

Over-the-counter and Natural Remedies for Onychomycosis: Do They Really Work?

Pierre Halteh; Richard K. Scher, MD; Shari R. Lipner, MD, PhD

PRACTICE POINTS

- Natural remedies, including tea tree oil, natural topical cough suppressants, natural coniferous resin lacquer, *Ageratina pichinchensis* extract, and ozonized sunflower oil, have shown antifungal activities in in vitro studies.
- Some of these products have efficacy and appear to be safe in clinical studies.
- Larger randomized clinical trials demonstrating efficacy are required before we can recommend these products to our patients.

Onychomycosis is a fungal infection of the nail unit that may lead to dystrophy and disfigurement over time. It accounts for up to 50% of all nail conditions, with toenails affected more commonly than fingernails. Onychomycosis may affect quality of life and increase the prevalence and severity of foot ulcers in patients with diabetes. Available oral agents approved by the US Food and Drug Administration (FDA) for the treatment of onychomycosis include terbinafine and itraconazole, which have demonstrated good efficacy but are associated with the risk of systemic side effects and drug-drug interactions. Topical medications that are FDA approved for onychomycosis include ciclopirox, efinaconazole, and tavaborole. These therapies generally have incomplete efficacy compared to systemic agents as well as long treatment courses and possible local side effects such as erythema and/or blisters. Given the need for safe,

effective, and cost-effective options for onychomycosis therapy, there has been a renewed interest in natural and over-the-counter (OTC) alternatives. This review will synthesize the laboratory data, known antifungal mechanisms, and clinical studies assessing the efficacy of OTC and natural products for onychomycosis treatment.

Cutis. 2016;98:E16-E25.

Onychomycosis is a fungal infection of the nail unit by dermatophytes, yeasts, and non-dermatophyte molds. It is characterized by a white or yellow discoloration of the nail plate; hyperkeratosis of the nail bed; distal detachment of the nail plate from its bed (onycholysis); and nail plate dystrophy, including thickening, crumbling, and ridging. Onychomycosis is an important problem, representing 30% of all superficial fungal infections and an estimated 50% of all nail diseases.¹ Reported prevalence rates of onychomycosis in the United States and worldwide are varied, but the mean prevalence based on population-based studies in Europe and North America is estimated to be 4.3%.² It is more common in older individuals, with an incidence rate of 20% in those older than 60 years and 50% in those older than 70 years.³ Onychomycosis is more common in patients with diabetes and

Mr. Halteh is from Weill Cornell Medical College, Qatar, Ar-Rayyan. Drs. Scher and Lipner are from the Department of Dermatology, Weill Cornell Medical College, New York, New York. Mr. Halteh reports no conflict of interest. Dr. Scher is a consultant for Valeant Pharmaceuticals International, Inc. Dr. Lipner has served on the advisory board for Sandoz, a Novartis company. Correspondence: Shari R. Lipner, MD, PhD, Department of Dermatology, Weill Cornell Medical College, 1305 York Ave, New York, NY 10021 (shl9032@med.cornell.edu)

1.9 to 2.8 times higher than the general population.⁴ Dermatophytes are responsible for the majority of cases of onychomycosis, particularly *Trichophyton rubrum* and *Trichophyton mentagrophytes*.⁵

Onychomycosis is divided into different subtypes based on clinical presentation, which in turn are characterized by varying infecting organisms and prognoses. The subtypes of onychomycosis are distal and lateral subungual (DLSO), proximal subungual, superficial, endonyx, mixed pattern, total dystrophic, and secondary. Distal and lateral subungual onychomycosis are by far the most common presentation and begins when the infecting organism invades the hyponychium and distal or lateral nail bed. *Trichophyton rubrum* is the most common organism and *T mentagrophytes* is second, but *Candida parapsilosis* and *Candida albicans* also are possibilities. Proximal subungual onychomycosis is far less frequent than DLSO and is usually caused by *T rubrum*. The fungus invades the proximal nail folds and penetrates the newly growing nail plate.⁶ This pattern is more common in immunosuppressed patients and should prompt testing for human immunodeficiency virus.⁷ Total dystrophic onychomycosis is the end stage of fungal nail plate invasion, may follow DLSO or proximal subungual onychomycosis, and is difficult to treat.⁶

Onychomycosis causes pain, paresthesia, and difficulty with ambulation.⁸ In patients with peripheral neuropathy and vascular problems, including diabetes, onychomycosis can increase the risk for foot ulcers, with amputation in severe cases.⁹ Patients also may present with aesthetic concerns that may impact their quality of life.¹⁰

Given the effect on quality of life along with medical risks associated with onychomycosis, a safe and successful treatment modality with a low risk of recurrence is desirable. Unfortunately, treatment of nail fungus is quite challenging for a number of reasons. First, the thickness of the nail and/or the fungal mass may be a barrier to the delivery of topical and systemic drugs at the source of the infection. In addition, the nail plate does not have intrinsic immunity. Also, recurrence after treatment is common due to residual hyphae or spores that were not previously eliminated.¹¹ Finally, many topical medications require long treatment courses, which may limit patient compliance, especially in patients who want to use nail polish for cosmesis or camouflage.

Currently Approved Therapies for Onychomycosis

Several definitions are needed to better interpret the results of onychomycosis clinical trials. Complete cure is defined as a negative potassium hydroxide

preparation and negative fungal culture with a completely normal appearance of the nail. Mycological cure is defined as potassium hydroxide microscopy and fungal culture negative. Clinical cure is stated as 0% nail plate involvement but at times is reported as less than 5% and less than 10% involvement.

