Protective effects of a cream containing Dead Sea minerals against UVB-induced stress in human skin

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Abstract

Background: Dead Sea (DS) mud and water are known for their unique composition of minerals, and for their therapeutic properties on psoriasis and other inflammatory skin diseases. Their mode of action, however, remains poorly known.

Objectives: To analyse the ability of Dermud™, a leave-on skin preparation containing DS mud and other ingredients like DS water, zinc oxide, aloe-vera extract, pro-vitamin B5 and vitamin E, to antagonize biological effects induced by UVB irradiation in skin when topically applied in organ cultures.

Methods: We have used human skin organ cultures as a model to assess the biological effects of UVB irradiation and of Dermud™ cream topical application. Skin pieces were analysed for mitochondrial activity by MTT assay, for apoptosis by caspase 3 assay, for cytokine secretion by solid phase ELISA, for overall antioxidant capacity by ferric reducing antioxidant power and Oxygen radical absorbance capacity assays (epidermis) or by cyclic voltammetry (external medium), and for uric acid (UA) content by HPLC.

Results: We report that UVB irradiation decreases cell viability, total antioxidant capacity and UA contents in the epidermis of skin organ cultures, while increasing the levels of apoptosis in cells and their cytokine secretion. Topical application of Dermud™ decreased all these effects significantly.

Conclusions: Our results clearly show that Dermud™ has protective, anti-oxidant and anti-inflammatory properties that can antagonize biological effects of UVB irradiation in skin. It may therefore be able to reduce skin photodamage and photoaging, and more generally to reduce oxidative stress and inflammation in skin pathologies.

Keywords: apoptosis – Dead Sea mud – inflammatory cytokines – reactive oxygen species (ROS) – UVB irradiation

Introduction

Recent lifestyle evolution has boosted the development of open-air leisure activities, and consequently increased the levels of skin exposure to solar ultraviolet rays (UV) (1). This phenomenon is believed to be determinant in the elevation of skin cancer frequencies observed in the last decades (2,3).

UVC rays, defined by the 200–280 nm wavelength range, are efficiently blocked by the atmosphere and do not reach the skin. UVB (280–320 nm) affect the basal layer of epidermis, causing DNA lesions and protein damage (4–6). UVA (320–400 nm) penetrate deeper and reach the dermis, inducing endothelial cell necrosis, blood vessel damage and collagen degradation (7–9).

Skin irradiation by either UVA or UVB is believed to affect biological tissues through initiation of photo-oxidative reactions, impairment of antioxidant balance and increase of reactive oxygen species (ROS) cellular levels. The activation of ROS-sensitive signalling pathways (6,10) may actively participate in short- and long-term skin pathologies like erythema, inflammation, photoaging and skin tumors (11,12). Recent data suggest that sunscreens may not be so efficient to protect skin against UV-induced cancers, failing to avoid long-term consequences of photodamage (13–17). Topically applied substances able to modulate ROS-sensitive signalling pathways induced by UV exposure might provide a better protection, by interfering with UV-induced...
biochemical pathways that actually cause pathologic or undesired effects. Moreover, this protective role could be extended to other skin disorders where the same pathways are involved.

The therapeutic and cosmetic properties of Dead Sea (DS) mud and water have been well established, especially when combined with irradiation by atmosphere-filtered sun rays at low-altitude (18–21). Their unique composition is specially rich in magnesium, calcium, sodium, potassium, zinc and strontium (22,23), some of which are known to influence metabolism. For instance, topically applied Mg\(^{2+}\) ions have an anti-inflammatory effect (24) and accelerate skin barrier recovery in cooperation with Ca\(^{2+}\) ions (25); zinc was shown to be involved in epidermis proliferation and wound healing (26). Underlying biological mechanisms, however, have not been elucidated, and how hydrophilic salts can cross the hydrophobic barrier of stratum corneum (SC) and reach deep skin layers to exert their effects, is one more question (27). Minimal penetration through non-lipidic channels such as hair follicles and sweat ducts may occur, but its functional importance is under debate (28). Therapeutic efficacy of DS minerals on psoriasis, contact and atopic dermatitis might be enhanced by easier trans-epidermal penetration in lesional areas, due to SC damage (29). Alternatively, limited penetration may be enough to activate signalling pathways by receptor binding (26,27), or even non-binding activation may occur, as hypothesized by Speich and Bousquet (30). In fact, we have observed that topical application of DS salts on skin organ cultures, or skin in vivo, can down-regulate some aging biomarkers and stimulate mitochondrial activity (31).

