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REVIEW

A Review of The Efficacy of Complementary and Alternative Medicines in Managing Dermatologic Infectious Diseases

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Dermatologic infections, particularly fungal and viral, are globally prevalent and often lead patients to seek complementary and alternative medicines (CAMs). This review critically evaluates 17 studies investigating CAM efficacy in treating dermatologic infectious diseases, focusing on those evaluated in randomized controlled trials (RCTs). Tea tree oil shows modest benefit for fungal infections such as tinea pedis and onychomycosis, though studies are limited by poor blinding and dropout rates. For herpes simplex virus (HSV), propolis and *Melissa officinalis* demonstrate potential antiviral effects, but findings are limited by subjective outcomes and industry sponsorship. Green tea extract (polyphenon E) shows efficacy in treating genital warts, though adverse skin reactions and publication bias warrant caution. Other agents, including garlic-derived ajoene, honey mixtures, and podophyllin, show promise but lack robust RCT validation. While CAMs offer intriguing therapeutic avenues, rigorous trials with standardized outcomes are essential to guide evidence-based integration into dermatologic care and improve patient-centered treatment strategies. **KEYWORDS:** Complementary and alternative medicine, herpes virus, HSV, fungal infections, condyloma, onychomycosis, botanical

Dermatologic infections, including both fungal and viral etiologies, are prevalent worldwide, leading to significant chronic health burdens. In 2013, skin diseases ranked fourth among all nonfatal diseases globally, underscoring their prevalence and impact.[1] Fungal infections, such as dermatophytosis and endemic mycoses, are particularly common in tropical regions due to favorable environmental conditions; thus, they affect an estimated 25% of the world population.[2] Skin infections also impose a considerable economic burden, with substantial costs attributed to outpatient visits, hospitalizations, and long-term treatment regimens.[3] Consequently, patients often rely on complementary and alternative medicines (CAMs) that might provide therapeutic relief. National surveys indicate widespread use of CAMs among the public, with roughly 30% to 50% of the adult population reporting use of some form of CAM therapy. There is also a greater than average use among certain subgroups, including women, older adults, non-White, and immigrant groups.[4] Remarkably, 85% of patients in the National Health Interview Survey who reported having skin problems have also used some form of CAM.[5] Furthermore, surveyed physicians overwhelmingly report that patients, not physicians, initiate discussions about CAM use, and while expressing skepticism about CAM efficacy, the substantial majority desire to learn more about CAM therapies to better counsel patients.[6,7] The widespread use of CAMs among dermatology patients suggests patient needs may not be fully met by conventional dermatology. Comprehensive, objective knowledge of CAM therapies could help dermatologists connect better with patients and guide treatment plans with more sensitivity and potentially better success.[8]

This review offers an overview of CAM therapies investigated for dermatologic infectious diseases, emphasizing viral and fungal infections and detailing only those evaluated in randomized controlled trials (RCTs) or other significant clinical studies. Where applicable, the quality of evidence for a CAM therapy will be assessed using the Jadad Scale to guide practitioners on potential efficacy (Table 1).[9] Heightened scrutiny should help differentiate between scientifically proven CAM agents and those merely claimed effective by advocates.

FUNGAL INFECTIONS

Tea tree oil (TTO) has been examined in RCTs for use in the treatment of onychomycosis and tinea pedis. The onychomycosis study compared 6-month treatment with 100% TTO and 1% clotrimazole solution, finding comparable mycologic culture and subjective clinical cure rates.[10] Unfortunately, this study suffered from unclear blinding, no intent-to-treat analysis despite heavy loss to follow-up, and completely unspecified clinical outcome measures. One tinea pedis study by Satchell et al[11] compared 4-week treatment response of two concentrations of TTO to a vehicle only control, finding significant improvement in subjective clinical assessment and skin scraping cure rates only in the active treatment