Terbinafine and itraconazole are the only US Food and Drug Administration (FDA)–approved systemic therapies, and ciclopirox, efinaconazole, and tavaborole are the only FDA-approved topicals. Advantages of systemic agents generally are higher cure rates and shorter treatment courses, thus better compliance. Disadvantages include greater incidence of systemic side effects and drug-drug interactions as well as the need for laboratory monitoring. Pros of topical therapies are low potential for adverse effects, no drug-drug interactions, and no monitoring of blood work. Cons include lower efficacy, long treatment courses, and poor patient compliance.

Terbinafine, an allylamine, taken orally once daily (250 mg) for 12 weeks for toenails and 6 weeks for fingernails currently is the preferred systemic treatment of onychomycosis, with complete cure rates of 38% and 59% and mycological cure rates of 70% and 79% for toenails and fingernails, respectively.¹² Itraconazole, an azole, is dosed orally at 200 mg daily for 3 months for toenails, with a complete cure rate of 14% and mycological cure rate of 54%.¹³ For fingernail onychomycosis only, itraconazole is dosed at 200 mg twice daily for 1 week, followed by a treatment-free period of 3 weeks, and then another 1-week course at the same dose. The complete cure rate is 47% and the mycological cure is 61% for this pulse regimen.¹³

Ciclopirox is a hydroxypyridone and the 8% nail lacquer formulation was approved in 1999, making it the first topical medication to gain FDA approval for the treatment of toenail onychomycosis. Based on 2 clinical trials, complete cure rates for toenails are 5.5% and 8.5% and mycological cure rates are 29% and 36% at 48 weeks with removal of residual lacquer and debridement.¹⁴ Efinaconazole is an azole and the 10% solution was FDA approved for the treatment of toenail onychomycosis in 2014.¹⁵ In 2 clinical trials, complete cure rates were 17.8% and 15.2% and mycological cure rates were 55.2% and 53.4% with once daily toenail application for 48 weeks.¹⁶ Tavaborole is a benzoxaborole and the 5% solution also was approved for the treatment of toenail onychomycosis in 2014.¹⁷ Two clinical trials reported complete cure rates of 6.5% and 9.1% and mycological cure rates of 31.1% and 35.9% with once daily toenail application for 48 weeks.¹⁸

Given the poor efficacy, systemic side effects, potential for drug-drug interactions, long-term

treatment courses, and cost associated with current systemic and/or topical treatments, there has been a renewed interest in natural remedies and over-the-counter (OTC) therapies for onychomycosis. This review summarizes the in vitro and in vivo data, mechanisms of action, and clinical efficacy of various natural and OTC agents for the treatment of onychomycosis. Specifically, we summarize the data on tea tree oil (TTO), a popular topical cough suppressant (TCS), natural coniferous resin (NCR) lacquer, *Ageratina pichinchensis* (AP) extract, and ozonized sunflower oil.

Tea Tree Oil

Background—Tea tree oil is a volatile oil whose medicinal use dates back to the early 20th century when the Bundjabung aborigines of North and New South Wales extracted TTO from the dried leaves of the *Melaleuca alternifolia* plant and used it to treat superficial wounds.¹⁹ Tea tree oil has been shown to be an effective treatment of tinea pedis,²⁰ and it is widely used in Australia as well as in Europe and North America.²¹ Tea tree oil also has been investigated as an antifungal agent for the treatment of onychomycosis, both in vitro²²⁻²⁸ and in clinical trials.^{29,30}

In Vitro Data—Because TTO is composed of more than 100 active components,²³ the antifungal activity of these individual components was investigated against 14 fungal isolates, including *C albicans*, *T mentagrophytes*, and *Aspergillus* species. The minimum inhibitory concentration (MIC) for α -pinene was less than 0.004% for *T mentagrophytes* and the components with the greatest MIC and minimum fungicidal concentration for the fungi tested were terpinen-4-ol and α -terpineol, respectively.²² The antifungal activity of TTO also was tested using disk diffusion assay experiments with 58 clinical isolates of fungi including *C albicans*, *T rubrum*, *T mentagrophytes*, and *Aspergillus niger*.²⁴ Tea tree oil was most effective at inhibiting *T rubrum* followed by *T mentagrophytes*,²⁴ which are the 2 most common etiologies of onychomycosis.⁵ In another report, the authors determined the MIC of TTO utilizing 4 different experiments with *T rubrum* as the infecting organism. Because TTO inhibited the growth of *T rubrum* at all concentrations greater than 0.1%, they found that the MIC was 0.1%.²⁵ Given the lack of adequate nail penetration of most topical therapies, TTO in nanocapsules (TTO-NC), TTO nanoemulsions, and normal emulsions were tested in vitro for their ability to inhibit the growth of *T rubrum* inoculated into nail shavings. Colony growth decreased significantly within the first week of treatment, with TTO-NC showing maximum

efficacy ($P < .001$). This study showed that TTO, particularly TTO-NC, was effective in inhibiting the growth of *T rubrum* in vitro and that using nanocapsule technology may increase nail penetration and bioavailability.³¹

Much of what we know about TTO's antifungal mechanism of action comes from experiments involving *C albicans*. To date, it has not been studied in *T rubrum* or *T mentagrophytes*, the 2 most common etiologies of onychomycosis.⁵ In *C albicans*, TTO causes altered permeability of plasma membranes,³² dose-dependent alteration of respiration,³³ decreased glucose-induced acidification of media surrounding fungi,³² and reversible inhibition of germ tube formation.^{19,34}

