Efficacy of Orange Peel Extract in Psoriasis

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Abstract: Monoterpenes, and especially *d*-Limonene, display anti-inflammatory and anti-angiogenic effects which could be efficient in such inflammatory diseases as psoriasis. A pilot study was initiated to test this hypothesis in an open non-randomized setting enrolling nine patients. Orange peel extract containing known amounts of *d*-Limonene were given twice daily as soft gel capsules ingested and/or emptied and massaged on skin lesions, for 45 days. In spite of the small size of the cohort, highly significant positive effects were observed, with a reduction of clinical scores such as Psoriasis Area Severity Index and Videodermoscopy Scalp Psoriasis Severity Index. Moreover, adding to the global subjective satisfaction of the patients and improvement of the objective Dermatology Life Quality Index was also recorded. This encouraging pilot study should serve to prompt a larger randomized blind study. Indeed, implementation of a non-toxic substance of natural origin in the widespread condition of psoriasis could represent a significant advance in the treatment of this disease.

Keywords: Psoriasis, orange peel extract, *d*-Limonene, inflammation.

INTRODUCTION

The search for an efficient treatment of psoriasis has been a long quest and still remains an elusive target. Significant progress has been provided by the use of such immunosuppressants as corticosteroids, methotrexate or, more recently, biologics. However, besides being expensive and requiring intravenous administration, the latter share with more classical drugs a limited activity and the threat of potential side effects [1]. Several scores have been established to assess the disease. The 75 PASI (Psoriasis Area Severity Index, [2]), now commonly used, reports the percentage of patients reaching a 75% decrease of lesions after a given treatment. Yet, the most efficient recent biologics provide less than 80% of 75 PASI after several months of treatment [3]. The same is true when other scores are used such as the Videodermoscopy Scalp Psoriasis Severity Index (VSCAPSI [4]) or the Nail Psoriasis Severity Index (NAPSI [5]). They often are also associated to a measurement of the improvement of the patient's quality of life (DLQI [6]) since psoriatic lesions often impair social life.

The pathophysiology of psoriasis is reckoned to associate inflammation and angiogenesis, favoring the uncontrolled outgrowth of keratinocytes. The anti-inflammatory and anti-angiogenic efficacy of such monoterpenes as *d*-Limonene, contained in orange peel extract (OPE) could therefore be of interest in this disease [7, 8]. This is supported by pre-clinical experiments in mouse models where *d*-Limonene and its metabolite perillyl alcohol (POH) were demonstrated to significantly reduce skin inflammation and neoangiogenesis [8].

PILOT STUDY

Based on the preclinical data reported above, a pilot non-randomized study testing OPE efficacy was initiated at University La Sapienza, Rome, Italy. Nine patients with mild to moderate psoriasis were enrolled. They were 3 males and 6 females, aged between 13 and 73 years old. The patients respectively received for 45 days topical (n=5), oral (n=1) or both topical and oral (n=3) daily administration of OPE. Patients were given 222 mg OPE capsules containing 118 mg of *d*-Limonene. Oral administration consisted of 2 capsules per day. For topical application (twice daily), capsules were crunched and the content spread and massaged on the lesions in order to cover them, thus depending on the surface to cover.

Both at inclusion and after treatment, erythema and desquamation were scored on predefined body areas. Moreover, patients were assessed through the three psoriasis severity scores, respectively, PASI, VSCAPSI and NAPSI. They also answered a DLQI questionnaire of quality of life.

Data collected on days 0 and 45 were analyzed by paired Wilcoxon tests using the Medcalc® (Ostend, Belgium) software.

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Table 1: Patients Characteristics, Treatment and Skin Response to Orange Peel Extract

Pt #	Sex	Age	Tt	Scalp		Upperlimbs		Torso		Lowerlimbs	
				Before	After	Before	After	Before	After	Before	After
1	M	23	Po+T	E3 D4	E1 D1	E1 D0	E0 D0	E0 D0	E0 D0	E1 D0	E1 D0
2	F	26	T	E1D2	E1 D1	E2 D2	E1 D0	E0 D0	E0 D0	E1 D1	E1 D1
3	F	62	T	E1 D1	E1 D1	E3 D3	E1 D1	E1 D0	E0 D0	E1 D0	E1 D0
4	F	73	T	E1 D1	E1 D1	E3 D2	E2 D1	E1 D0	E1 D0	E2 D2	E1 D1
5	F	42	T	E1 D0	E1 D0	E1 D0	E1 D1	E2 D1	E2 D0	E1 D1	E1 D0
6	F	21	Po+T	E2 D2	E2 D1	E3 D1	E1 D0	E0 D0	E0 D0	E3 D0	E1 D0
7	F	29	Po+T	E1 D1	E1 D0	E2 D0	E1 D1	E1 D0	E1 D1	E2 D0	E1 D0
8	M	30	Po	E2 D1	E1 D0	E2 D1	E2 D1	E0 D0	E0 D0	E0 D0	E0 D0
9	M	13	T	E2 D1	E1 D1	E1 D1	E1 D1	E2 D2	E1 D0	E2 D2	E1 D0

Tt=treatment, Po=Peros, T=topical, E= erythema, D=desquamation.