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groups. However, no information was provided on investigator blinding, the parameters of the clinical cure outcome were not provided, only intragroup comparisons were made, and an intent-to-treat analysis was not performed despite high dropouts in the TTO group. Notably, moderate-to-severe dermatitis was observed in some patients in the TTO group. Finally, Tong et al[12] performed a 5-week study (n=104) examining treatment of tinea pedis with 10% TTO in sorbolene cream, 1% tolnaftate cream, or sorbolene vehicle only control; the study assessed mycological cure and improvement in a multicomponent clinical outcome score (scaling, inflammation, itching, burning). While the TTO group did show some statistically significant differences over vehicle in clinical improvements, mycological cure rate was equivalent but poor in the TTO and placebo groups (tolnaftate group was significantly greater than both) and complete cure rate (mycological + clinical response) was only significantly greater in the tolnaftate group compared to placebo. This study was overall well designed, though no intent-to-treat analysis was performed despite some dropouts, and there was a baseline significant difference in sex between the groups (but no difference in baseline clinical symptoms). Another study on TTO, subject to questionable statistical measures, also found this agent to be effective for managing fungal infections.[13] Taking these studies together, we assign the quality of the evidence supporting the use of TTO for the treatment of fungal infections an average Jadad score of 3.75, due to issues with risk of bias, and poor design and noting a heightened potential for contact dermatitis with TTO use.

Many other agents have been suggested as effective CAM treatments for fungal infections, including honey, aloe vera, and lavender, but no RCT-level study yet exists to assess their effectiveness.[14] One study demonstrated effectiveness of a topical gel containing ajoene, an organosulfur derived from garlic, in treating tinea pedis, but there was no control group for comparison.[15] The authors performed two additional follow-up studies, where both trials compared ajoene-based treatment with terbinafine, and showed clinically improved findings that lacked proper significant analysis; adequate blinding was also in question.[16,17] As a result, the average Jadad score for these two studies is 3.5. Two open studies have shown effectiveness in treating tinea infections with of a mixture of honey, olive oil and beeswax[18] and an extract of snow gum (*Eucalyptus pauciflora*),[19] but more robust controlled studies with these agents have yet to be performed.

HERPES SIMPLEX VIRUS (HSV)

A few studies have examined the honeybee-derived substance propolis for treatment of herpes simplex virus (HSV) infections due to purported anti-inflammatory and virucidal effects of its constituent flavonoids.[14] Vynograd et al[20] compared ointments containing 3% propolis, 5% acyclovir, or vehicle only for the treatment of genital herpes, with subjective lesion healing as an outcome measured for participants classified by lesion stage at presentation (vesicular or ulcerated). Investigators found significantly improved healing rates in vesicular and combined lesions in the propolis group compared to the acyclovir group, and improved healing rates in all three measures (vesicular, ulcerated, and combined) compared to placebo. While the study was generally well designed, the authors noted that it was only a single-blind design, because the active treatment ointments varied substantially in appearance and odor, and the outcome measure relied only on intragroup measure of subjective healing with no less subjective intergroup comparisons (number of lesions, size, etc). A RCT prior to this study concluded that propolis ointment helped induce healing of outbreaks of HSV and herpes zoster significantly faster than a placebo ointment, but this study is unavailable in English for review.[14] Another study on propolis also found this agent to be effective for managing HSV infections, albeit with frequent applications (5 times daily).[21]

