

Beauty is not only Skin Deep: the Dead Sea features and Cosmetics

Marco HARARI⁽¹⁻²⁾

⁽¹⁾DMZ Medical Center at the Dead Sea, Ein Bokek 86930 (Israel)

⁽²⁾Dead Sea & Arava Science Center, Neve Zohar 86910 (Israel)
marco.harari@gmail.com

Abstract

Introduction: The Dead Sea area possesses extraordinary geo-climatic factors and represents a natural health resort known worldwide for its success treating skin and rheumatic diseases. Dead Sea cosmetics – or cosmetics arguing being from this place and containing Dead Sea water or minerals – are also known worldwide but still controversies take place in the medical milieu regarding their true effect on the skin.

Material and Methods: All relevant articles cited in Medline were reviewed, including studies on minerals and mud from the Dead Sea.

Results: In vivo and in vitro studies demonstrated clearly the high potential of the Dead Sea minerals for cosmetic purposes. Magnesium and Sulfur appear to be the prominent actors in rheumatology and dermatology, when incorporated to cream or mud.

Conclusion: Even if only few studies are able to elucidate the real effect of the Dead Sea minerals in cosmetics preparations, there is enough evidence for encouraging such investigations and developing more products. These will enable a better use of the extraordinary reservoir of minerals represented by the deepest and most saline lake in the world.

Key words: Dead Sea, Minerals, Mud, Cosmetics.

La belleza no está sólo en la superficie de la piel: características del Mar Muerto y los cosméticos

Resumen

Introducción: La zona del Mar Muerto posee extraordinarios factores geo-climáticos, y representa un centro de salud natural conocido mundialmente por su éxito en el tratamiento de las enfermedades de la piel y reumáticas. Los Cosméticos del Mar Muerto-o cosméticos originarios de este lugar, y que contiene agua o minerales del Mar Muerto-son conocidos en todo el mundo, pero aún existen controversias en el entorno médico con respecto a su verdadero efecto sobre la piel.

Material y Métodos: Se revisaron todos los artículos importantes citados en Medline, incluyendo estudios sobre los minerales y el barro del Mar Muerto.

Resultados: Estudios in vivo e in vitro han demostrado claramente el gran potencial de los minerales del Mar Muerto con fines cosméticos. El magnesio y el azufre parecen ser los componentes más importantes en reumatología y dermatología, cuando se incorporan a la crema o el barro.

Conclusión: Aun cuando sólo unos pocos estudios son capaces para de dilucidar el efecto real de los minerales del Mar Muerto en la preparación de cosméticos, hay suficiente evidencia para impulsar estas investigaciones y desarrollar más productos. Esto permitirá un mejor uso del depósito extraordinario de minerales representado por el lago más profundo y más salino en el mundo.

Palabras clave: Mar Muerto, Minerales, Barro, Cosmético.

REFERENCE STANDARD

Harari M. Beauty is not only Skin Deep: the Dead Sea features and Cosmetics. *Anal Hidrol Med.* 2012, Vol. 5, Núm. 1, 75-88.

INTRODUCTION

The Dead Sea is the lowest saline lake on earth (420 meters, or about 1,300 feet, below sea level). Its therapeutic benefits have been well known for 1,500 years, with the modern era for such treatments beginning in 1959¹⁻². Over the past 60 years, the Dead Sea has become well recognized for its balneologic activity, allowing climatotherapy to be used for dermatologic and rheumatologic conditions.

In particular, Dead Sea climatotherapy is considered to be very effective in the treatment of psoriasis³⁻⁴⁻⁵⁻⁶ and, to a lesser extent, atopic dermatitis⁷⁻⁸ and Vitiligo⁹⁻¹⁰. Climate therapy cannot be exported. Moreover, all skin diseases treated at the Dead Sea are mainly improved by the extraordinary ultra-violet radiation of this region¹¹⁻¹² and not by any cream or topical treatment. However, products that contain Dead Sea minerals are since years and currently used to treat several dermatologic conditions and many companies offer product lines that feature Dead Sea minerals. The array of such products includes hand and body lotions, bath salts, body butter, eye cream, cleansing mud masks, mineral mud soaps, mineral peeling soaps, body exfoliates, collagen firming creams with Sun Protection Factor, acne lotions, lightening cream with SPF, firming night creams, antidandruff and numerous other shampoos, scalp masks, and sunscreens.