Topical application of DS mud, known as ‘mud pack’, is a classical procedure in DS climatotherapy and normally requires final washing off with clear water. The originality of Dermud\(^{TM}\) cream resides in its formulation as a leave-on-skin emulsion with a high content in DS mud and minerals, in combination with aloe-vera, pro-vitamin B5 and vitamin E. Dermud\(^{TM}\) was patented as a pharmaceutical composition by Ahava-Dead Sea Laboratories Ltd. (Mao’r et al., 2000, US Patent No. 6582689). Preliminary results from our laboratory revealed that DS mud and salts can preserve epidermal cells against UV-induced photoaging and inflammatory effects. In this work, we analyse the capability of Dermud\(^{TM}\) to protect human skin against UVB-induced biological effects when topically applied in vitro.

**Methods**

**Materials**

Unless otherwise specified, fine chemicals were obtained from Sigma-Aldrich, Steinheim, Germany.

**Human skin organ culture model for biological tests on epidermis**

Skin fragments were obtained with informed consent from 20 to 60-years-old healthy women, who underwent breast or abdomen reduction. Samples were cut into pieces of approximately 0.5 × 0.5 cm and placed, dermal side down and epidermal side up, in 35 mm diameter Petri dishes containing DMEM (Dulbecco’s Modified Eagle’s Medium, Biological Industries Beit Haemek, Israel) at 37°C, under 5% CO\(_2\). Dermud\(^{TM}\) cream was applied on to the air-exposed epidermis, 36 h before irradiation as described below. The samples were incubated for another 0.5 h (oxidative stress), 24 h (epidermis viability, apoptosis level and inflammatory cytokine secretion), or 48 h (epidermis viability). At the end of the postirradiation period, epidermis was separated from dermis by 1-min heating in phosphate buffered saline (PBS) at 56°C. Remaining culture medium was collected.

**Skin exposure to UVB irradiation**

Before irradiation, all culture medium was discarded and the skin fragments were washed in PBS to remove all traces of cream. Enough PBS was added to cover the dermis, and the sample was irradiated with a UVB source (VL-6.M lamp, emission spectrum 280–350 nm, emission peak 312 nm, filter size 145*48 mm, Vilber Lourmat, Torcy, France) at 200 mJ/cm\(^2\). Immediately after irradiation, PBS was replaced by DMEM growth medium, and skin was further incubated for various periods of time.

**Preparation of epidermal extracts**

Epidermis was separated after heat treatment as described above, then immediately deep-frozen in liquid nitrogen and kept at −68°C. Tissue homogenisation was carried out in phosphate buffer (pH 7.2) on ice, using a mechanical homogenizer (Polytron\(^{®}\) PT MR 2100, Kinematica AG, Lucern, Switzerland). The amount of epidermal proteins in the extract was measured by the Bradford method (32), using bovine serum albumin as a standard (Pierce, Rockford, IL, USA). Samples were stored at −68°C until analysis.

**Viability measurements through mitochondrial assay**

Epidermis viability was estimated using a simple colorimetric assay of mitochondrial activity. Skin slices were heated and epidermis was separated as described above. Samples were transferred into wells containing 200 µl of 0.5 mg/ml (3-4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (“MTT”, Cat # 475989, Calbiochem, San Diego, CA, USA), and incubated 1 h at 37°C. The resulting, precipitated stain (formazan crystals) was extracted for 30 min at room temperature in 0.5 ml isopropanol (Frutarom, Haifa,
Apoptosis determination by caspase 3 assay
Epidermis samples were incubated in 100 μl PBS containing 2.5 μM Ac-DEVD-AMC as a substrate, with 0.02% Triton X-100 and 10 mM DTT, at 37°C in a 96-well plate (34). Fluorescence of the released coumarin derivative was measured at 390/435 nm, using a Fluostar-BMG spectrofluorimeter (Offenburg, Germany). Activity was given by the fluorescence-versus-time slope, calculated over 30 min in linear range. Results were normalized with respect to MTT assays, performed on each sample after the caspase 3 reaction.