A few RCTs have examined the use of balm mint/lemon balm (*Melissa officinalis*) in the treatment of herpes infections due to purported virustatic activity.[22] One report, which contained no description of author blinding or placebo matching, compared the response of 1% balm mint cream to placebo for the treatment of herpes labialis.[23] Measuring a multicomponent scoring system (complaints, blisters, affected area), investigators concluded efficacy based on a significant difference in scores between groups at Day 2. This conclusion is remarkably exaggerated, as all other measured outcomes, including disease scores at the three other timepoints and secondary outcomes like patient evaluation and blister number, showed no difference between groups (trending in favor of placebo). In a separate large study, Wölbling and Leonhardt[24] examined patients with a variety of HSV infections and topical application of a commercial *M. officinalis* cream or vehicle placebo to lesions over 5 days. Authors concluded effectiveness but recorded mixed results: improvements in Day 2 rubor and swelling, but not Day 5 values, and improvement in herpes labialis subgroup total lesion area but no improvement in scabbing and lesion area of the entire study group. While the study was large with well-matched groups and intergroup comparisons, the process of investigator blinding was not well described; this is of increased importance with this study because it was sponsored by the manufacturer of the treatment lotion. Other agents that have purported effects on HSV infections include extracts of licorice and hibiscus, but these have yet to be fully tested in an RCT-level study. When assessing the quality of evidence for CAMs used to HSV, the average Jadad score assigned is 3.75 due to possible risks of bias and improper study design.

TABLE 1. Jadad scale for assessing the quality of randomized controlled trials

YES	DESCRIPTION	NO
+1	The study was randomized.	0
+1	The study's method of randomization was appropriate (computer-generated, random numbers).	0
+1	The study was double-blinded.	0
+1	The study included details of appropriate double-blinding (identical placebo, dummy).	0
+1	All patients within the study, including withdrawals and dropouts, were accounted.	0

WARTS

Several CAMs have been suggested as treatments for condyloma and verruca warts, including various herbal agents, green tea extract (GTE), homeopathy, and hypnosis. Two recent reports from the same group have examined the effectiveness of a commercial green tea extract cream (polyphenon E) in large RCTs for the treatment of genital and perianal warts.[25,26] The investigators found increased wart clearance rates in both groups

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using the treatment ointment at 10% and 15% concentrations compared to the control (>50% vs. ~35% for vehicle only). Secondary outcomes showed significant improvement in median wart number and coverage area,[25] significantly shorter time to complete clearance, and similar recurrence rates.[26] Overall, these studies were well designed and properly performed; however, while the studies were labeled double-blind, no information was provided on blinding procedures and the authors were paid employees or consultants of the treatment cream manufacturer. Both of these issues may be deserving of heightened scrutiny given that the primary outcome was subjective clearance. Furthermore, the more objective outcomes were less impressive. While a difference was seen in median wart area and count (unsurprising, as they were reported as zero in treatment groups), no difference was seen in the average of these parameters, with averages perhaps being of greater relevance because this parameter would factor in a variability in response with standard deviations. Despite this, the average Jadad score for both studies is 4, due to risk of bias (publication bias, industry sponsor) and design flaw (blinding, outcome measures). It is also worth noting that unlike many other GTE studies, treatment groups in these studies did see a significantly higher incidence of adverse local skin reactions including erythema, edema, and erosion (no difference in systemic adverse events).

Another herbal agent of note in treating warts is podophyllin, derived from the root of the American mayapple (*Podophyllum peltatum*). Podophyllin has been widely reported as effective in treating condylomata acuminata, but one of the few RCTs available to fully assess effectiveness was not published in English.[27] A recently published study comparing podophyllin to diphenylcyclopropenone found that the latter had a shorter wart duration and was significantly more effective than podophyllin with a lower recurrence at the 1-year follow-up[28]; however, we give this study a Jadad score of 3 due to lack of randomization details and proper blinding. Other herbal agents with purported effectiveness but no RCT published include nightshade (*Solanaceae dulcamara*), calotropis (*Calotropis procera*), celandine (*Chelidonium majus*), and thujone—an active constituent found in *Thuja occidentalis* herbs that has shown efficacy in case reports.[29,30]

