**Hypericum perforatum and Azadirachta indica (Neem) oil in the management of chronic leg ulcers: An uncontrolled retrospective observational case review**

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**ABSTRACT**

Chronic nonhealing leg ulcers are debilitating with high morbidity in a vulnerable patient population and pose a frequent clinical and socioeconomic problem. Numerous local treatment options exist, but clinical trials are rare and wound management still represents a big challenge. Recently a wound dressing based on the natural remedies *Hypericum perforatum* and *Neem oil* has been proposed for chronic wound management, but trials on nonhealing leg ulcers are missing. Uncontrolled retrospective observational case review on all patients under our supervision with chronic leg ulcers who underwent treatment with a plant-derived wound dressing based on *Hypericum perforatum* and *Azadirachta indica* (Neem) oil. It could be retrieved in a total 16 cases (11 female) with a median age of 71 years. All ulcers (7 ulcers on the leg and 9 ulcers on the feet) showed a complete healing after a median healing time of 82 days (Mean 85, range 14-180 days). No side effects occurred, medication was painless or even reduced pain. Wound dressings based on *Hypericum perforatum* and *Neem oil* are well tolerated and could be a potential additional simple treatment option in the management of non-healing leg ulcers. Prospective controlled trials are needed to confirm these observations.

**INTRODUCTION**

Chronic nonhealing leg ulcers are debilitating with high morbidity in a vulnerable patient population. They pose a frequent clinical and socioeconomic problem, especially in the elderly, affecting their quality of life and are often associated with severe complications. Numerous local treatment options exist but clinical trials are rare and wound management still represents a big challenge.1,2 Topical use of natural remedies has a long tradition. Recently a local wound dressing with a plant-derived wound therapeutic consisting of *Hypericum perforatum* and *Neem oil* was proposed.3,9 Recent pharmacological research of the bioactive constituents of *Hypericum perforatum* showed antioxidant, anti-inflammatory and antimicrobial proprieties.10 Furthermore *H. perforatum* extract is thought to be able to stimulate growth and differentiation of keratinocytes.10 Study results for the medical use of *Azadirachta indica* (Neem) oil showed, that it is rich in antioxidants and that its leaf extracts promote wound healing activity through increased inflammatory response and neovascularization.11 Studies of these components on chronic ulcers of the lower extremities are rare. This retrospective case study was performed...
to evaluate the safety and clinical efficacy of a plant-derived wound dressing, a mixture of *Hypericum oil* (*Hypericum perforatum*) and *Neem oil* (*Azadirachta indica*), in the treatment of chronic leg and foot ulcers.

**MATERIALS AND METHODS**

A retrospective observational study was performed on all patients presenting with chronic leg and foot ulcers treated with a plant-derived wound dressing consisting of a mixture of *Hypericum perforatum* and *Azadirachta indica* oil (Holoil™, RI.MOS. srl, Modena, Italy) at the University La Sapienza (Rome) and at the Dermatology and Venereology Department of Bolzano/Bozen hospital. All cases where complete photographic follow up was available were included. Time to healing, wound sizes, ease of handling, pain and complications were evaluated. The plant-derived wound dressing was used in different formulations (oil, gel and gauzes).

**RESULTS**

In total 16 cases could be retrieved, 11 of them were female (69%) and 5 male (31%), with a median age of 71 years (range 1.25 – 93 years, mean age 69 years). Ulcers were located on the patients’ legs in 7 (44%) and on their feed in 9 (56%) cases. Median ulcer size was 7 cm² (range 1-200cm², mean ulcer size was 20.7cm²). Median depth was 0.5 cm (range 0.1-2cm, mean depth was 0.8cm). 15/16 patients (94%) showed at least one comorbidity, 13/16 (81%) two or more. Comorbidities found were peripheral arterial disease in 6 (37%), diabetes mellitus in 7 (44%), obesity in 5 (31%), lymphedema, thrombosis or post thrombotic syndrome in 5 (31%), chronic venous insufficiency in 4 (25%), neurodegenerative diseases in 4 (25%), cardiopathy in 4 (25%), Hepatitis C in 2 (12%), dialysis or chronic renal insufficiency in 2 (12%) and osteomyelitis, Gonarthrosis or COPD each in 1 (6%) case. Dressings were changed twice a week for the first weeks, then once a week. All ulcers showed a complete healing with a median healing time of 82 days (range 14-180 days, mean healing time 85 days, Table 1). Medication was painless or did even reduce pain, no side effects were noted, no signs of deterioration, infection or hypersensitivity reaction occurred during the treatments (Figure 1).