RESULTS

The satisfactory subjective impression of the patients was confirmed through clinical examination by the physicians. Objective assessment through the use of quantitative scores confirmed these good results as shown in Table **1**.

The PASI score decreased from a median of 2 down to 1.2 (p=0.01), and the VSCAPSI from 3 to 2.36 (p=0.03). There was no significant difference in nail lesions but the DLQI scores also were significantly modified by the 45 days of OPE treatment (medians before and after 6 and 0, p= 0.003).

The best improvement was seen in patients only applying OPE on their skin lesions, suggesting that topical application had the best effect. However, the single patient who refused to use topical applications and only followed an oral intake of OPE for 45 days was improved at the end of treatment with less scalp lesions and a better DLQI. Of note, no adverse side effect was reported by any of the patients.

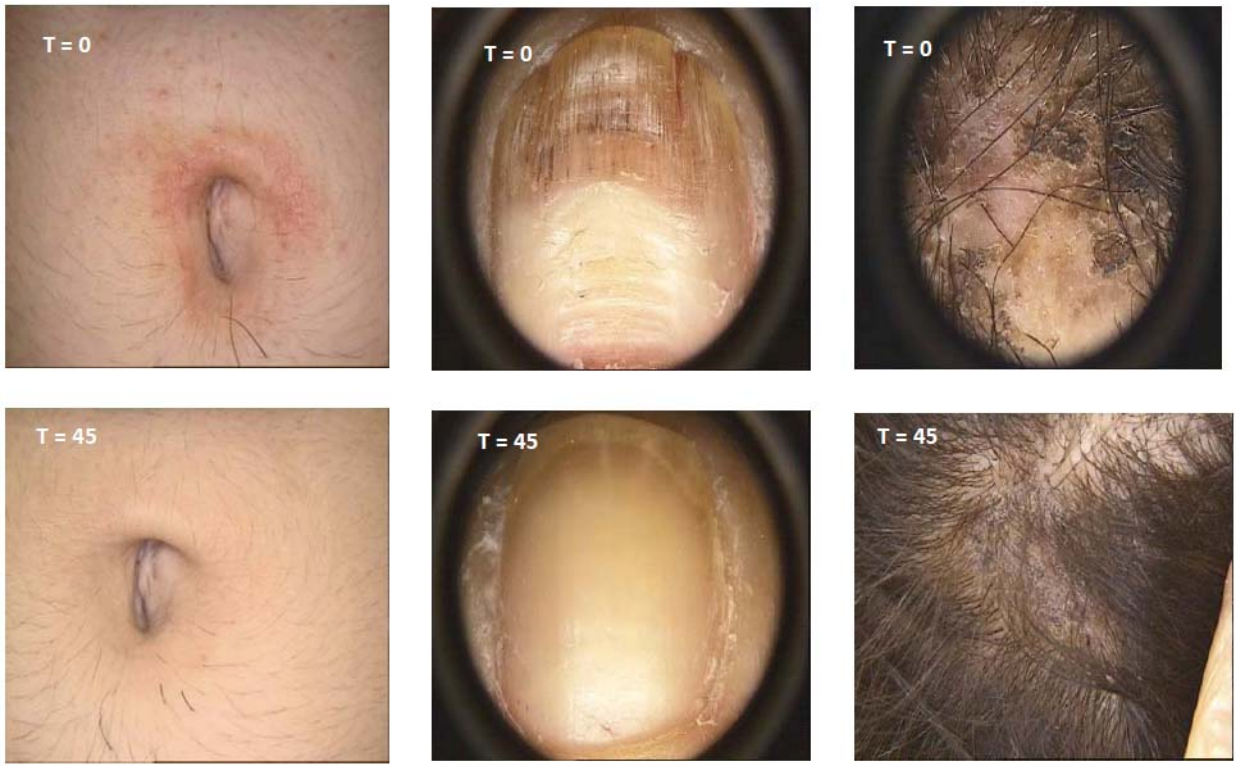

Figure 1: Clinical improvement of a navel lesion (left), of a nail (middle) and of a scalp (right).

