A Chinese Herb, Indigo Naturalis, Extracted in Oil (Lindioil) Used Topically to Treat Psoriatic Nails: A Randomized Clinical Trial

Indigo naturalis, a Chinese herb, has been used for decades. Olive oil was used to remove the blue component within indigo naturalis to yield a purple-red product to treat skin and nail psoriasis without obvious staining. This trial compared indigo naturalis extract in oil (Lindioil) with topical calcipotriol in treating psoriatic nails.

Methods | Lindioil was prepared by mixing indigo naturalis powder with olive oil. Calcipotriol solution (Daivonex scalp solution, 50 μg/mL) was purchased from LEO Pharmaceutical Products, Ltd. Both were distributed in 5-mL eyedropper bottles. This trial was approved by the Chang Gung Medical Foundation Institutional Review Board and was randomized by participant, rater blinded, and active controlled. All participants provided written consent prior to the study. Participants, who were recruited from January 2011 through May 2012, were aged 20 to 65 years and had symmetrically comparable nail disease severity on each hand. The full study protocol synopsis can be found in Supplement 1.

Participants applied 1 to 2 drops (0.05 mL/drop) of Lindioil to the fingernails of one hand and calcipotriol to the other hand twice daily for 24 weeks. Participants were followed up every 4 weeks for 24 weeks and photographs of their nails were taken at each follow-up visit. Psoriatic nail severity was assessed by 2 blinded dermatologists (Y.-C. C. and Y.-H. H.) using the single-hand Nail Psoriasis Severity Index (shNAPSI) and modified target NAPSI (mtNAPSI). Statistical analysis was performed with SAS statistical software, version 9.3 (SAS Institute Inc). The mixed-effect model and pairwise comparisons were used, with $P < .05$ considered significant.

Results | Of the 33 enrolled and randomized participants (22 men, 11 women), 28 completed the study (Figure 1 in Supplement 2). Mean (SD) age was 41.9 (9.4) years; duration of skin and nail psoriasis was 11.8 (10.9) and 5.8 (6.4) years, respectively. Mean Psoriasis Area Severity Index score was 8.9 (8.2) and NAPSI score was 54.3 (15.4). Eighteen participants used Lindioil on their right hand and 15 used Lindioil on their left hand.

The mixed-effect model revealed significant interactions between treatments and time for shNAPSI scores ($P < .001$) and mtNAPSI scores ($P < .001$) (Figure 1). At baseline, there was no statistically significant difference in shNAPSI scores ($P = .45$) or in mtNAPSI scores ($P = .03$) between the use of Lindioil and the use of calcipotriol. At week 24, use of Lindioil showed significant improvements compared with calcipotriol for shNAPSI and mtNAPSI scores ($P < .001$ for both).

The percentage reduction in shNAPSI scores between baseline and week 24 for the use of Lindioil (51.3%; 95% CI, 40.6%-62.0%) was greater than that with the use of calcipotriol (27.1%; 95% CI, 16.2%-38.0%) ($P < .001$). Fourteen participants (50%) had shNAPSI scores that improved 50% or greater with the use of Lindioil and 7 participants (25%) had shNAPSI scores that improved 50% or greater with the use of calcipotriol (Figure 2). More participants preferred Lindioil (82.1%) compared with calcipotriol to treat their psoriatic nails (17.9%).

Onycholysis and subungual hyperkeratosis had the most improvement among the 8 nail features for both treatments. Although results are not shown, Lindioil was statistically superior for onycholysis.

Two participants (6.1%) experienced irritation with the use of Lindioil and 10 participants (30.3%) experienced irritation with the use of calcipotriol, but no participants experienced serious adverse effects.

Figure 1. Comparison of shNAPSI and mtNAPSI Scores Between Lindioil and Calcipotriol Through Week 24

A, Mean (SD) single-hand Nail Psoriasis Severity Index (shNAPSI) score at baseline (week 0) (Lindioil group, 27.2 [7.8] and calcipotriol group, 27.4 [7.6]) and at week 24 (Lindioil group, 14.4 [8.9] and calcipotriol group, 20.4 [8.5]).
B, Mean (SD) modified target NAPSI (mtNAPSI) score at baseline (week 0) (Lindioil group, 17.7 [6.2] and calcipotriol group, 16.9 [6.5]) and at week 24 (Lindioil group, 5.9 [4.1] and calcipotriol group, 9.5 [5.2]). Error bars indicate the standard error.