**DISCUSSION**

The present study describes our clinical experience with the use of a combination of *Hypericum perforatum* and

![Figure 1](image-url). Clinical outcomes of treatment. Pictures before (left) and after treatment (right). a) case 8 (day 0, day 60), b) case 13 (day 0, day 50), c) case 9 (day 0, day 55), d) case 3 (day 0, day 122), e) case 2 (day 0, day 121), f) case 16 (day 0, day 67).
Table 1. Overview and summary of the retrospective uncontrolled case review.

| Case Nr. | Age (years) | Sex | Comorbidities | Duration of ulcer | Localization of ulcer | Depth and dimension cm/cm² | Treatment | Healing time |
|----------|-------------|-----|---------------|------------------|-----------------------|-----------------------------|-----------|--------------|
| 1        | 70          | F   | PAD, Hepatitis C | 7 months         | Dorsal foot, failed surgical intervention | Depth 0.3 cm, Area 20 cm²   | Hypericum p. and Neem oil gauzes | 1 month  |
| 2        | 90          | F   | Alzheimer disease | 4 months         | Heel                  | Depth 1.6 cm, Area 5 cm²    | Hypericum p. and Neem oil gauzes | 4 months |
| 3        | 93          | M   | Parkinson’s disease | 4 months       | Heel                  | Depth n.d. “deep”, Area 4 cm² | Hypericum p. and Neem oil gauzes | 5 months |
| 4        | 77          | F   | NIDDM, Obesity, Lymphedema | 6 months | Right leg | Superficial, Area ca. 200 cm² | Hypericum p. and Neem oil/ gauzes gel | 2 months |
| 5        | 1.25        | M   | None | 1 month | Right dorsal foot | Superficial, Area 3 cm² | Hypericum p. and Neem oil/ gauzes | 2 weeks  |
| 6        | 85          | F   | PAD IIb, Hepatitis C, Alzheimer disease | 24 months | Right malleolar region | Depth 0.2 cm, Area 20 cm² | Hypericum p. and Neem oil gauzes | 6 months |
| 7        | 81          | F   | PAD IIa, CVI, Obesity, Lymphedema, Gonarthrosis | N.d. (“months”) | Left anterior leg | N.d. multiple deep “punched ulcers” | Hypericum p. and Neem oil gauzes | 2 months |
| 8        | 85          | F   | PAD IIa, Diabetes, Cardiopathy, COPD | N.d. (“months”) | Left heel | Depth 1 cm, Area 4 cm² | Hypericum p. and Neem oil gauzes | 3 months |
| 9        | 76          | M   | IDDM, Thrombosis, Fistula dig III, Pain VAS 10 | 6 months | Left planter ulcer | Depth 3 cm fistula, Area 3 cm² | Hypericum p. and Neem oil gauzes | 2 months |
| 10       | 73          | F   | PAD, Cardiopathy, Chronic renal insufficiency | 6 months | Right internal heel, exposed bone | Depth 0.6 cm, Area 5 cm² | Hypericum p. and Neem oil gauzes | 2.5 months |
| 11       | 51          | F   | PAD IIa, NIDDM, Dialysis, Obesity | 12 months | Left heel | Depth 0.6 cm, Area 6 cm² | Hypericum p. and Neem oil gauzes | 5 months |
| 12       | 72          | M   | Cardiopathy, NIDDM, Post Thrombotic Syndrome, CVI | 18 months | Right anterior leg | Depth 0.1 cm, Area 18 cm² | Hypericum p. and Neem oil gauzes | 1 month  |
| 13       | 66          | F   | Cardiopathy, Hypertension, Obesity, CVI | 4 months | Two ulcers left leg above malleolar region | Superficial, Area 7 cm² and 4 cm² | Hypericum p. and Neem oil/oil/gauzes | 1.5 months |
| 14       | 71          | M   | Obesity, Post Thrombotic Syndrome, CVI | 6 months | Left leg lateral malleolar region | Depth 0.4 cm, Area 1 cm² | Hypericum p. and Neem oil/oil/gauzes | 4 months |
| 15       | 52          | F   | Diabetes, Osteomyelitis | N.d. (“months”) | Necrotic decubital ulcer left heel | Depth 1 cm, Area 30 cm² | Hypericum p. and Neem oil/oil/gauzes | 4 months |
| 16       | 61          | F   | Hypertension, IDDM, Neureopathy | 4 months | Digit I right foot, failed Hydrofiber Ag | Depth 0.3 cm, Area 1.7 cm² | Hypericum p. and Neem oil oil/gel | 2 months |