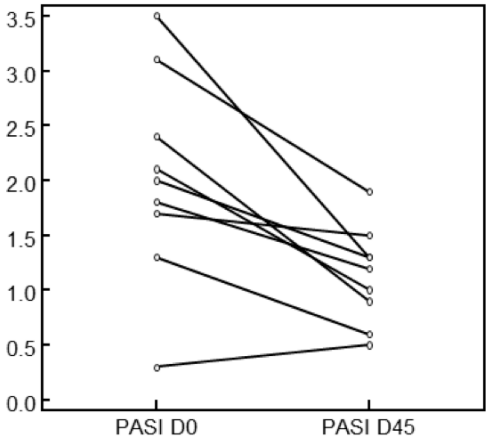

Figure 2: Evolution of Psoriasis Area Severity Index.

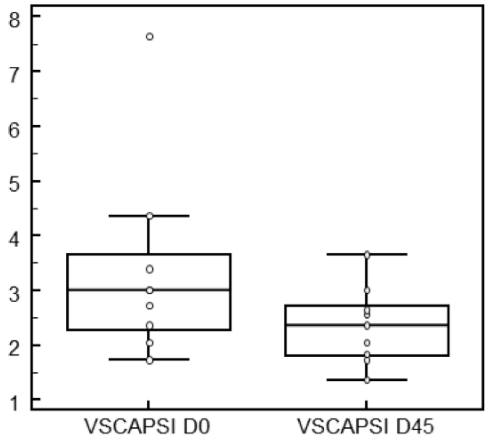

Figure 3: Evolution of Videodermoscopy Scalp Psoriasis Severity Index.

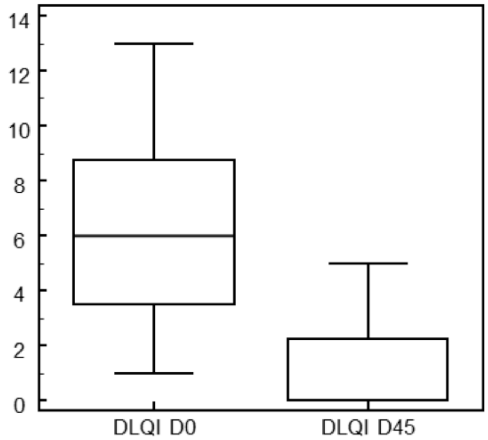

Figure 4: Evolution of Dermatology Life Quality Index.

DISCUSSION

Here we report an objective demonstration of the clinical efficacy of the monoterpene *d*-Limonene, extracted from OPE, in the multifactorial complex disorder that is psoriasis. In spite of the small size of the series, clearly significant results were obtained in a very short time in all types of body areas. Previous studies have demonstrated the beneficial effect of monoterpenes and especially of *d*-Limonene in the control of cytokines release and thus inflammation. This involves the NF-κB pathway [8, 9], itself crucial in the pathophysiology of psoriasis [10]. In addition, OPE displays anti-angiogenic properties [8] also targeting one of the roots of inflammation in psoriasis [11]. As for the mechanism of action, the animal models of skin lesions mentioned above [8] indicate that the most potent compound is the OPE metabolite POH, which can be generated *in vivo* after oral intake and/or topical application. POH was moreover directly demonstrated to display anti-angiogenic properties *in vitro* on the generation of vascular tubules from human bone marrow endothelial cells [8]. An emollient role for sunflower oil should also be considered, potentialized by the enhancer effect of *d*-Limonene [12] which, through its detergent properties, facilitates the penetration of lipids through the skin or intestinal barrier. Of note, *d*-Limonene of natural origin, i.e. extracted from orange peel was used here. The preparation procedure makes *d*-Limonene the major compound of the OPE used, yet it is accompanied by a number of other terpenes in minute proportions which alleviate its potential toxicity. Indeed, synthetic pure *d*-Limonene displays irritating properties which precludes its use as a drug. Moreover, the dosage used here was carefully devised after experimental dose-escalation studies to ensure its innocuity and maximize its efficacy [9].

CONCLUSION

This pilot study demonstrates the efficacy of fruit terpenes, more specifically *d*-Limonene-containing OPE, in the rapid resolution of psoriasis lesions. The absence of side effects of these natural compounds, at a proper dosage, could make them extremely useful as new therapeutic agents. These results should prompt the initiation of larger scale trials.

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