Nonbotanical CAM agents that have been used in the treatment of warts include homeopathy and hypnosis. Multiple homeopathic preparations have been suggested for wart treatment by practitioners of homeopathic medicine. However, limited studies have confirmed their effectiveness, and a few well designed RCTs have found no improvement compared to placebo in common wart area reduction following serial application of several different homeopathic preparations.[31-33] Labrecque et al[34] also found no improvement in clearance of plantar warts with a mixture of three different preparations, suggesting that the extreme dilution of active agents in homeopathy ensures lack of effectiveness. In a different approach, a group of studies from the 1950s and 1960s claimed effectiveness of hypnotic suggestion on clearance of warts, but these results have not been reliably replicated in studies with robust methodology and appropriately stringent outcome measures.[35]

CONCLUSION

It is evident that, whether physician-guided or not, the use of CAM has become a widespread and notable component of many patients' treatment regimens in dermatology. Driven by positive anecdotal evidence and significant in vitro findings, investigators have sought to transition many CAM agents into scientific medicine by conducting placebo-controlled, double-blind RCTs. Unfortunately, this effort has not been widely successful, as most studies concluding CAM benefit suffer major methodological problems that impact credibility, such as poor blinding, subjective outcomes, unreported baseline measures, lack of intergroup comparisons, and tendency to overstate positive findings while overlooking null results. Despite these reservations, some study results and the wealth of in vitro and murine data suggest many CAM agents warrant further rigorous investigation and consistent replication in well conducted RCTs. Moving forward, a pragmatic focus on comparing CAM treatments to conventional therapies, alone or integratively, would accurately reflect clinical use by patients and prove more useful for practitioners. In the interim, dermatologists should remain aware of demonstrated or purported CAM efficacy from published studies, while vigilantly monitoring for adverse effects that could impact conventional treatment plans. The widespread use of CAMs necessitates that physicians objectively evaluate their role to optimally guide patient interactions and improve outcomes through an informed, empathetic approach that integrates all therapeutic modalities.

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SUPPLEMENTAL TABLE 1. Complementary and alternative medicines for dermatologic infections

REFERENCE	n	JADAD SCORE	CAM	DOSAGE	ROA	STUDY RESULTS	ADVERSE EFFECTS
Fungal infections							
Buck et al[10]	117	3	Tea tree oil	2 times daily	Topical	After six months, the groups were comparable, with culture cure rates of 11% CL and 18% TTO and partial or full clinical resolution of 61% CL and 60% TTO.	No adverse effects were reported.
Satchell et al[11]	158	4	Tea tree oil	2 times daily	Topical	A marked clinical response occurred in 68% of the 50% TTO group and 72% of the 25% TTO group, vs. 39% with placebo. Mycological cure was 64% with 50% TTO, compared to 31% with placebo.	4 (3.8%) patients applying tea tree oil developed moderate-to-severe dermatitis that improved quickly on stopping the study medication.
Tong et al[12]	104	5	Tea tree oil	N/A	Topical	Significantly more tolnaftate patients (85%) converted to negative culture than those on TTO (30%) or placebo (21%) ($p<0.001$), with no significant difference between TTO and placebo.	No adverse effects were reported.
Syed et al[13]	60	3	Tea tree oil	3 times daily	Topical	After 16 weeks, 80% of patients using medicated cream were cured, as opposed to none in the placebo group.	4 patients in the treatment group experienced subjective reversible mild inflammation.
Ledezma et al[16]	60	3	Ajoene	N/A	Topical	At 30 days, healing rates were 77% with ajoene and 75% with terbinafine. At 60 days, they were 73% and 71%, respectively.	No adverse effects were reported.
Ledezma et al[17]	70	4	Ajoene	2 times daily	Topical	Clinical follow-up showed rapid symptom improvement in all groups. At 60 days post-therapy, mycologic cure rates were 72% with 0.6% ajoene, 100% with 1% ajoene, and 94% with 1% terbinafine.	No adverse effects were reported.
Herpes simplex virus (HSV)							
Vynograd et al[20]	90	3	Propolis	4 times daily	Topical	Healing progressed faster in the propolis group: by Day 3, 15 had crusted lesions vs. 8 with acyclovir and none with placebo ($p=0.0006$). By Day 7, healing occurred in 10 propolis patients, 4 acyclovir patients, and 3 placebo patients.	No adverse effects were reported.
Jautová et al[21]	397	5	Propolis	5 times daily	Topical	The predefined clinical endpoint was reached in a median of 3 days with propolis versus 4 days with acyclovir ($p<0.0001$), with all secondary outcomes also favoring propolis.	No allergic reactions, local irritations, or other adverse events occurred.
Koytchev et al[23]	66	3	Balm mint	4 times daily	Topical	There was a significant difference in the primary symptom score on Day 2: verum 4.03±0.33 (median: 3.0) vs. placebo 4.94±0.40 (median: 5.0).	No adverse effects were reported.
Wölbling and Leonhardt[24]	231	4	*Melissa officinalis*	N/A	Topical	Results showed improvements in Day 2 with rubor and swelling and in total lesion area for the herpes labialis subgroup, but not in Day 5 values or in scabbing and lesion area for the overall study group.	No adverse effects were reported.