Antioxidant capacity
Overall antioxidant scavenging capacity, i.e. ability to donate electrons to ROS, was measured either in epidermis or in external medium, using different methods.

Ferric reducing antioxidant power assay
This method, described by Benzie and Strain (35), consists in measuring the ability of epidermal extracts to reduce ferric (Fe³⁺) ions by using a redox-linked colorimetric assay. Briefly, Fe³⁺ ions form a complex with 2,4,6-tri-(2-pyridyl)-1,3,5-triazine (TPTZ, Fluka, Buchs, Switzerland), which turns intense blue when reduced to the ferrous form at low pH. Ferric reducing antioxidant power (FRAP) reagent was prepared by mixing 300 μl acetate buffer (pH 3.6), 10 μl TPTZ (3.1 mg/ml in 40 mM HCl) and 20 μl FeCl₃·6H₂O (5.4 mg/ml in H₂O), in a ratio of 10:1:1. A total of 40 μl of epidermal extracts were added to 300 μl of FRAP reagent, and 150 μl aliquotes were transferred to a 96-well plate. Absorbance was measured 10 min after mixing at 595 nm, using a ‘PowerWave 340’ microplate spectrophotometer (Bio-tek Instruments, Winooski, VT, USA). Phosphate buffer (homogenization solution) was used as blank. Results were quantified by comparison with standard curves obtained with a Trolox solution, and expressed in μmoles Trolox per milligram protein. All measurements were performed at room temperature, sheltered from direct sunlight.

Oxygen radical absorbance capacity assay
Amounts of epidermal antioxidants were also measured with 2,2′-Azobis(2-aminopropane) dihydrochloride (AAPH) as a peroxyl generator, using the Oxygen radical absorbance capacity (ORAC) assay described by Benzie and Strain (35), adapted to fluorescein labelling (36). Measurements were performed on a Fluostar Galaxy plate reader (BMG, Offenburg, Germany) equilibrated at 37°C, with excitation and emission set up at 485 nm and 520 nm, respectively. We used Trolox as a calibration standard. All reagents were prepared in 75 mM phosphate buffer (pH 7.4). A total of 40 μl aliquotes of epidermal extracts, Trolox dilutions, or phosphate buffer as a blank, were transferred into a 96-well microtiter plate. Fluorescein was added to a final concentration of 96 nm. ORAC fluorescence was read every 2 min for 70 min. Peroxyl radical-induced oxidation started immediately after AAPH addition. Results were quantified by comparison with Trolox as above. Total antioxidant capacity was calculated by measuring the area below the kinetic curve.

Voltammetric assay of reducing power
The overall reducing power of extracellular media was assayed using a cyclic voltameter (Electrochemical Analyzer, CH Instruments, Austin, TX, USA). Culture media samples were placed in a well with three electrodes: a glassy carbon, working electrode of 3.3 mm diameter, an Ag/AgCl reference electrode and a platinum wire as auxiliary electrode (37). Potential was applied to the working electrode at a constant rate (100 mV/s). Reducing power was determined from the cyclic voltammogram and was composed of two parameters: the peak potential (Ep(a)), which reflects the ability of several compounds with close potentials to donate electrons, and the anodic current (AC), which measures the concentrations of these compounds (35). The working electrode was checked before each series of measurements, by performing a cyclic voltammogram of 1 mM potassium ferricyanide in PBS.

Uric acid dosage
Although uric acid (UA) is a waste product derived from purine metabolism, it has the ability to react with harmful oxidants like peroxynitrite, and its consumption may therefore be an indicator of ongoing oxidation. We determined UA levels in epidermis using a HPLC system (36) composed of a LC 320 pump (Kontron, San Diego, CA, USA), a 20 μl injection loop, a reversed phased, 4.6 mm C-18 column (Supelco, Bellefonte, PA, USA) and a voltammetric detector. Skin extracts were thawed and centrifuged at 14 000 rpm for 10 min at 4°C, and supernatants were collected for analysis. After filtration on nylon filters (0.2 μm pores, 17 mm diameter, National Scientific, Rockwood, TN, USA) 25 μl aliquotes were injected to the HPLC system. The mobile phase (100 mg/ml EDTA, 0.1 M Acetic acid buffer at pH 4.75, 1% Tetrabutylammonium hydroxide) was delivered at a flow rate of 0.8 ml/min. The voltage applied to the samples was +600 mV, with a sensitivity of 50 nA. Uric acid concentration was determined by comparison with standard UA solutions (Sigma Chemicals, St Louis, MO, USA).