Clinical Trials—A randomized, double-blind, multicenter trial was performed on 117 patients with culture-proven DLSO who were randomized to receive TTO 100% or clotrimazole solution 1% applied twice daily to affected toenails for 6 months.²⁹ Primary outcome measures were mycologic cure, clinical assessment, and patient subjective assessment (Table 1). There were no statistical differences between the 2 treatment groups. Erythema and irritation were the most common adverse reactions occurring in 7.8% (5/64) of the TTO group.²⁹

Another study was a double-blind, placebo-controlled trial involving 60 patients with

Table 1.
Primary Outcome Measures in
TTO vs CL Onychomycosis Trial

| | TTO Group, % (n=64) | CL Group, % (n=53) |
|------------------------------------------------------------------------------|---------------------|--------------------|
| Mycologic cure | 18 | 11 |
| Clinical assessment (partial or full resolution) | 60 | 61 |
| Patient subjective assessment (telephone survey, partial or full resolution) | 56 | 55 |

Abbreviations: TTO, tea tree oil; CL, clotrimazole.

Adapted with permission from *The Journal of Family Practice*®. 1994;38:601-605. ©1994, Frontline Medical Communications Inc.²⁹

clinical and mycologic evidence of DLSO who were randomized to treatment with a cream containing butenafine hydrochloride 2% and TTO 5% (n=40) or a control cream containing only TTO (n=20), with active treatment for 8 weeks and final follow-up at 36 weeks.³⁰ Patients were instructed to apply the cream 3 times daily under occlusion for 8 weeks and the nail was debrided between weeks 4 and 6 if feasible. If the nail could not be debrided after 8 weeks, it was considered resistant to treatment. At the end of the study, the complete cure rate was 80% in the active group compared to 0% in the placebo group ($P<.0001$), and the mean time to complete healing with progressive nail growth was 29 weeks. There were no adverse effects in the placebo group, but 4 patients in the active group had mild skin inflammation.³⁰

Topical Cough Suppressant

Background—Topical cough suppressants, which are made up of several natural ingredients, are OTC ointments for adults and children 2 years and older that are indicated as cough suppressants when applied to the chest and throat and as relief of mild muscle and joint pains.³⁵ The active ingredients are camphor 4.8%, eucalyptus oil 1.2%, and menthol 2.6%, while the inactive ingredients are cedarleaf oil, nutmeg oil, petrolatum, thymol, and turpentine oil.³⁵ Some of the active and inactive ingredients in TCSs have shown efficacy against dermatophytes *in vitro*,³⁶⁻³⁸ and although they are not specifically indicated for onychomycosis, they have been popularized as home remedies for fungal nail infections.^{36,39} A TCS has been evaluated for its efficacy for the treatment of onychomycosis in one clinical trial.⁴⁰

In Vitro Data—An *in vitro* study was performed to evaluate the antifungal activity of the individual and combined components of TCS on 16 different dermatophytes, nondermatophytes, and molds. The zones of inhibition against these organisms were greatest for camphor, menthol, thymol, and eucalyptus oil. Interestingly, there were large zones of inhibition and a synergistic effect when a mixture of components was used against *T rubrum* and *T mentagrophytes*.³⁶ The *in vitro* activity of thymol, a component of TCS, was tested against *Candida* species.³⁷ The essential oil subtypes *Thymus vulgaris* and *Thymus zygis* (subspecies *zygis*) showed similar antifungal activity, which was superior to *Thymus mastichina*, and all 3 compounds had similar MIC and minimal lethal concentration values. The authors showed that the antifungal mechanism was due to cell membrane damage and inhibition of germ tube formation.³⁷ It should be noted that *Candida* species are less common causes of onychomycosis,

and it is not known whether this data is applicable to *T rubrum*. In another study, the authors investigated the antifungal activity of *Thymus pulegioides* and found that MIC ranged from 0.16 to 0.32 $\mu\text{L/mL}$ for dermatophytes and *Aspergillus* strains and 0.32 to 0.64 $\mu\text{L/mL}$ for *Candida* species. When an essential oil concentration of 0.08 $\mu\text{L/mL}$ was used against *T rubrum*, ergosterol content decreased by 70%, indicating that *T pulegioides* inhibits ergosterol biosynthesis in *T rubrum*.³⁸

Clinical Observations and Clinical Trial—There is one report documenting the clinical observations on a group of patients with a clinical diagnosis of onychomycosis who were instructed to apply TCS to affected nail(s) once daily.³⁶ Eighty-five charts were reviewed (mean age, 77 years), and although follow-up was not complete or standardized, the following data were reported: 32 (38%) cleared their fungal infection, 21 (25%) had no record of change but also no record of compliance, 19 (22%) had only 1 documented follow-up visit, 9 (11%) reported they did not use the treatment, and 4 (5%) did not return for a follow-up visit. Of the 32 patients whose nails were cured, 3 (9%) had clearance within 5 months, 8 (25%) within 7 months, 11 (34%) within 9 months, 4 (13%) within 11 months, and 6 (19%) within 16 months.³⁶

