 3                |
| Aghaei (2006)| 6                   | DPCP                | 2% in acetone on the medial arm | 0.001–1% DPCP weekly, at most 10 weeks | 0        | 4 (67%)/6 received complete response, 2 (33%)/6 with partial improvement | Uncontrolled, prospective | Level 3                |
| Armour (2006)| 50                  | DPCP + salicylic acid | 2% in acetone to left upper arm | 0.01–0.2% DPCP + 15% salicylic acid in white soft paraffin daily | 2 (LOFU) | 44 (92%)/48 with total clearance | Uncontrolled, prospective | Level 3                |
| Choi (2008)  | 72 (A) + 75 (B)     | DPCP (A) or cryotherapy (B) | 1% in acetone | DPCP every 1–3 weeks | 0        | 45 (62.5%)/72 (A) and 38 (50.8%)/75 showed complete clearance, with A having a lower recurrence rate | Uncontrolled, prospective | Level 3                |
| Hama (2009)  | 2                   | SADBE               | 2% on left upper arm | 0.01–0.05% on each lesion every 2 weeks | 0        | Both cases received complete remission | Case series | Level 4                |
| Authors         | Participant number | Agent(s)                                                                 | Sensitization protocol                                                                 | Intervention                        | Dropouts | Outcomes                                                                                     | Study design            | OCEBM levels of evidence |
|-----------------|--------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------|----------|-----------------------------------------------------------------------------------------------|-------------------------|--------------------------|
| Choi (2011)     | 61 (A) + 14(B) + 49 (C) | Cryotherapy (A) + DPCP (B) or 5-FU/salicylic acid (C)                    | 0.1% at the upper arm with tape occlusion (B)                                        | 0.001-0.01% of DPCP daily (B)      | 0        | Group B required less cryotherapy sessions (3.58 ± 1.25) compared with group A (5.10 ± 0.44), while no significant difference between group A and group C (4.80 ± 0.69) | Controlled, retrospective | Level 3                  |
| Silverberg (2012)| 5 (SADBE, A) + 16 (SADBE + TCA, B) + 10 (SADBE + cantharidin, C) + 43 (SADBE + TCA + cantharidin, D) (children) | SADBE or trichloroacetic acid (TCA) or cantharidin                                | 2% on all nonfacial warts            | SADBE: 0.2% every 2–4 weeks       | 7 (LOFU) | A (60% complete response, 20% partial, 20% minimal), B (100% complete response), C (80% complete response, 20% partial), D (83.7% complete response, 14% partial, 2.3% minimal) | Controlled, retrospective | Level 3                  |
| Audrain (2013)  | 10 (immunosuppressed, A) + 28 (immunocompetent, B)                    | DPCP                                                                                      | 1% applied daily for 1 week if needed                                           | 0.001–6% of DPCP every 2–4 weeks  | 0        | 6 (60%)/10 in group A cleared completely, 27 (96%)/28 for group B                              | Controlled, nonprospective | Level 3                  |
| Authors        | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes | Study design      | OCEBM levels of evidence |
|---------------|--------------------|----------|-------------------------|--------------|----------|----------|------------------|--------------------------|
| Choi (2013)   | 27                 | DPCP with (16) or without (11) other modalities | 0.05% (children) or 0.1% (adults) on the upper arm | 0.1–2% of DPCP weekly | 2 (CBS) | 23 (85%)/27 with total success (11 by DPCP only) | Uncontrolled, retrospective | Level 3 |
| Kang (2014)   | 152 (72 children + 71 adults + 9 LOFU)/180 cases | DPCP | 0.1% on the buttock | 0.1% of DPCP except face (0.01%) | 9 (LOFU) | 159 (88.3%)/180 completely cured, with 86 (92.5%)/93 of children and 73 (83.9%)/87 of adults | Controlled, nonprospective | Level 3 |
| Suh (2014)    | 170                | DPCP | 0.1% in acetone on the upper arm | 0.0001–2% of DPCP weekly | 0 | 141 (82.9%)/170 with total clearance, with younger age and lesion on the hand having better clearance rate | Uncontrolled, nonprospective | Level 3 |
| Pandey (2015) | 72 (children)      | SADBE    | 2% on the upper arm | 0.2–2% of SADBE from 3 times a week to daily | 24 (LOFU) | 40 (83%)/48 reported complete resolution | Uncontrolled, retrospective | Level 3 |
| Park (2016)   | 72                 | DPCP | 0.1% on the buttock | 0.1–2% of DPCP every week | 11 (LOFU) | Application number for sensitization and erythema and blister index contribute to a shorter time for complete cure | Uncontrolled, retrospective | Level 3 |
| Authors           | Participant number | Agent(s)                                      | Sensitization protocol | Intervention                        | Dropouts | Outcomes                                                                 | Study design                  | OCEBM levels of evidence |
|-------------------|--------------------|-----------------------------------------------|------------------------|-------------------------------------|----------|--------------------------------------------------------------------------|------------------------------|----------------------------|
| Dall'Oglio (2017) | 18 (SADBE) + 18 (control) | SADBE or vehicle 3% or vehicle directly to the lesions | 0.3% of SADBE or vehicle once weekly for 8 weeks | 3 (LOFU) | Significantly higher clearing rates (41.2%) in SADBE group than in control group (12.5%) | Randomized, double-blind, vehicle-controlled | Level 2                   |
| Park (2018)       | 43 (DPCP, A) + 171 (cryotherapy, B) + 36 (pulsed dye laser, C) | DPCP or cryotherapy or pulsed dye laser 0.1–0.5% to the lesion for 24 h | 0.0001–1% of DPCP once a week | 22 (CBS) | Group A (75.6%) showed lower response rate than group B (89.8%) and group C (90.3%), and initial sensitization to DPCP does not predict response rate (76.3% versus 74.4%) | Uncontrolled, retrospective | Level 3                   |