Summary

16 cases

Median ulcer duration 6 months
Mean ulcer duration 7.8 month
Median dimension 5 cm²
Mean dimension 20.7 cm²
Median healing time 3 months
Mean healing time 2.84 months

Overview and summary of the retrospective uncontrolled case review showing all included cases, reporting sex, age in years, comorbidities, duration of ulcers in months, localization of ulcers, depth and dimension of the ulcers, exact treatment product and healing time in months. Abbreviations: M male; F female; PAD peripheral arterial disease; CVI chronic venous insufficiency; COPD chronic obstructive pulmonary disease; IDDM insulin dependent diabetes mellitus type II; NIDDM non insulin dependent diabetes mellitus; n.d. not determined; Hypericum p.: Hypericum perforatum.
Neem oil in 16 patients with chronic ulcers on the lower extremities, non-responding to several previous local or surgical treatments (see Table 1). All treated ulcers eventually healed after a mean healing time of 82 days.

The extracts of Hypericum perforatum and Azadirachta indica show effects in different kinds of dermatological conditions. Increasing knowledge about pharmacological activities of its characteristic ingredients, such as hypericin and hyperforin, has given new impetus to investigate the potential of topical preparations in dermatological problems of current interest such as skin diseases like atopic dermatitis, psoriasis, herpes infections, nonmelanoma skin cancer and last but not least in skin care.

Different types of skin wounds like surgical wounds, burns, diabetic foot ulcers, vascular/venous ulcers, pressure sores and calcinosis-related skin ulcers also seem to respond to the pharmacological active ingredients of Hypericum perforatum and Ayadirachta indica oil.

This report includes different types of chronic skin ulcers of the lower extremities with a wide range of severity. 15/16 patients (94%) showed at least one comorbidity, 13/16 (81%) two or more. Nevertheless, a complete wound healing could finally be observed in all types of treated ulcers. Inflammation and pain rapidly improved clinically.

The antibacterial activity of Hypericum perforatum extract against S. aureus was recently shown by Whitehead et al. In this case series no clinical signs of relapse of inflammation or bacterial infection was noted during the treatment period, meaning that additional systemic antibiotic or local antiseptic use, with potential induction of bacterial resistance or cytotoxic effects on the wound, that might interfere with wound healing, could be avoided or reduced.

Moreover, all patients confirmed that the wound dressing was painless or even able to reduce pain, probably due to improvement of inflammation. In practical terms, this can lead to better compliance and an easier management of patients with chronic leg ulcers. Further tolerance was excellent, no hypersensitivity or other adverse reactions were recorded.

Singh et al. compared the topical use of Neem (A. indica) oil and systemic use of Haridra (Curcuma longa) in 60 patients with chronic non-healing ulcers. Both drugs proved to be of value in the management of non-healing wounds. Angiogenic properties and a potentially increase of cellular DNA content, in terms of cell growth stimulation, could be shown as well.

A recent study of Giuggioli et al. retrospectively analyzed the use of the combination of Hypericum perforatum and Neem oil in patients with scleroderma skin ulcers related to calcinosis and compared them to a control group. Control patients treated with standard therapies showed significantly longer healing times and a higher percentage of infectious complications. Bridi et al. recently showed the in vitro capacity of phloroglucinol derivatives from Hypericum species to induce proliferation of cells involved in the wound healing process, therefore reinforcing the importance of Hypericum species as potential source of wound healing compounds.

Being a simple wound dressing, no specific training or equipment is required. Hypericum perforatum and Neem oil therefore might be of use as an additional, simple and cost-effective local treatment option in non-healing wounds. The retrospective case selections are a limitation of this study and further prospective controlled trials are needed to confirm these findings.

CONCLUSIONS

This retrospective, non-controlled case review suggests that a plant-derived wound dressing consisting of a combination of Hypericum perforatum and Neem oil is well tolerated and might be a simple, safe and potentially effective treatment option for chronic leg and foot ulcers. Prospective controlled trials should be performed to confirm these findings.

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