A small pilot study was performed to evaluate the efficacy of daily application of TCS in the treatment of onychomycosis in patients 18 years and older with at least 1 great toenail affected.⁴⁰ The primary end points were mycologic cure at 48 weeks and clinical cure at the end of the study graded as complete, partial, or no change. The secondary end point was patient satisfaction with the appearance of the affected nail at 48 weeks. Eighteen participants completed the study; 55% (10/18) were male, with an average age of 51 years (age range, 30–85 years). The mean initial amount of affected nail was 62% (range, 16%–100%), and cultures included dermatophytes, nondermatophytes, and molds. With TCS treatment, 27.8% (5/18) showed mycologic cure of which 4 (22.2%) had a complete clinical cure. Ten participants (55.6%) had partial clinical cure and 3 (16.7%) had no clinical improvement. Interestingly, the 4 participants who had complete clinical cure had baseline cultures positive for either *T mentagrophytes* or *C parapsilosis*. Most patients were content with the treatment, as 9 participants stated that they were very satisfied and 9 stated that they were satisfied. The average ratio of affected to total nail area declined from 63% at screening to 41% at the end of the study ($P<.001$). No adverse effects were reported with study drug.⁴⁰

NCR Lacquer

Background—Resins are natural products derived from coniferous trees and are believed to protect trees against insects and microbial pathogens.⁴¹ Natural coniferous resin derived from the Norway spruce tree (*Picea abies*) mixed with boiled animal fat or butter has been used topically for centuries in Finland and Sweden to treat infections and wounds.⁴²⁻⁴⁴ The activity of NCR has been studied against a wide range of microbes, demonstrating broad-spectrum antimicrobial activity against both gram-positive bacteria and fungi.⁴⁵⁻⁴⁸ There are 2 published clinical trials evaluating NCR in the treatment of onychomycosis.^{49,50}

In Vitro Data—Natural coniferous resin has shown antifungal activity against *T mentagrophytes*, *Trichophyton tonsurans*, and *T rubrum* in vitro, which was demonstrated using medicated disks of resin on petri dishes inoculated with these organisms.⁴⁶ In another study, the authors evaluated the antifungal activity of NCR against human pathogenic fungi and yeasts using agar plate diffusion tests and showed that the resin had antifungal activity against *Trichophyton* species but not against *Fusarium* and most *Candida* species. Electron microscopy of *T mentagrophytes* exposed to NCR showed that all cells were dead inside the inhibition zone, with striking changes seen in the hyphal cell walls, while fungal cells outside the inhibition zone were morphologically normal.⁴⁷ In another report, utilizing the European Pharmacopoeia challenge test, NCR was highly effective against gram-positive and gram-negative bacteria as well as *C albicans*.⁴²

Clinical Trials—In one preliminary observational and prospective clinical trial, 15 participants with clinical and mycologic evidence of onychomycosis were instructed to apply NCR lacquer once daily for 9 months with a 4-week washout period, with the primary outcome measures being clinical and mycologic cure.⁴⁹ Thirteen (87%) enrolled participants were male and the average age was 65 years (age range, 37–80 years). The DLSO subtype was present in 9 (60%) participants. The mycologic cure rate at the end of the study was 65% (95% CI, 42%–87%), and none achieved clinical cure, but 6 participants showed some improvement in the appearance of the nail.⁴⁹

The second trial was a prospective, controlled, investigator-blinded study of 73 patients with clinical and mycologic evidence of toenail onychomycosis who were randomized to receive NCR 30%, amorolfine lacquer 5%, or 250 mg oral terbinafine.⁵⁰ The primary end point was mycologic cure at 10 months, and secondary end points were clinical efficacy, cost-effectiveness, and patient compliance. Clinical

efficacy was based on the proximal linear growth of healthy nail and was classified as unchanged, partial, or complete. Partial responses were described as substantial decreases in onycholysis, subungual hyperkeratosis, and streaks. A complete response was defined as a fully normal appearance of the toenail. Most patients were male in the NCR (91% [21/23]), amorolfine (80% [20/25]), and terbinafine (68% [17/25]) groups; the average ages were 64, 63, and 64 years, respectively. *Trichophyton rubrum* was cultured most often in all 3 groups: NCR, 87% (20/23); amorolfine, 96% (24/25); and terbinafine, 84% (21/25). The remaining cases were from *T mentagrophytes*. A summary of the results is shown in Table 2. Patient compliance was 100% in all except 1 patient in the amorolfine treatment group with moderate compliance. There were no adverse events, except for 2 in the terbinafine group: diarrhea and rash.⁵⁰

AP Extract

Background—*Ageratina pichinchensis*, a member of the Asteraceae family, has been used historically in Mexico for fungal infections of the skin.^{51,52} Fresh or dried leaves were extracted with alcohol and the product was administered topically onto damaged skin without considerable skin irritation.⁵³ Multiple studies have demonstrated that AP extract has in vitro antifungal activity along with other members of the Asteraceae family.⁵⁴⁻⁵⁶ There also is evidence from clinical trials that AP extract is effective against superficial dermatophyte infections such as tinea pedis.⁵⁷ Given the positive antifungal in vitro data, the potential use of this agent was investigated for onychomycosis treatment.^{53,58}

In Vitro Data—The antifungal properties of the Asteraceae family have been tested in several in vitro experiments. *Eupatorium aschenbornianum*, described as synonymous with *A pichinchensis*,⁵⁹ was found to be most active against the dermatophytes *T rubrum* and *T mentagrophytes* with MICs of 0.3 and 0.03 mg/mL, respectively.⁵⁴ It is thought that the primary antimycotic activity is due to encecalinalin, an acetylchromene compound that was identified in other plants from the Asteraceae family and has activity against dermatophytes.⁵⁵ In another study, *Ageratum houstonianum* Mill, a comparable member of the Asteraceae family, had fungitoxic activity against *T rubrum* and *C albicans* isolated from nail infections.⁵⁶

Clinical Trials—A double-blind controlled trial was performed on 110 patients with clinical and mycologic evidence of mild to moderate toenail onychomycosis randomized to treatment with AP lacquer or ciclopirox lacquer 8% (control).⁵⁸ Primary end points were clinical effectiveness (completely

Table 2.