CBS cannot be sensitized. LOFU lost to follow-up
| Authors                  | Participant number | Agents  | Sensitization protocol | Intervention                | Dropouts | Outcomes                                                                 | Study design            | OCEBM levels of evidence |
|--------------------------|--------------------|---------|-------------------------|-----------------------------|----------|---------------------------------------------------------------------------|-------------------------|--------------------------|
| Moore (1978)             | 12 (DNCB) + 11 (5-FU) | DNCB or 5-FU | No                      | 0.2% of DNCB or 5% 5-FU ointment, frequency undocumented | 6 (DNCB) + 7 (5-FU) | 5 (83%)/6 received complete clearance in DNCB group; compared to 2 (50%)/4 in 5-FU group | Randomized, nonprospective | Level 2                  |
| Georgala (1989)          | 15 DNCB            | DNCB    | 0.15 ml of 2% in acetone on the right arm | 0.5 or 1% of DNCB weekly for 6–8 weeks | 2 (1 discontinued treatment, 1 due to side effects) | Lesions all cleared in other 13 patients | Uncontrolled, nonprospective | Level 3                  |
| Dall’ Oglio (2002)       | 7 (adults) + 2 (children) | SADBE   | 3% in acetone to the lesion (adult) or dorsum of hand (children) | 0.0003–0.3% of SADBE twice a week | 1 (lost to follow-up) | Lesions all cleared in 8 patients without recurrence in 18 months | Uncontrolled, nonprospective | Level 3                  |
| Miyata (2019)            | 3 (children)       | DPCP    | 0.1% to the left arm for 24 h | 0.5 or 0.05% of DPCP to the lesion twice a week | 0 | All the lesions regressed completely in 6 months | Case series | Level 4                  |
| Yen (2020)               | 1                  | DPCP    | 1% to the left upper arm for 24 h | 0.1% of DPCP to the lesion every 2 weeks for 2 months | 0 | The lesion disappeared completely after 6 months | Case report | Level 4                  |
group showed significantly lower induration of lesions in the 4th, 8th, and 12th week compared with controls [81]. Until now, there is still no approved topical agent, and therefore, DPCP or SADBE possesses potential for the treatment of leishmaniasis.

**Molluscum Contagiosum**

Molluscum contagiosum (MC) is caused by the poxvirus known as molluscum contagiosum virus (MCV). It is commonly seen in children aged 1–4 years, and in immunocompromised patients. In most cases, MC is considered self-limiting and treatment is done for cosmetic purposes or to prevent the spread of the virus. However, some patients develop into severe cases and are recalcitrant to conventional therapy. There is no standardized therapy for MC, and options include cryotherapy, curettage, cantharidin, and potassium hydroxide (KOH) solution, all by the mechanism of direct destruction to the tissue [31], which may cause intolerable pain in cases with numerous lesions and in younger children. Thus, DPCP treatment might be an attractive choice. Fourteen of 22 children (63.6%) with MC treated by weekly DPCP achieved a complete clearance in the mean treatment period of 5.1 weeks, and partial clearance was observed in 3 patients (13.6%) who were treated at inadequate intervals [82]. There was also one case report documenting a human immunodeficiency virus (HIV)-infected patient with MC successfully treated by DPCP [83]. However, owing to the self-limiting nature in most cases (up to 70% in 18 months) [31], the true efficacy of DPCP remained to be confirmed. Currently, there is no approved topical medication for the treatment of molluscum contagiosum.

**Tumor and Malignancy (Table 4)**

**Actinic Keratosis**

Actinic keratosis is a precancerous lesion found on sun-exposed areas. Physical treatments such as cryotherapy, curettage, and excision are used most frequently. For patients with involvement of large areas, 5-FU, imiquimod, and photodynamic therapy are also available options. A comparative study was done in patients treated with 5-FU ± DNCB [84]. The results showed a only slightly better response with combination therapy compared with 5-FU alone. Therefore, the researchers suggested the use of 5-FU monotherapy to avoid the unwanted inflammation caused by DNCB. Currently, many topical treatments that have been approved for actinic keratosis include tirbanibulin ointment, diclofenac gel, imiquimod cream, and 5-fluorouracil cream. Thus, the use of topical DNCB, DPCP, and SADBE in actinic keratosis seems limited.

**Basal Cell Carcinoma and Basal Cell Nevus Syndrome**

Basal cell nevus syndrome (NBCCS) is a genodermatosis characterized by the development of numerous BCC that ultimately progress into infiltrative cancers, in addition to other complex abnormalities and tumors. Routine method for BCC removal is by surgical excision. DNCB was tried for treating patients with multiple BCC or NBCCS [85, 86]. Unfortunately, the result in patients with NBCCS was unsatisfactory.