Cytokine secretion
Skin organ culture media were collected after 24 h incubation in standardized conditions. Concentrations of IL-1α,
IL-6, IL-8, IL-10 and TNFα were measured by solid phase ELISA (37) using highly sensitive immunoassay kits (Siemens Medical Solutions Diagnostics, Hounslow, UK). Briefly, a polystyren microtiter plate was coated with a cytokine-specific monoclonal antibody. Standards and samples were then placed in the wells and incubated with the immobilized antibody. After immune binding of the antigen, unspecific compounds were washed away, and a second enzyme-linked, monoclonal or polyclonal antibody directed to the same antigen, was added. After completion of a ‘sandwich’ formation, unbound molecules were washed away, and a colorogenic substrate was added to reveal the enzyme-linked antibody. The enzymatic reaction was stopped in linear phase, and assessed by colorimetry using an Immulite 1000 analyzer (Siemens Healthcare Diagnostics, Germany). Cytokine concentrations were determined by comparison with standard solutions.

Statistical analysis
Each experiment was performed at least in triplicate. Average values are given with standard error of the mean (SEM). Differences between average values were tested for significance using the unpaired Student t-test and considered as significant for \( P < 0.05 \).

Results
UVB dose range
UVB effects on cultured keratinocyte are optimally studied at doses ranging between 5 and 50 mJ/cm² (38, 39). But living epidermis resides in deep layers efficiently protected by the SC and requires harsher irradiation to be efficiently challenged. Experimental doses commonly range from 150 to 250 mJ/cm² (38, 40). We determined that in our conditions, apoptotic caspase 3 activity in epidermis increased linearly with UVB dose up to 300 mJ/cm² (Fig. 1a), while cell viability measured by MTT mitochondrial assay underwent a limited decrease, generally about 40% (Fig. 1b). Hence we chose to use a single dose of 200 mJ/cm² in all experiments, which in fact corresponds to 15 min–4 h of solar irradiation (41), a common period of time for outdoor exposure.

Reduction of UVB-induced cytotoxicity by Dermud™ treatment
Two kinds of tests were performed to evaluate the ability of Dermud™ to interfere with UVB-induced cell toxicity in epidermis. First, mitochondrial activity was monitored using the MTT test. UVB exposure caused a 20% decrease 48 h after irradiation, but previous application of Dermud™ reversed this trend, with a 20% increase in the same conditions (Fig. 1c). Second, the final stage of apoptosis was investigated by assaying caspase 3 activity in epidermal extracts prepared 24 h after UVB irradiation. UVB exposure caused a drastic 10-fold increase, but a previous treatment with Dermud™ reduced this increase by 80% (Fig. 1d). These results demonstrate a profound effect of Dermud™ to curb UV-induced cytotoxicity in epidermal cells.

Anti-oxidative effect of Dermud™
Antioxidant potential of skin samples was assessed by three different methods. FRAP was measured in epidermis extracts, and displayed a significant 30% decrease after UVB irradiation. Topical treatment by DermudTM enhanced FRAP by 50% in non-irradiated controls, and remarkably, this Dermud™-enhanced antioxidant power was not affected by UV irradiation (Fig. 2a).

Oxygen radical absorbance capacity in epidermis, contrary to FRAP, was not significantly modified by UVB irradiation. Topical treatment by Dermud™ enhanced FRAP by 50% in non-irradiated controls, and remarkably, this Dermud™-enhanced antioxidant power was not affected by UV irradiation (Fig. 2b).
cyclic voltammetry. Two anodic waves, corresponding to two groups of LMWA with similar oxidation potentials, were detected in all tested conditions, one at 619–668 mV and the other at 720–890 mV. After UV exposure, the exogenous reducing powers associated with these two waves were significantly decreased, by 20% and 10%, respectively. This effect disappeared when Dermud™ was applied before irradiation, as shown in Fig. 3.