Results From NCR, Amorolfine, and Terbinafine Onychomycosis Trial

| | NCR Group (n=23) | Amorolfine Group (n=25) | Terbinafine Group (n=25) |
|-----------------------------------------------------------|---------------------|----------------------------|-----------------------------|
| Treatment course | Once daily for 9 mo | Once weekly for 9 mo | Once daily for 3 mo |
| Mycologic cure, ^a % | 13 | 8 | 56 |
| Clinical efficacy (complete), ^b % | 0 | 0 | 16 |
| Clinical efficacy (partial), ^b % | 30 | 28 | 36 |
| Cost per patient per treatment period, US \$ ^c | 47.08 | 63.72 | 58.97 |
| Cost per patient per treatment day, US \$ ^c | 0.17 | 0.24 | 0.66 |

Abbreviation: NCR, natural coniferous resin.

^aThe mycological cure of terbinafine was compared to amorolfine and the NCR group; NCR had significantly lower efficacy ($P=.002$) as well as amorolfine ($P<.001$).

^bBoth NCR and amorolfine had significantly lower efficacy ($P<.05$).

^cPrices were given in euros. At the time of this publication (November 2016), €1 is equivalent to US \$1.10.

Data from Auvinen et al.⁵⁰

normal nails) and mycologic cure. Patients were instructed to apply the lacquer once every third day during the first month, twice a week for the second month, and once a week for 16 weeks, with removal of the lacquer weekly. Demographics were similar between the AP lacquer and control groups, with mean ages of 44.6 and 46.5 years, respectively; women made up 74.5% and 67.2%, respectively, of each treatment group, with most patients having a 2- to 5-year history of disease (41.8% and 40.1%, respectively).⁵⁸ A summary of the data is shown in Table 3. No severe side effects were documented, but minimal nail fold skin pain was reported in 3 patients in the control group in the first week, resolving later in the trial.⁵⁸

A follow-up study was performed to determine the optimal concentration of AP lacquer for the treatment of onychomycosis.⁵³ One hundred twenty-two patients aged 19 to 65 years with clinical and mycologic evidence of mild to moderate DLSO were randomized to receive 12.6% or 16.8% AP lacquer applied once daily to the affected nails for 6 months.

Table 3.

Results From AP vs Ciclopirox Lacquer 8% Onychomycosis Trial

| | AP Lacquer, % (n=55) | Ciclopirox Lacquer 8%, % (n=55) |
|---------------------------------------|-------------------------|---------------------------------------|
| Clinical effectiveness ^{a,b} | 71.1 | 80.9 |
| Mycologic cure ^{a,c} | 59.1 | 63.8 |
| Treatment compliance | 95.9 | 100 |

Abbreviation: AP, *Ageratina pichinchensis*.

^aDid not reach statistical significance.

^b $P=.596$.

^c $P=.328$.

Data from Romero-Cerecero et al.⁵⁸

The nails were graded as healthy, mild, or moderately affected before and after treatment. There were no significant differences in demographics between the 2 treatment groups, and 77% of patients were women with a median age of 47 years. There were no significant side effects from either concentration of AP lacquer.⁵³

Ozonized Sunflower Oil

Background—Ozonized sunflower oil is derived by reacting ozone (O₃) with sunflower plant (*Helianthus annuus*) oil to form a petroleum jelly-like material.⁶⁰ It was originally shown to have antibacterial properties in vitro,⁶¹ and further studies have confirmed these findings and demonstrated anti-inflammatory, wound healing, and antifungal properties.⁶²⁻⁶⁴ A formulation of ozonized sunflower oil used in Cuba is clinically indicated for the treatment of tinea pedis and impetigo.⁶⁵ The clinical efficacy of this product has been evaluated in a clinical trial for the treatment of onychomycosis.⁶⁵

In Vitro Data—A compound made up of 30% ozonized sunflower oil with 0.5% of α -lipoic acid was found to have antifungal activity against *C albicans* using the disk diffusion method, in addition to other bacterial organisms. The MIC values ranged from 2.0 to 3.5 mg/mL.⁶² Another study was designed to evaluate the in vitro antifungal activity of this formulation on samples cultured from patients with onychomycosis using the disk diffusion method. They found inhibition of growth of *C albicans*, *C parapsilosis*, and *Candida tropicalis*, which was inferior to amphotericin B, ketoconazole, fluconazole, and itraconazole.⁶⁴

Clinical Trial—A single-blind, controlled, phase 3 study was performed on 400 patients with clinical and mycologic evidence of onychomycosis. Patients were randomized to treatment with an ozonized sunflower oil solution or ketoconazole cream 2% applied to affected nails twice daily for 3 months, with filing and massage of the affected nails upon application of treatment.⁶⁵ Cured was defined as mycologic cure in addition to a healthy appearing nail, improved as an increase in healthy appearing nail in addition to a decrease in symptoms (ie, paresthesia, pain, itching) but positive mycological testing, same as no clinical change in appearance with positive mycological findings, and worse as increasing diseased nail involvement in the presence of positive mycological findings. Demographics were similar between groups with a mean age of 35 years. Men accounted for 80% of the study population, and 65% of the study population was white. The mean duration of disease was 30 months. They also reported on a 1-year follow-up, with 2.8% of patients in

the ozonized sunflower oil solution group and 37.0% of patients in the ketoconazole group describing relapses. *Trichophyton rubrum* and *C albicans* were cultured from these patients.⁶⁵