**Bowen’s Disease**

Bowen’s disease is a carcinoma in situ of squamous cell carcinoma (SCC) which may turn invasive if left untreated. It may be caused by numerous factors, such as arsenic ingestion, sun exposure, radiation exposure, and human papillomavirus (HPV) infection. Treatment options for Bowen’s disease are various, including surgical excision, curettage, cryotherapy, topical 5-FU cream, imiquimod cream, photodynamic therapy, and so on. One case report documented a patient with multiple Bowen’s disease due to arsenic ingestion. Treatment with 5-FU and DNCB resulted in complete remission after a few months [87]. However, no topical medication has been approved for the treatment of Bowen’s disease. Compared with topical destructive therapy, topical immunotherapy is painless but needs multiple treatment courses.
| Authors            | Disease                          | Participant number | Agent(s)  | Sensitization protocol | Intervention | Dropouts | Outcomes                                                                 | Study design               | OCEBM levels of evidence |
|--------------------|----------------------------------|--------------------|-----------|------------------------|--------------|----------|--------------------------------------------------------------------------|----------------------------|--------------------------|
| Price (1979)       | Actinic keratosis                | 15                 | 5-FU ± DNCB| 0.15 ml of 2% DNCB in acetone to the upper arm | 1% 5-FU cream applied every other day to twice a day to both arms and hands; 0.001–0.1% of DNCB daily to only one side of arm and hand; 6–8 weeks | 5 (LOFU) | 4 (40%)/10 showed complete response in both arms; 5/10 (50%) showed better response in the side with DNCB + 5-FU; 1 (10%)/10 showed fewer lesions in 5-FU only side | Controlled (half body), nonprospective | Level 3                  |
| Levis (1973)       | Multiple basal cell carcinomas   | 5 patients with 113 tumors | DNCB      | 0.1 ml of 2% DNCB in acetone to the upper arm for 1 week | 0.000001–0.1% of DNCB to the lesion daily | 0        | 36 (32%)/113 of BCCs with complete regression, 33 (29%)/113 with partial regression, compared to untreated group, which showed no regression | Controlled (half body), nonprospective | Level 3                  |
| Hazen (1984)       | Basal cell nevus syndrome        | 1                  | DNCB      | 0.5% in acetone         | 0.5% of DNCB daily for 4 months | 0        | No improvement                                                             | Case report                | Level 4                  |
| Raff (1976)        | Bowen’s disease                  | 1                  | DNCB and 5-FU | Yes, but undocumented | 0.001% of DNCB cream twice daily, and added 5% 5-FU cream for the largest lesion at flank | 0        | All the lesions disappeared within 2 months, while the largest one completely diminished in 8 months | Case report                | Level 4                  |
| Ferry (1976)       | Conjunctival papilloma           | 1                  | DNCB      | 2 mg to the forearm     | 0.2% of DNCB in acetone weekly for five times, and one intralesional injection to the tumor at the canalicular opening | 0        | All the lesions disappeared after treatment and free of recurrence after 3-year follow-up | Case report                | Level 4                  |
| Petrelli (1981)    | Conjunctival papilloma           | 1                  | DNCB      | 0.1 ml of 2% DNCB in acetone to right arm twice, and then 1 mg of DNCB to right arm once | 0.25% of DNCB topically once a week, with a few subconjunctival injections | 0        | Complete remission after multiple irregular treatments at a span of 14 months | Case report                | Level 4                  |
### Table 4 continued

| Authors     | Disease                              | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes                                                                 | Study design                  | OCEBM levels of evidence |
|-------------|--------------------------------------|--------------------|----------|------------------------|--------------|----------|---------------------------------------------------------------------------|-------------------------------|--------------------------|
| Novick (1986) | Conjunctival papilloma                | 1                  | DNCB     | 2% in acetone to left arm for 24 h | 0.1–2% of DNCB once a week | 0        | No improvement                                                            | Case report                  | Level 4                  |
| Kutty (2013)  | Eccrine porocarcinoma                | 1                  | DPCP     | 2% in acetone to left forearm | 1% of DPCP once a week | 0        | Complete remission after 6 weeks                                          | Case report                  | Level 4                  |
| Lew (1985)    | Fibrous histiocytoma                 | 1                  | DNCB     | 10% in acetone to right forearm by intradermal inoculation | 0.25% of DNCB topically once a week, with a subconjunctival injection | 0        | Complete remission after twice topical treatment and one injection        | Case report                  | Level 4                  |
| Ireland (1988) | Abnormal vaginal cytology following hysterectomy | 32                 | Vaginectomy (15) or laser (11) or DNCB (2) or 5-FU (2) | Undocumented | Undocumented | 0        | Both patients treated with DNCB ultimately received further management    | Uncontrolled, prospective   | Level 3                  |
| Guthrie (1975) | CIS of vagina                        | 6                  | DNCB     | 0.1% of cream to arm or leg once daily until reaction appeared | 0.0005–0.1% DNCB in cream inserted at the vaginal vault daily for 3 days | 0        | All the patients (6) had normal vaginal smear ever since                  | Uncontrolled, prospective   | Level 3                  |
| Guthrie (1979) | CIS of cervix                        | 180                | DNCB     | 0.1% of cream to skin once daily until reaction appeared | 0.0005–0.1% DNCB in cream inserted at the cervix once | 25       | Only 50 (32%)/155 became negative in smear test                          | Uncontrolled, prospective   | Level 3                  |
| Foster (1981)  | CIS of vulva                         | 6                  | DNCB     | 2% in acetone to forearm | 10^30−0.1% of DNCB cream daily until the lesion grossly eradicated | 0        | 4 (66.7%)/6 had total eradication of the disease, 1 recurred within 1 year | Uncontrolled, prospective   | Level 3                  |
| Pagliarello (2017) | Kaposi sarcoma                     | 2                  | DPCP     | No                     | 0.2% of DPCP cream weekly | 0        | Lesion cleared within 1 month (case 1)/4 months (case 2)                | Case series                  | Level 4                  |
Conjunctival Papilloma
Conjunctival papilloma is a heterogeneous entity that can be further classified into viral (HPV), squamous cell, limbal, and inverted types. Several case reports using topical immunotherapy have been published. However, the results are controversial [88–91]. Topical immunotherapy should be considered only when conventional therapies show minimal effects.