CAM: complementary and alternative medicine; CL: 1% clotrimazole; N/A: not applicable; ROA: route of administration; TTO: tea tree oil

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SUPPLEMENTAL TABLE 1 CONTINUED. Complementary and alternative medicines for dermatologic infections

REFERENCE	n	JADAD SCORE	CAM	DOSAGE	ROA	STUDY RESULTS	ADVERSE EFFECTS
Warts							
Stockfleth et al[25]	503	4	Green tea extract	3 times daily	Topical	Complete clearance of all baseline and new anogenital warts occurred in 53% of patients with polyphenon E 15% ointment, 51% with 10% ointment, and 37% with vehicle (p=0.01 and p=0.03, respectively).	There were local site reactions assessed as mild or moderate. Local reactions declined during continued treatment.
Tatti et al[26]	1005	4	Green tea extract	3 times daily	Topical	Statistically significant differences in clearance emerged after 6 weeks of active treatment, which also shortened time to complete clearance. Recurrence rates during follow-up were low and similar across groups.	Adverse events were even across groups (~30% of patients). Severe local signs were more frequent but moderate in the active treatment groups.
Halim et al[28]	57	3	Podophylin	Weekly	Topical	Clearance was higher with diphenylcyclopropenone (65.5%) than with podophylin (32.1%). Shorter wart duration predicted better response in both groups. No recurrences occurred with diphenylcyclopropenone, while seven podophylin patients experienced recurrence at 1-year follow-up.	No serious adverse effects occurred in either group.
Smolle et al[31]	60	5	Homeopathy	1 bottle/person	N/A	9/30 subjects (homeopathy) and 7/30 subjects (placebo) experienced at least 50% reduction in area occupied by warts (p=0.56).	No adverse effects were reported.
Kainz et al[32]	60	3	Homeopathy	1:1012 dilution	N/A	Total cure of warts occurred in 5 patients (treated group) and in 1 patient (placebo group) (p=0.22).	No adverse effects were reported.
Dey et al[33]	60	5	Homeopathy	N/A	Oral	Intragroup improvements were greater in the treatment group than in placebo; however, intergroup differences were not statistically significant and showed small effect sizes for both primary outcomes (wart number and size at 3 months) and secondary outcomes.	No harms, homeopathic aggravations, or serious adverse events were reported.
Labrecque et al[34]	174	4	Homeopathy	30 CH (200 pellets weekly), 7 CH (5 pellets daily), and 7 CH (200 pellets daily)	Sublingual	Healing rates were similar between both groups at 6, 12 and 18 weeks: 4.8%, 13.4% and 20.0% respectively in the homeopathic group and 4.6%, 13.1% and 24.4% in the placebo group.	Minor side effects (stomachache, loose stools, tiredness, and acne) occurred rarely in two patients in the homeopathic treatment group and in four in the placebo group.

CAM: complementary and alternative medicine; CH: centésimal hahnemannien ; N/A: not applicable; ROA: route of administration