Comment

Due to the poor efficacy, long-term treatment courses, inability to use nail polish, and high cost associated with many FDA-approved topical treatments, along with the systemic side effects, potential for drug-drug interactions, and cost associated with many oral therapies approved for onychomycosis, there has been a renewed interest in natural remedies and OTC treatments. Overall, TTO, TCS, NCR, AP extract, and ozonized sunflower oil have shown efficacy in vitro against some dermatophytes, nondermatophytes, and molds responsible for onychomycosis. One or more clinical trials were performed with each of these agents for the treatment of onychomycosis. They were mostly small pilot studies, and due to differences in trial design, the results cannot be compared with each other or with currently FDA-approved treatments. We can conclude that because adverse events were rare with all of these therapies—most commonly skin irritation or mild skin pain—they exhibit good safety.

For TTO, there was no statistical difference between the clotrimazole and TTO treatment groups in mycologic cure, clinical assessment, or patient subjective assessment of the nails.²⁹ Although there was an 80% complete cure in the butenafine and TTO group, it was 0% in the TTO group at week 36.³⁰ Trial design, longer treatment periods, incorporation into nanocapsules, or combination treatment with other antifungal agents may influence our future use of TTO for onychomycosis, but based on the present data we cannot recommend this treatment in clinical practice.

With TCS, 27.8% of participants had a mycologic cure and 22.2% had complete clinical cure.⁴⁰ Although it is difficult to draw firm conclusions from this small pilot study, there may be some benefit to treating toenail onychomycosis due to *T mentagrophytes* or *C parapsilosis* with TCS but no benefit in treating onychomycosis due to *T rubrum*, the more common cause of onychomycosis. Limitations of this study were lack of a placebo group, small sample size, wide variety of represented pathogens that may not be representative of the true population, and lack of stratification by baseline severity or involvement of nail. A larger randomized controlled clinical trial would be necessary to confirm the results of this small study and make formal recommendations.

In one clinical trial with NCR, mycologic cure was 65% at the end of the study.⁴⁹ No participants achieved clinical cure, but 6 participants showed some improvement in the appearance of the nail. Because this study was small (N=15), it is difficult to draw firm conclusions.⁴⁹ In another study with NCR, mycologic cure rates with NCR, amorolfine, and terbinafine were 13%, 8%, and 56%, respectively. Based on these results, NCR has similar antifungal efficacy to amorolfine but was inferior to oral terbinafine.⁵⁰ A larger randomized controlled clinical trial with more homogenous and less severely affected patients and longer treatment periods would be necessary to confirm the results of these small studies and make formal recommendations.

Because there were no significant differences in clinical effectiveness of mycologic cure rates between AP lacquer 10% and ciclopirox lacquer 8% in one clinical trial,⁵⁸ AP does not seem to be more effective than at least one of the current FDA-approved topical treatments; however, because AP lacquer 16.8% was shown to be more effective than AP lacquer 12.6% in one onychomycosis clinical trial, using higher concentrations of AP may yield better results in future trials.⁵³

One trial comparing ozonized sunflower oil to ketoconazole cream 2% showed 90.5% and 13.5% cure rates, respectively.⁶⁵ Although there is good in vitro antifungal activity and a clinical trial showing efficacy using ozonized sunflower oil for the treatment of onychomycosis, confirmatory studies are necessary before we can recommend this OTC treatment to our patients. Specifically, we will get the most data from large randomized controlled trials with strict inclusion/exclusion and efficacy criteria.

Conclusion

Over-the-counter and natural remedies may be an emerging area of research in the treatment of onychomycosis. This review summarizes the laboratory data and clinical trials on several of these agents and, when available, compares their clinical and mycologic efficacy with FDA-approved therapies. Shortcomings of some of these studies include a small study population, lack of adequate controls, nonstandardized mycologic testing, and abbreviated posttreatment evaluation times. It may be concluded that these products have varying degrees of efficacy and appear to be safe in the studies cited; however, at present, we cannot recommend any of them to our patients until there are larger randomized clinical trials with appropriate controls demonstrating their efficacy.