Eccrine Porocarcinoma
Eccrine porocarcinoma (EPC) is a rare malignancy that develops from the eccrine gland, most commonly at the lower extremities. Surgical resection is the treatment of choice, while radiotherapy and chemotherapy show limited effect. A case report presented the case of an 82-year-old lady with multiple primary EPC on the dorsa of both feet [92]. After topical DPCP treatment, all lesions resolved completely without recurrence after 6 months of follow-up. The success in this case suggested the potential of immunotherapy in this rare skin cancer. Currently, no topical medication has been approved for the treatment of porocarcinoma.

Fibrous Histiocytoma
Fibrous histiocytoma is a common benign mesenchymal tumor, and complete excision is the treatment of choice. A case report presented the case of a 66-year-old male with local recurrent conjunctival fibrous histiocytoma despite two prior complete excisions [93]. After applying DNCB twice, the tumors resolved completely without recurrence for over 2 years. The report suggested the potential of topical immunotherapy in fibrous histiocytoma, especially in cosmetically sensitive areas or in recurrent cases.

Gynecological Cancer (Carcinoma In Situ of Vulva, Vagina, and Cervix)
Gynecological carcinoma in situ (CIS) may become invasive after several years if left untreated. Topical immunotherapy using DNCB had been attempted to treat CIS of vulva, vagina, and cervix. While CIS of the vagina showed an excellent response, there were

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*Table 4 continued*

| Authors | Disease | Participant number | Agent(s) | Sensitization protocol | Intervention | Outcomes | Study design | OCEBM level of evidence |
|---------|---------|--------------------|---------|------------------------|--------------|----------|--------------|------------------------|
| Herrmann (2004) | Merkel cell carcinoma | 1 | DNCB and additional radiotherapy (RT) in case of recurrence | 0.25% of DNCB in petroleum weekly for 1 month and 1.8 Gy of RT for 30 days | Lesions disappeared in 4 weeks and remained clear since then | Lesions disappeared in 4 weeks and remained clear since then | Case report | Level 4 |
| Vonderheid (1977) | Mycosis fungoides | 19 | Meclorethamine: 10, 1, 0.1 l; DNCB: 50, 25, 2.5 µg to 3 x 5 cm of normal skin for 48 h | Undocumented | 8/19 (42%) received complete clinical remission, but the case number of each agent remained unknown | 0 | Uncontrolled, nonprospective | Level 3 |

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Eccrine porocarcinoma (EPC) is a rare malignancy that develops from the eccrine gland, most commonly at the lower extremities. Surgical resection is the treatment of choice, while radiotherapy and chemotherapy show limited effect. A case report presented the case of an 82-year-old lady with multiple primary EPC on the dorsa of both feet [92]. After topical DPCP treatment, all lesions resolved completely without recurrence after 6 months of follow-up. The success in this case suggested the potential of immunotherapy in this rare skin cancer. Currently, no topical medication has been approved for the treatment of porocarcinoma.
unsatisfactory results in CIS of cervix and only a partial effect in CIS of vulva [94–96]. Another study recruiting patients with abnormal vaginal cytology after hysterectomy showed DNCB treatment to be ineffective [97]. The main limitation of the studies is the small participating case numbers. Research involving more cases must be conducted before it can be considered a viable option for patients who refuse to receive surgical treatment. Currently, no topical medication has been approved for the treatment of gynecological carcinoma in situ.

**Kaposi Sarcoma**

Kaposi sarcoma is a multifactorial disease caused by HHV8 infection and an immunosuppressed status [98]. Conventional therapies include surgical excision, cryotherapy, chemotherapy, and radiotherapy. Owing to the success in the treatment of melanoma, topical DPCP has been used in two patients with recurrent Kaposi sarcoma after surgical excision, and both achieved complete remission [99]. Compared with intralesional chemotherapy, cryotherapy, or surgery, topical DPCP in Kaposi sarcoma is inexpensive and pain free, and can be applied to multiple areas. Currently, no topical medication has been approved for Kaposi sarcoma. Compared with topical destructive therapy, topical immunotherapy is painless but needs multiple treatment courses.