Limitation of UVB-induced uric acid decrease
Uric acid concentration was measured in epidermal extracts of skin organ cultures as described in the Methods section. Fig. 4 shows a 30% decrease of UA levels after UVB irradiation, partially restored by Dermud™ pretreatment.

Limitation of UVB-induced cytokine secretion in skin organ cultures
We found that UVB irradiation increased the secretion of inflammatory cytokines in skin samples in vitro: the amounts of TNFα in culture media were raised by a factor 5, while those of interleukins IL-1α, IL-6 and IL-8 were significantly increased. Dermud™ application prior to irradiation drastically inhibited this effect (Fig. 5). It also decreased the basic levels of cytokine secretion in non-irradiated skin samples by 40% for IL-6 and IL-8, and by 70% for IL-10, with IL-1α and TNFα remaining unchanged. As a whole, these results suggest that Dermud™ may have a wide anti-inflammatory competence in skin tissue.

Discussion
Skin exposure to UVB rays damages epidermal cells enhances ROS generation and inflammatory processes and leads to different skin pathologies (42,43). Therefore, topical application of anti-inflammatory and antioxidant agents may reduce UVB-induced skin disorders. It has been shown indeed that UVB-induced damage in skin cells can be efficiently limited by plant-derived antioxidant compounds (38,44–47).

This study has been focused on Dermud™, a patented, leave-on skin emulsion enriched with DS mineral mud, DS water, zinc oxide (ZnO), α-tocopherol (vitamin E) and...
panthenol (pro-vitamin B5). DS minerals are expected to interfere with UV-induced inflammation and photoaging, because of their anti-inflammatory and antipsoriatic properties, that are commonly exploited in climatotherapeutic cure at the DS site (21). Moreover, DS minerals were shown to down-regulate aging pathways in epidermal cells, presumably through intracellular signalling (48).

Among other Dermud™ components, ZnO is common in dermal creams. It can absorb UV rays and behaves as an antioxidant (49). However, direct smearing of Dermud™ on the probe of a UV light meter (Lutron UV-340, Taiwan) did not change UVB intensity measurements (Ma’or Z, unpublished results). Hence, we can exclude the possibility that Dermud™ could work as a UV filter. Vitamin E in topical applications can protect skin against UV effects by increasing the levels of small antioxidant molecules (50), increasing ROS-scavenging activities (50, 51), reducing lipid peroxidation (51, 52) and preventing DNA photodamage (53). Panthenol is converted into panthotenic acid when topically applied on skin and can reduce experimental ultraviolet-induced erythema (54). It is also common in cosmetic preparations due to its emollient, anti-inflammatory and cell-regenerative properties. The whole set of Dermud™ constituents is therefore expected to cooperate in a protective anti-oxidant and anti-inflammatory effect in UVB-exposed skin.

UVB rays target epidermal DNA and produce pyrimidine dimers, resulting in activation of p53 transcription factor, excision repair and/or apoptosis (55). Fos and Jun are activated and AP-1-dependent transcription is induced; matrix-degrading metalloproteinases (MMPs) are upregulated and collagen synthesis is inhibited. While this DNA-dependent response occurs several hours after irradiation, a DNA-independent pathway, mediated by ROS derived from extranuclear chromophores, can be detected earlier and with lower UVB doses (56, 57). It activates EGF receptor, ERK, JNK and p38 MAP kinases, stimulates c-Jun synthesis and activates AP-1-dependent transcription (58). DNA-dependent and independent pathways cooperate to induce MMPs and inhibit collagen synthesis, thereby harming dermal extracellular matrix and causing photoaging symptoms. As Dermud™ is not a UVB filter, it cannot prevent direct photodamage. But because it combines antioxidant potency with anti-inflammatory properties, it is expected to antagonize the ROS-derived, early UVB response, and possibly also MAP kinase-dependent steps induced by DNA damage, all of them leading to photoaging.