REFERENCES

1. Scher RK, Daniel CR. *Nails: Diagnosis, Therapy, Surgery*. 3rd ed. Oxford, England: Elsevier Saunders; 2005.
2. Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population: a literature study. *J Eur Acad Dermatol Venereol*. 2014;28:1480-1491.
3. Thomas J, Jacobson GA, Narkowicz CK, et al. Toenail onychomycosis: an important global disease burden. *J Clin Pharm Ther*. 2010;35:497-519.
4. Mayser P, Freund V, Budihardja D. Toenail onychomycosis in diabetic patients: issues and management. *Am J Clin Dermatol*. 2009;10:211-220.
5. Ghannoum MA, Hajjeh RA, Scher R, et al. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *J Am Acad Dermatol*. 2000;43:641-648.
6. Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. *J Am Acad Dermatol*. 2011;65:1219-1227.
7. Elewski B. Clinical pearl: proximal white subungual onychomycosis in AIDS. *J Am Acad Dermatol*. 1993;29:631-632.
8. Scher RK. Onychomycosis is more than a cosmetic problem. *Br J Dermatol*. 1994;130(suppl 43):15.
9. Boyko EJ, Ahroni JH, Cohen V, et al. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diabetes Care*. 2006;29:1202-1207.
10. Szepietowski JC, Reich A, Pacan P, et al. Evaluation of quality of life in patients with toenail onychomycosis by Polish version of an international onychomycosis-specific questionnaire. *J Eur Acad Dermatol Venereol*. 2007; 21:491-496.
11. Scher RK, Baron R. Onychomycosis in clinical practice: factors contributing to recurrence. *Br J Dermatol*. 2003;149(suppl 65):5-9.
12. Lamisil [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.
13. Sporanox [package insert]. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc; 2001
14. Penlac [package insert]. Bridgewater, NJ: Dermik Laboratories; 2006.
15. Jublia [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2014.
16. Elewski BE, Rich P, Pollak R, et al. Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicenter, randomized, double-blind studies. *J Am Acad Dermatol*. 2013;68:600-608.
17. Kerydin [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc; 2014
18. Elewski BE, Aly R, Baldwin SL, et al. Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis: results from 2 randomized phase-III studies

- [published online May 5, 2015]. *J Am Acad Dermatol*. 2015;73:62-69.
19. D'Auria FD, Laino L, Strippoli V, et al. In vitro activity of tea tree oil against *Candida albicans* mycelial conversion and other pathogenic fungi. *J Chemother*. 2001;13:377-383.
 20. Satchell AC, Saurajen A, Bell C, et al. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol*. 2002;43:175-178.
 21. Carson CF, Hammer KA, Riley TV. *Melaleuca alternifolia* (tea tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev*. 2006;19:50-62.
 22. Hammer KA, Carson CF, Riley TV. Antifungal activity of the components of *Melaleuca alternifolia* (tea tree) oil. *J Appl Microbiol*. 2003;95:853-860.
 23. Brophy JJ, Davies NW, Southwell IA, et al. Gas chromatographic quality control for oil of *Melaleuca terpinen-4-ol* type (Australian tea tree). *J Agric Food Chem*. 1989;37:1330-1335.
 24. Concha JM, Moore LS, Holloway WJ. 1998 William J. Stickel Bronze Award. Antifungal activity of *Melaleuca alternifolia* (tea-tree) oil against various pathogenic organisms. *J Am Podiatr Med Assoc*. 1998;88:489-492.
 25. Bengler S, Townsend P, Ashford RL, et al. An in vitro study to determine the minimum inhibitory concentration of *Melaleuca alternifolia* against the dermatophyte *Trichophyton rubrum*. *Foot*. 2004;14:86-91.
 26. Hammer KA, Carson CF, Riley TV. In-vitro activity of essential oils, in particular *Melaleuca alternifolia* (tea tree) oil and tea tree oil products, against *Candida* spp. *J Antimicrob Chemother*. 1998;42:591-595.
 27. Altman P. Australian tea tree oil. *Aust J Pharm*. 1998;69:276-278.
 28. Guterres SS, Alves MP, Pohlmann AR. Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications. *Drug Target Insights*. 2007;2:147-157.
 29. Buck DS, Nidorf DM, Addino JG. Comparison of two topical preparations for the treatment of onychomycosis: *Melaleuca alternifolia* (tea tree) oil and clotrimazole. *J Fam Pract*. 1994;38:601-605.
 30. Syed TA, Qureshi ZA, Ali SM, et al. Treatment of toenail onychomycosis with 2% butenafine and 5% *Melaleuca alternifolia* (tea tree) oil in cream. *Tropical Med Int Health*. 1999;4:284-287.
 31. Flores FC, de Lima JA, Ribeiro RF, et al. Antifungal activity of nanocapsule suspensions containing tea tree oil on the growth of *Trichophyton rubrum*. *Mycopathologia*. 2013;175:281-286.
 32. Hammer KA, Carson CF, Riley TV. Antifungal effects of *Melaleuca alternifolia* (tea tree) oil and its components on *Candida albicans*, *Candida glabrata* and *Saccharomyces cerevisiae*. *J Antimicrob Chemother*. 2004;53:1081-1085.
 33. Cox SD, Mann CM, Markham JL, et al. The mode of antimicrobial action of the essential oil of *Melaleuca alternifolia* (tea tree oil). *J Appl Microbiol*. 2000;88:170-175.
 34. Hammer KA, Carson CF, Riley TV. *Melaleuca alternifolia* (tea tree) oil inhibits germ tube formation by *Candida albicans*. *Med Mycol*. 2000;38:355-362.
 35. Vicks VapoRub [package insert]. Gross-Gerau, Germany: Proctor & Gamble; 2010.
 36. Ramsewak RS, Nair MG, Stommel M, et al. In vitro antagonistic activity of monoterpenes and their mixtures against 'toe nail fungus' pathogens. *Phytother Res*. 2003;17:376-379.
 37. Pina-Vaz C, Gonçalves Rodrigues A, Pinto E, et al. Antifungal activity of *Thymus* oils and their major compounds. *J Eur Acad Dermatol Venereol*. 2004;18:73-78.
 38. Pinto E, Pina-Vaz C, Salgueiro L, et al. Antifungal activity of the essential oil of *Thymus pulegioides* on *Candida*, *Aspergillus* and dermatophyte species. *J Med Microbiol*. 2006;55:1367-1373.
 39. Vicks VapoRub might help fight toenail fungus. *Consumer Reports*. 2006;71:49.
 40. Derby R, Rohal P, Jackson C, et al. Novel treatment of onychomycosis using over-the-counter mentholated ointment: a clinical case series. *J Am Board Fam Med*. 2011;24:69-74.
 41. Trapp S, Croteau R. Defensive resin biosynthesis in conifers. *Ann Rev Plant Physiol Plant Mol Biol*. 2001;52:689-724.
 42. Sipponen A, Laitinen K. Antimicrobial properties of natural coniferous rosin in the European Pharmacopoeia challenge test. *APMIS*. 2011;119:720-724.
 43. Sipponen A, Lohi J. Lappish gum care "new" treatment of pressure ulcers? People's improvement at it's best. *Eng Med J*. 2003;58:2775-2776.
 44. Benedictus O. *Een Nyttigh Läkare*. Malmö: Kroon; 1938.
 45. Rautio M, Sipponen A, Peltola R, et al. Antibacterial effects of home-made resin salve from Norway spruce (*Picea abies*). *APMIS*. 2007;115:335-340.
 46. Laitinen K, Sipponen A, Jokinen JJ, et al. Resin salve from Norway spruce is antifungal against dermatophytes causing nail infections. *EWMA*. 2009;56:289-296.
 47. Rautio M, Sipponen A, Lohi J, et al. In vitro fungistatic effects of natural coniferous resin from Norway spruce (*Picea abies*). *Eur J Clin Microbiol Infect Dis*. 2012; 31:1783-1789.
 48. Sipponen A, Peltola R, Jokinen JJ, et al. Effects of Norway spruce (*Picea abies*) resin on cell wall and cell membrane of *Staphylococcus aureus*. *Ultrastruct Pathol*. 2009;33:128-135.
 49. Sipponen P, Sipponen A, Lohi J, et al. Natural coniferous resin lacquer in treatment of toenail onychomycosis: an observational study. *Mycoses*. 2013;56:289-296.
 50. Auvinen T, Tiuhonen R, Soini M, et al. Efficacy of topical resin lacquer, amorolfine, and oral terbinafine for treating toenail onychomycosis: a prospective, randomized, controlled, investigator-blinded, parallel-group clinical trial. *Br J Dermatol*. 2015;173:940-948.
 51. Argueta A, Cano L, Rodarte M. *Atlas de las Plantas de la Medicina Tradicional Mexicana*. Vol 3. Mexico City, Mexico: Instituto Nacional Indigenista; 1994:72-680.