**Melanoma (Table 5)**

In 1973, the first attempt to treat melanoma with DNCB was documented [100]. However, a standardized treatment protocol was lacking until recently [101]. The primary treatment for melanoma is still surgical excision, with chemotherapy, target therapy, or immune-checkpoint inhibitors for metastatic cases. In spite of the established guideline, there are still cases for which surgery is inappropriate owing to age or general conditions. With numerous reports of spontaneous regression, it is clear that host immunity plays an important role in suppressing melanoma. Topical immunotherapy for melanoma has been studied extensively [17, 101–135], and its role is evidenced by the approval of a topical DPCP gel named Samcyprone in the USA for the treatment of cutaneous melanoma stage IIb–IV despite the presence of many treatment choices now available, including pembrolizumab and nivolumab. Topical immunotherapy is often used in combination therapies with synergistic effect, and for cases with visceral or distant metastases, topical contact agent as monotherapy shows effect on only cutaneous lesions and cannot slow down the progression [120, 133]. Patients with lower disease burden responded more favorably than those with a greater disease burden [107, 126, 128, 136]. Also, patients who showed less response to initial therapy had greater tendency to progress [131]. Some researchers combined topical agents with systemic chemotherapy or radiotherapy, and showed positive results [128–131].

The exact mechanism by which these topical agents can cause regression of melanoma remains speculative. Initially, it was postulated that they work as nonspecific immune stimulators or even melanocytotoxic agents [133]. As more research was conducted, Th17 cells and CD70-CD27 co-stimulatory pathways were found to be the most responsible for the destruction of melanoma in murine models, with therapeutic effects dependent on interferon-γ production instead of IL-17A and IL-23 [137]. Moreover, a follow-up study in a patient with regression of melanoma after DPCP revealed increased expression of IL-17C/D/E/F prior to treatment, and undetectable levels thereafter. Also, expression of CTLA4 and PLZF was elevated after treatment while undetectable before treatment [135]. As studies showed the relationship between anti-PD1 therapy and Th17 cells, contact agents are postulated to act by a mechanism similar to that of anti-PD1 treatment [138]. Currently, no topical medication has been approved for melanoma.

**Merkel Cell Carcinoma**

Merkel cell carcinoma is a rare but very aggressive cutaneous malignancy. It may be caused by Merkel cell polyomavirus or high exposure to UV radiation. Merkel cell carcinoma often occurs in patients with immunocompromised status, such as old age, HIV infection, or hematological malignancy, or in those with
| Authors          | Participant number | Agent(s)          | Sensitization protocol | Intervention                                                                 | Dropouts | Outcomes                                                                 | Study design  | OCEBM levels of evidence |
|------------------|---------------------|-------------------|------------------------|-------------------------------------------------------------------------------|----------|---------------------------------------------------------------------------|---------------|--------------------------|
| Cohen (1978)     | 18 patients with 199 (BCG) + 567 (DNCB) lesions | DNCB or BCG       | 2 mg in 0.1 ml of acetone on the forearm | Intrallesional injection of 0.5% DNCB every 4–6 weeks until all lesions injected | 0        | BCG group (167/199) and DNCB group (480/567) showed similar efficacy, with dermal lesions (90%) more efficient than subcutaneous ones (43%) | Uncontrolled, comparative, nonprospective | Level 3 |
| Illig (1984)     | 50                  | DNCB              | 0.66% in acetone near the tumor | 1 g of DNCB in Vaseline for 6 days, then washed out and reapplied the following day | 0        | 46 (92%)/50 with complete regression in primary tumor, but 5 showed local recurrence, 3 died of metastases; 4 (8%)/50 with poor response due to secondary nodular melanoma | Uncontrolled, prospective | Level 3 |
| Budzanowska (1988) | 19                 | DNCB              | 2% in acetone to normal skin for 48 h | 1–2% of DNCB brushed onto the lesion, with 1–3% of DNCB for recalling once a week | 0        | 3 (16%)/19 with complete remission, 3 (16%)/19 with partial remission, 1 (5%)/19 with stable status, other 12 (63%)/19 with progressive disease after 20 month follow-up | Uncontrolled, prospective | Level 3 |
| Strobbe (1997)   | 59                  | DNCB + dacarbazine (DTIC) | 2% in acetone on day 1, 8, 15, then 3% ointment used 3 times a week; DTIC started after 4 weeks of DNCB application, every 3–4 weeks | 0.1 ml of 2% DNCB on day 1, 8, 15, then 3% ointment used 3 times a week; DTIC started after 4 weeks of DNCB application, every 3–4 weeks | 0        | 15 (25%)/59 with complete response, 7 (12%)/59 with partial response, 37 (63%)/59 showed no response | Uncontrolled, retrospective | Level 3 |
| Göring (1998)    | 1                   | DNCB + fotemustine | 2% in Vaseline on skin lesions | 0.5–1% of ointment applied to skin lesions weekly; 100 mg/m² of fotemustine after 3 weeks of DNCB every month | 0        | Skin and brain metastases all disappeared without recurrence in 6 months | Case report | Level 4 |
| Authors          | Participant number | Agent(s)                  | Sensitization protocol | Intervention                                                                 | Dropouts | Outcomes                                                                 | Study design     | OCEBM levels of evidence |
|-----------------|--------------------|---------------------------|------------------------|-----------------------------------------------------------------------------|---------|--------------------------------------------------------------------------|------------------|-------------------------|
| Trefzer (2005)  | 1                  | DPCP + DTIC + radiation   | 1% of DPCP on left thigh | 850 mg/m² of DTIC intravenously and 1% of DPCP topically every month; 40 Gy of electron radiation in the first 2 cycles | 0       | Complete remission of the lesion after 15 cycles and remained recurrence-free for 14 months, but died 2 weeks after the newly diagnosed brain metastases that caused brain hemorrhage | Case report | Level 4                  |
| Terheyden (2007)| 75                 | DNCB + DTIC               | 2% in Vaseline to one skin metastasis or occipital region | 0.005–2% of DNCB to all skin lesions weekly, 850 mg/m² of DTIC every 3 weeks | 3 (secondary neoplasm) | Stage 3: 24 (62%)/39 with objective response | Uncontrolled, retrospective | Level 3                  |
| Damian (2014)   | 58                 | DPCP                      | 2% in acetone on upper arm for 48 h | 0.00001–10% of DPCP once a week for 2–24 h, up to 5 years | 8 (5 progressed rapidly, 3 due to discomfort by treatment) | 23 (46%)/50 achieved complete clearance, 19 (38%)/50 showed partial response | Uncontrolled, nonprospective | Level 3                  |
| Fujimura (2016) | 2                  | SADBE or DPCP + nivolumab | No                     | 0.3–1% of SADBE or 0.1–1% of DPCP every 2 weeks + nivolumab 2 mg/kg every 3 weeks | 0       | Both cases received nearly complete remission after 6 months of treatment | Case series     | Level 4                  |
| Moncrieff (2016)| 35                 | DPCP                      | 2% in acetone to inner arm for 48 h | 0.000001–0.05% of DPCP cream once weekly | 0       | 10 (28.6%)/35 with complete remission, 11 (31.4%)/35 with partial response, 14 (40%)/35 with no response | Uncontrolled, retrospective | Level 3                  |
| Authors       | Participant number | Agent(s) | Sensitization protocol | Intervention protocol | Dropouts | Outcomes                                             | Study design           | OCEBM level of evidence |
|--------------|--------------------|----------|------------------------|-----------------------|----------|------------------------------------------------------|------------------------|------------------------|
| Read (2017)  | 58                 | DPCP     | 2% in acetone to upper arm for 48 h | 0.005–1% of DPCP cream once to twice per week | 4        | 12 (22%)/54 with complete response, 21 (39%)/54 with partial response, 13 (24%)/54 with stable disease, 8 (15%)/54 with progressive disease | Uncontrolled, prospective | Level 3                |
| Yeung (2017) | 15                 | DPCP     | 2% in acetone to upper arm for 48 h | 0.01–0.1% of DPCP once a week | 3        | 2 (13%)/15 with complete response, 4 (27%)/15 with partial response, 21 (39%)/15 with stable disease | Uncontrolled, retrospective | Level 3                |
| Gibbons (2018)| 15                 | DPCP     | 2% in acetone to upper arm or back for 48 h | 0.0025–0.005% of DPCP weekly for 3 months | 0        | 6 (37.5%)/15 with complete response, 4 (25%)/15 with partial response, 3 (15%)/15 with stable disease | Uncontrolled, prospective | Level 3                |
| Veerka (2018) | 13                 | DPCP     | 0.5 or 2% of 0.0001–2% of DPCP solution to inner arm weekly | 1 could not be sensitized, 1 due to side effect | 0        | 4 (22.2%)/9 with full regression, 3 (33.3%)/9 with partial regression, 1 (11.1%)/9 with stable disease, 3 (33.3%)/9 progressed | Uncontrolled, retrospective | Level 3                |
solid organ transplants. Current treatment options available are surgical excision, radiotherapy, systemic chemotherapy, and immune checkpoint inhibitors. A man diagnosed with stage 2 Merkel cell carcinoma on the scalp, with local and regional metastases, has been treated with topical DNCB and additional radiotherapy. The lesions disappeared without signs of recurrence during 1 year of follow-up [139]. The role of topical immunotherapy in Merkel cell carcinoma deserves further investigation. Currently, no topical medication has been approved for Merkel cell carcinoma.