Significance between the 2 groups within the same visit using the Bonferroni adjustment with a significance level of $P = .007$. (The comparison of the efficacy of the different treatments was conducted by a paired t test. The overall significance level of this study was $P = .05$; however, the Bonferroni method reduced the significance level. This was accomplished by dividing the numbers of multiple comparisons when comparing shNAPSI or mtNAPSI between the 2 hands over time [.05/(7 visits).]
Discussion | This study comparing a Chinese herb, indigo naturalis, with a current topical medication, calcipotriol solution, showed that Lindioil is a safe and effective alternative therapy for psoriatic nails. Psoriasis is a refractory disease; therefore, owing to the long-term nature of the treatment, efficacy and safety are very important. Lindioil had the greatest effects on onycholylosis and subungual hyperkeratosis, which arise from hyperproliferation, hyperkeratosis, and parakeratosis of the nail bed. Our studies indicated that indigo naturalis regulates proliferation and differentiation of epidermal keratinocytes, restores the epidermal barrier function, and inhibits inflammatory reactions.5,6 Lindioil may improve psoriasis of the nails via these mechanisms; however, further investigation is necessary.

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Figure 2. The Effects of Lindioil and Calcipotriol in Treating Psoriatic Nails

A, Fingers on the right hand at baseline (week 0), with a single-hand Nail Psoriasis Severity Index (shNAPSI) score of 26. B, Fingers on the left hand at baseline (week 0), with a shNAPSI score of 23. C, Fingers on the right hand after 24 weeks of treatment with Lindioil, with a shNAPSI score of 5. D, Fingers on the left hand after 24 weeks of treatment with calcipotriol, with a shNAPSI score of 16.

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Bullous Lichen Planus of the Nails

Nail involvement may occur in 1% to 10% cases of lichen planus (LP) and mostly in the setting of widespread cutaneous disease. \(^1\) Longitudinal ridging, thinning, and distal splitting of the nail plate are the most common nail changes in LP. \(^2\)

**Report of a Case**

A man in his 60s presented with painful swelling of the proximal nail folds, dripping of blood from his fingernails and toenails for the last year, and occasional pus discharge. There was no history of preceding trauma or drug intake.

On physical examination, the proximal nail folds were found to be swollen and showed violaceous discoloration of 7 fingernails and 3 toenails. The index fingernails also demonstrated longitudinal ridging, thinning, and focal fragmentation of the nail plate, while the remaining fingernails and involved toenails showed partial to complete loss of nail plate with oozing of blood resulting in hemorrhagic crusting of the nail beds and folds (Figure 1A). Oral mucosa showed lichenoid plaques on the right angle of mouth, bilateral buccal mucosa, and erosions covered with hemorrhagic crusts on the upper and lower lips. A provisional diagnosis of bullous lichen planus of the nails was made. Laboratory investigations revealed raised liver enzyme levels and positive anti-hepatitis C virus antibody status.

The patient was treated with oral antibiotics for 1 week and a topical steroid-antibiotic combination for 6 weeks, and the hemorrhagic crusting and nail fold swelling subsided completely, resulting in anonomy of the affected nails (Figure 1B). A skin biopsy was performed from the proximal nail fold of the right index finger 1 month after the initial presentation to avoid secondary changes due to infection that was present at the time of the initial presentation. Histopathologic examination demonstrated hyperkeratosis, hypergranulosis, acanthosis, basal cell degeneration, numerous apoptotic keratinocytes in the epidermis with dense bandlike lymphohistiocytic infiltrate in the papillary dermis consistent with the diagnosis of LP (Figure 2).

**Discussion**

Nail LP (NLP) usually presents in association with cutaneous, mucosal, or scalp lesions but may be the sole manifestation of the disease. It may involve the nail matrix, proximal and lateral nail folds, nail bed, and/or the hyponychium. Proximal matrix involvement resulting in longitudinal ridging is the most common and the earliest manifestation of NLP. \(^3\) Trachyonychia usually occurs in children as an isolated finding in the absence of LP at other sites and of other typical signs of NLP. Pterygium, irregular nail pitting, onychorrhexis, crumbling, and fragmentation of the nail plate are other clinical manifestations of nail matrix involvement. Nail bed involvement may take the form of small red papules visible as violaceous lines or papules through the nail plate, subungual hyperkeratosis, and onycholysis. \(^4\) Complete destruction of the nail matrix and nail bed results in total nail atrophy. Idiopathic atrophy of the nails is a distinct manifestation of NLP that results in rapid and diffuse scarring of nails in children. Less frequent signs of NLP described by Tosti et al\(^-\) include erythematous patches of the lunula, melanonychia, splinter hemorrhages, koilonychia, and yellow nail syndrome-like changes. \(^3\) \(^4\)

Our case exemplifies the unusual presentation of bullous LP of the nails in the form of hemorrhagic lesions resulting in complete shedding of the nail plate and nail atrophy. Bullous LP of the nails is an uncommon and extreme variant of LP that may be associated with bullous and ulcerative lesions on the feet and toes, with or without cicatricial alopecia and oral involvement. \(^5\) \(^6\) Diagnosis is often challenging, and the presence of characteristic lesions at other sites in conjunction with histopathologic examination aid in confirmation of diagnosis.

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