52. Avilés M, Suárez G. *Catálogo de Plantas Medicinales del Jardín Etnobotánico*. Peru: Instituto Nacional de Antropología e Historia; 1994.
53. Romero-Cerecero O, Roman-Ramos R, Zamilpa A, et al. Clinical trial to compare the effectiveness of two concentrations of the *Ageratina pichinchensis* extract in the topical treatment of onychomycosis. *J Ethnopharmacol*. 2009;126:74-78.
54. Navarro García VM, Gonzalez A, Fuentes M, et al. Antifungal activities of nine traditional Mexican medicinal plants. *J Ethnopharmacol*. 2003;87:85-88.
55. Castañeda P, Gómez L, Mata R, et al. Phyto-growth-inhibitory and antifungal constituents of *Helianthella quinquenervis*. *J Nat Prod*. 1996;59:323-326.
56. Kumar N. Inhibition of nail infecting fungi of peoples of North Eastern UP causing *Tinea unguium* through leaf essential oil of *Ageratum houstonianum* Mill. *IOSR J Pharm*. June 2014;4:36-42.
57. Romero-Cerecero O, Rojas G, Navarro V, et al. Effectiveness and tolerability of a standardized extract from *Ageratina pichinchensis* on patients with tinea pedis: an explorative pilot study controlled with ketoconazole. *Planta Med*. 2006;72:1257-1261.
58. Romero-Cerecero O, Zamilpa A, Jimenez-Ferrer JE, et al. Double-blind clinical trial for evaluating the effectiveness and tolerability of *Ageratina pichinchensis* extract on patients with mild to moderate onychomycosis. a comparative study with ciclopirox. *Planta Med*. 2008; 74:1430-1435.
59. Rzedowski J, De Rzedowski GC. *Flora Fanerogámica del Valle de México*. Mexico City, Mexico: Instituto de Ecología Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional; 1985.
60. Bocci V. Biological and clinical effects of ozone. has ozone therapy a future in medicine? *Br J Biomed Sci*. 1999;56:270-279.
61. Sechi LA, Lezcano I, Nunez N, et al. Antibacterial activity of ozonized sunflower oil (Oleozon). *J Appl Microbiol*. 2001;90:279-284.
62. Rodrigues KL, Cardoso CC, Caputo LR, et al. Cicatrizing and antimicrobial properties of an ozonised oil from sunflower seeds. *Inflammopharmacology*. 2004;12:261-270.
63. Daud FV, Ueda SMY, Navarini A, et al. The use of ozonized oil in the treatment of dermatophytosis caused by *Microsporum canis* in rabbits. *Braz J Microbiol*. 2011; 42:274-281.
64. Guerrer LV, Cunha KC, Nogueira MC, et al. "In vitro" antifungal activity of ozonized sunflower oil on yeasts from onychomycosis. *Braz J Microbiol*. 2012;43:1315-1318.
65. Menéndez S, Falcón L, Maqueira Y. Therapeutic efficacy of topical OLEOZON in patients suffering from onychomycosis. *Mycoses*. 2011;54:E272-E277.