Mycosis Fungoides
Mycosis fungoides is the most common type of primary cutaneous lymphoma. It may also be due to the transformation from large-plaque type parapsoriasis. Conventional therapeutic options available are topical corticosteroids, nitrogen mustard, carmustine, phototherapy, radiotherapy, or systemic treatment including chemotherapy (although mostly resistant), immunotherapy (interferon-α), and oral retinoids. In one study evaluating topical chemotherapy and immunotherapy in patients with mycosis fungoides, it showed that cases treated with topical DNCB or meclorethamine had a complete clinical remission rate of 42% (8/19), but the exact case number of patients treated with DNCB or meclorethamine was unknown [140]. More studies are needed to prove the benefit. Currently, the most common topical treatment for mycosis fungoides is topical corticosteroid, and chlorethamine gel has been approved for patients with stages IA and IB mycosis fungoides. The role of DNCB, DPCP, and SADBE seems limited.

Immune-Mediated Inflammatory Skin Diseases (Table 6)

Atopic Dermatitis
Atopic dermatitis (AD) is a common inflammatory skin disease with rising prevalence. Recent approval of oral JAK inhibitors and IL-4/IL-13 inhibitors have reshaped the treatment of severe atopic dermatitis. However, the high cost of these novel treatments and risk of systemic immunosuppression and toxicity leave room for other alternative treatment modalities. Two trials of topical immunotherapy recruiting patients with refractory AD have been reported [141, 142]. In one trial, topical DNCB was given weekly in eight patients with refractory atopic dermatitis after initial sensitization. Six of 8 patients showed apparent improvement both on clinical scores and on laboratory data at 16 weeks. One patient did not show clear improvement, and another showed deterioration [141]. In the other study, weekly 12- to 18-h applications of DNCB patches were given in nine patients for 6 months, and seven patients showed a significant decrease in body surface area of involved skin [142]. One patient’s disease was aggravated, and one patient had early discontinuation due to the development of B-cell lymphoma. The use of topical DNCB in atopic dermatitis is interesting, but in view of the many topical treatments approved for atopic dermatitis, such as corticosteroids, topical calcineurin inhibitors (tacrolimus, pimecrolimus), and crisaborole, its role seems limited.