We applied Dermud™ cream topically on human skin organ cultures, then proceeded to UVB irradiation and analysed the effects on epidermis. Measurements of mitochondrial activity and of UVB-induced apoptosis by caspase 3 assay converged to show that Dermud™ efficiently inhibits UVB-mediated cytotoxicity. As UVB-induced apoptosis is considered as a vital process to eliminate potential tumor cells, however (4, 59), the possibility that anti-cytotoxic properties of Dermud™ might facilitate the persistence of UV-induced carcinogenic mutations has to be considered. This question is in fact relevant to antioxidants in general, as was discussed for green tea extracts in particular (46). We can argue that improved vitality is expected to stimulate the DNA-repair process and decrease the mutation rate, and common experience has indeed led to consider antioxidants as anticarcinogens (60). Yet, this issue has to be evaluated for each product.

We showed previously by voltammetric experiments that Dermud™ has antioxidant potency \[E_{pa} (a) \approx 1000 \text{ mV; AC} \approx 10 \mu\text{A},\] so that its ability to enhance mitochondrial activity and to limit apoptosis is likely to proceed by neutralization of UVB-induced ROS excesses. Using two different methods (FRAP and ORAC), we observed that Dermud™ treatment increases the total antioxidant power of epidermis, in both irradiated and unirradiated samples. Remarkably, UVB irradiation does not affect Dermud™-enhanced antioxidant power, showing that UVB-derived ROS are completely neutralized by Dermud™. As the cream does not penetrate through the SC, this can mean that most UVB-induced ROS may originate from surface chromophores located in upper epidermal layers. Alternatively, Dermud™ could prevent intrinsic epidermal ROS...
production through signal transduction, in accordance with reports that external ion concentrations can modulate cellular ROS levels (61). The fact that FRAP values decrease after UVB irradiation, while ORAC is not significantly affected can be explained by differences between the two methods: the FRAP assay titrates only Fe(II) reducing reagents, while the ORAC assay monitors all antioxidant molecules that is able to react with peroxy radicals.

Consistently with FRAP and ORAC experiments, the antioxidant power of external medium, corresponding to low molecular weight antioxidants (LMWA) secreted by skin, was decreased by UVB irradiation in untreated, but not in Dermud™-treated samples. This further suggests that UVB-derived, LMWA-consuming ROS, were totally neutralized by Dermud™. The slight decrease observed in non-irradiated samples upon Dermud™ treatment may be explained by an independent effect of Dermud™ to limit LMWA secretion.

Uric acid is one of the LMWAs (62). It is an example of adaptation to oxidative stress, being originally a waste product derived from hypoxanthine and xanthine oxidation by xanthine oxidase and xanthine oxidoreductase (63). UA is a scavenger of peroxynitrite, a harmful and versatile oxidant derived from interaction between nitric oxide and superoxide radicals (64–66). UVB irradiation reduces epidermal UA content, presumably through increased consumption by peroxynitrite and derivatives. Hence, the fact that Dermud™ prevents UA depletion indicates a possible role in peroxynitrite scavenging.

UVB irradiation stimulates the expression of nuclear factor-κB (NF-κB) (67), as do other pro-oxidants or ROS-regulated factors (68,69). NF-κB activation is an early event in inflammatory response, which targets TNFα, IL-1, IL-6 and IL-8 genes (70,71). Thus, NF-κB makes a link between ROS and inflammatory cytokine expression. Our results provide further evidence that UV irradiation induces these cytokines, as well as anti-inflammatory IL-10. Although paradoxical, the simultaneous induction of IL-10 and pro-inflammatory cytokines has already been reported (72). Topical application of Dermud™ drastically reduces the secretion of these cytokines following UV irradiation, thereby limiting keratinocyte contribution to UVB-induced inflammatory response. A similar inhibition of IL-6, IL-8 and IL-10 secretion was found in unirradiated samples, suggesting that Dermud™ may also control the basal level of inflammation in skin.

In conclusion, we have demonstrated that Dermud™ cream possesses antioxidant, anti-apoptotic and anti-inflammatory properties that reduce harmful effects of UVB involved in photoaging. Further studies are needed to elucidate the underlying mechanisms and to determine individual contributions of its constituents.

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References