Lichen Nitidus
Lichen nitidus is an uncommon inflammatory skin disease that often occurs in childhood, characterized by numerous, chronic, flesh-colored, dome-shaped papules most commonly on the forearms, abdomen, chest, and penis. Etiology is unknown, and the lesions resolve spontaneously within 12 months in most patients. Therefore, treatment is usually unnecessary unless requested by patients owing to cosmetic concern, severe pruritus, or prolonged course. Treatment options include phototherapy, corticosteroid, tacrolimus, or antihistamine. A case report documented the case of a 40-year-old man with peripheral CD4+ T lymphocytopenia and lichen nitidus for 5 years [143]. The lesions that were applied with DNCB resolved, but lesions elsewhere remained. However, 6 months after cessation of the therapy, the papules recurred again. It seems that DNCB is able to induce the resolution of lichen nitidus with only local effect. Also, the effects cannot persist over the long term. Although no
| Authors          | Disease               | Participant number | Agent(s) | Sensitization protocol | Intervention | Dropouts | Outcomes                                                                 | Study design          | OCEBM levels of evidence |
|------------------|-----------------------|--------------------|----------|------------------------|--------------|----------|---------------------------------------------------------------------------|-----------------------|--------------------------|
| Mills (2000)     | Atopic dermatitis     | 9                  | DNCB     | Patch with 1.5 mg of crystalline DNCB to skin for 12–18 h | Patch with 50–500 μg of DNCB for 12–18 h weekly | 0        | 7 (77.7%)/9 had decrease in involving areas; total involving areas decreased from 36 to 17% after 6 months | Uncontrolled, prospective | Level 3                  |
| Yoshizawa (2000) | Atopic dermatitis     | 8                  | DNCB     | 5% in acetone to upper arm | 1% of DNCB to upper arm weekly | 0        | 6 (75%)/8 with apparent improvement after 4 months; 1 showed no improvement; 1 deteriorated | Uncontrolled, prospective | Level 3                  |
| Kano (1998)      | Lichen nitidus        | 1                  | DNCB     | 1% in acetone          | 0.1 of DNCB every 2 weeks | 0        | Lesions resolved after 2–3 months, but recurred 6 months after cessation | Case report           | Level 4                  |
| Mandrea (1971)   | Parapsoriasis          | 1                  | DNCB     | No                     | 1% of DNCB in equal parts olive oil and propylene-glycol twice daily for 9 days | 0        | Lesion subsided in 3 months after 9 days of treatment                  | Case report           | Level 4                  |
| Yoshizawa (1999) | Prurigo nodularis      | 1                  | DNCB     | 10% of solution to upper arm | 2% of DNCB weekly to the normal skin of upper arm, and reduced to 0.2% after 5 weeks | 0        | Pruritus eased in 2 weeks, and lesions almost cleared by week 5         | Case report           | Level 4                  |
topical or systemic medications have been approved for the treatment of lichen nitidus, the clinical application of DNCB in the treatment of lichen nitidus in patients with immunodeficiency seems limited considering the multiplicity of lesions.

**Parapsoriasis**

Parapsoriasis is an etiologically heterogeneous group of disorders that tend to have a similar appearance of thin, scaly, pink patches and plaques. Some cases might transform into cutaneous T-cell lymphoma. Treatments include phototherapy and corticosteroids. A case report described a 44-year-old man with an eruption on the left abdomen (25 × 15 cm) for 1 year [144]. DNCB was used, and the lesion subsided after 3 months without evidence of recurrence. No medications have been approved specifically for parapsoriasis.

**Prurigo Nodularis**

Prurigo nodularis is a severe form of prurigo with multiple severely itchy firm nodules. People of all ages can be affected, especially those with atopic dermatitis, asthma, or hay fever. Although no medications have been specifically approved for its treatment, the beneficial effect of interferon-\(\gamma\), which is produced by Th1 cell stimulation, suggests the role of Th1 cells stimulation in prurigo nodularis treatment. Owing to the ability to boost the Th1 response seen in patients with acquired immune deficiency disease [145], DNCB has been tried in a 50-year-old woman without any systemic diseases who suffered from a 5-year history of chronic prurigo nodularis [146]. DNCB was applied weekly to normal skin, and the patient achieved complete remission of the lesions by week 5. Although efficacy of DNCB requires more data to confirm, DNCB therapy may be investigated as an alternative treatment for patients with prurigo nodularis who failed or were intolerant to topical corticosteroids, which are the only treatments approved for prurigo nodularis. Compared with topical destructive therapy, topical immunotherapy is painless but needs multiple treatment courses.
Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is characterized by production of autoantibodies against a number of self-antigens. Th2 response is believed to be dominant in patients with SLE, while Th1 response is suppressed [147]. A case report presented the case of a 71-year-old female patient with SLE whose arthralgia and cardiac function surprisingly improved after usage of DNCB, with ANA titer decreasing to an almost undetectable level [147]. Her SLE disease activity index improved by more than 50%. Clarifying the mechanism of topical DNCB in SLE may deepen the understanding of the disease and the role of topical immunotherapy in SLE.

Vitiligo

Vitiligo is still an unsolved problem without proven specific treatment. There are publications reporting moderate-to-severe hyperpigmentation in patients with alopecia areata treated with contact sensitizers [148]. A study recruited patients with limited vitiligo. With the application of DPCP, 13 of the 19 patients were evaluated at the end of 6 months. Four patients with focal vitiligo, one patient with vitiligo vulgaris, and three patients with segmental vitiligo showed marked (grade 3) repigmentation [149]. However, all repigmentation disappeared on stopping the treatment. In contrast, vitiligo as an adverse event has been reported following contact sensitizers [150–160]. Thus, topical immunotherapy has been considered as a depigmentation treatment option for patients with extensive vitiligo [161, 162]. The seemingly paradoxical effect requires further studies to clarify the relationship between contact sensitizers and pigmentation. Currently, topical ruxolitinib has recently been approved for repigmentation of vitiligo, but topical corticosteroid and topical calcineurin inhibitors (tacrolimus, pimecrolimus) are the most commonly used topical treatment for vitiligo. However, none of them provides universal satisfactory results. No topical medications were approved for depigmenting vitiligo. A search for alternative topical treatments, including DPCP or SADBE, is still needed.

ADVERSE EFFECTS AND SAFETY CONCERNS OF TOPICAL IMMUNOTHERAPY

Except for the expected adverse reactions, that is, contact dermatitis [148, 163–165] or lymphadenopathy [166–168], there are some rare or even serious adverse events reported. These include urticaria [169–177], depigmentation [155, 156, 160], vitiligo [150–154, 157–159, 178], erythema multiforme [179–183], discoid lupus erythematosus [184, 185], angioedema [186, 187], nickel sensitivity [188], allergic contact dermatitis from dyes in wigs [189], acquired hair curling [190], hair pigmentary changes [191], psoriatic koebnerization [192], pityriasis lichenoides [193], dyspepsia [173], epidermolysis bullosa acquisita [194], and anaphylaxis [195]. In addition, there are a few reports documenting sensitization to the medical staff that handle the chemical compound [196–201]. Appropriate precautions are strongly recommended when using or preparing the substance, such as a designated area with adequate ventilation, protective garments, and facilities for storage.

Ever since the contact sensitizers were introduced in clinical practice, the safety of the compounds has been debated. DNCB has been found to be mutagenic on Ames test, although the results remain controversial [58, 202–205]. The usual manufacturing method of DNCB produces a variety of contaminants, most of which are due to the incomplete composition and degradation [205]. To clarify the compound that truly causes mutagenicity, several studies were conducted with inconsistent results. Some claimed the contaminants are the mutagens [205], while others argued that DNCB itself is the one [204]. Although mutagenicity cannot be equated to carcinogenicity [203], the use of DNCB has declined and safer compounds such as SADBE and DPCP are now recommended [202, 204, 206]. SADBE does not cause mutagenicity on Ames test [207]. Also, no identifiable contaminants were detected. However, owing to the shorter shelf-life and higher cost, SADBE is less often used [208].
LIMITATIONS

The main limitations of the study include firstly the lack of control studies with active comparator arms in all studies, mainly due the lack of approved topical medications for most of the diseases. Most reports were uncontrolled cases series or single studies. Secondary, DCP and SABDE were self-compounded, so the stability of the compound is unknown. Thirdly, the evaluation of skin lesions needs standardization for the comparison of efficacy. Fourthly, for patients who were treated effectively, long-term follow-up and subsequent regimen for maintenance may be needed. Finally, the mechanisms of topical immunotherapy were poorly studied outside alopecia areata and verrucae.

CONCLUSION

Topical immunotherapy has long been used as an alternative therapy when conventional options show minimal effect, are unsuitable, or have been rejected by the patients. However, the use of contact immunotherapy with DNCB, DPCP, and SADBE has declined in part owing to the emergence of more effective treatment, and also owing to the restriction of self-compounding by the health authorities in many countries. However, DPCP and SADBE have already been officially approved as compounded chemicals that can be used for skin diseases. Also, an orphan drug status has been granted for DPCP gel for the treatment melanoma by the US Food and Drug Administration. In current practice, topical immunotherapy has been listed as a standard treatment for extensive alopecia areata in many national guidelines. Although less commonly used, it is also listed in some treatment guidelines in cutaneous warts. Topical immunotherapy has the advantage of relatively low cost, painlessness, and ease of application. Also, the treatment frequencies might be tapered for diseases that need long-term maintenance. Compared with immune-enhancing medications like PD-1/PD-L1 inhibitors for various malignancies and baricitinib for alopecia areata, the cost saving and better safety profile of topical immunotherapy is obvious. Thus, it may provide a preferable choice in developing countries, vulnerable groups, and cosmetically sensitive areas, or where there are multiple lesions. It has the potential to be used for neoplastic, inflammatory, and infectious cutaneous diseases. However, as the existing data outside alopecia areata are mostly case reports or trials on a smaller scale, more trials are required to prove the efficacy and optimize the regimen to allow the use in daily clinical practice. A better understanding of the exact mode of action of topical immunotherapy will also be needed.

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Data Availability. This is a review article and does not contain unpublished original data.

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