In this paper, we propose to review the last studies dealing with the specific features of the Dead Sea minerals and their applications to cosmetics. We'll try to draw an evaluation of their properties in two distinct parties, dealing with the use of minerals only and the application of black mud including these minerals.

A HUGE AMOUNT OF DISSOLVED MINERALS

The palliative effects of immersing in baths or pools of thermo-mineral water, known as balneotherapy, have been known for centuries, with modern practices dating back to the 1800s and natural health spas dating back more than 3,000 years¹³⁻¹⁴.

The Dead Sea contains exceedingly high salt concentrations and acts as a reservoir of minerals with distinct evaporation properties. Dead Sea bath or Dead Sea balneotherapy possesses extraordinary advantage because of these unique concentration and composition of salts. Not surprisingly, Dead Sea salts are the source of numerous chemical and health products. Specifically, various skin conditions and allergies, as well as arthritis and respiratory disorders, have been treated with Dead Sea-derived magnesium salts and sulfur-containing mud¹⁵⁻¹⁶⁻¹⁷. Magnesium salts, which are known to have anti-inflammatory activity, are the prevailing minerals in Dead Sea water¹⁸. From 10 to 80 times more present, Dead Sea minerals concentrations can hardly be matched up to those present in other seas. Compared with the world's oceans, the Dead Sea is more abundant in calcium, magnesium, potassium, and bromide, and lower in sodium, sulfate, and carbonate¹⁹.

BENEFICIAL EFFECTS OF DEAD SEA MINERALS

The beneficial effects of Dead Sea (DS) bath in inflammatory skin disorders had been repeatedly evoked and reported²⁰⁻²¹⁻²². DS minerals composition is especially rich in magnesium, calcium, sodium, potassium, zinc, strontium, sulfides and bromides. Some of these minerals are known to influence signal transduction and cell metabolism: it has been demonstrated that Mg^{2+} ions inhibit the antigen-presenting function of human epidermal Langerhans cells in vivo and in vitro²³⁻²⁴. Bathing in a magnesium-rich Dead Sea salt solution improves skin barrier function, enhances skin hydration, and reduces inflammation in atopic dry skin¹⁸. It has been also demonstrated that zinc is involved in epidermal proliferation and wound healing²⁵⁻²⁶.

The therapeutic properties of the mud are ascribed to its content of reduced sulfur species, its physical and chemical properties and its mineral content²⁷. Therapeutic value of DS minerals, often reported on various inflammatory skin disorders, such as psoriasis, contact and atopic dermatitis, (but not yet totally proven) might be enhanced by easier trans-epidermal penetration in lesion areas, due to stratum corneum damage²⁸. Alternatively, limited penetration may be enough to activate signaling pathways by receptor binding or even non-binding activation may occur²⁹.

There are only a few studies published on the specific properties of Dead Sea minerals, but they are all showing spectacular effects, in vitro and in vivo as well, in many fields. They should encourage more investigations and more use of these natural and non dangerous active agents.

Enzyme stimulation in clinical studies

In 1985, Shani et al. found that glutathione peroxidase activity was significantly increased in 35 psoriatic Danes who received 4-week therapy at the Ein Bokek International Psoriasis Treatment Center along the Dead Sea in Israel. The drinking water at the center was found to be rich in selenium.

The researchers assayed the activity of erythrocyte glutathione peroxidase, the most reliable marker for increases in selenium bioavailability, in the psoriasis patients, in 25 long-time local hotel workers, and in healthy volunteers who consumed low-selenium water. Enzymatic activity in the hotel workers was found to be 50% higher than in the low-selenium drinkers. The investigators concluded that selenium might play a beneficial role in psoriasis treatment³⁰.

In a study published the same year, several of the same researchers compared the penetration of electrolytes through the skin of healthy volunteers and psoriasis patients who bathed in the Dead Sea or comparable bath-salt solutions for a 4-week period. Only the psoriasis patients had significant increases in serum levels of bromine, calcium, and zinc²⁹.

Anti-proliferative Action

Two years later, Shani et al. tested diluted Dead Sea brine and salt solutions, and found that they reversibly suppressed cell proliferation *in vitro*. They noted that bromides were more potent inhibitors than chlorides, and that potassium salts exhibited greater effectiveness than sodium or magnesium salts. The authors speculated that the penetration of minerals through the skin, along with anti-proliferative effects, may help explain the effectiveness of Dead Sea spa treatments for psoriasis³¹.

Interestingly, in 1996, investigators sought to identify the anti-proliferative effects of certain Dead Sea minerals that play a role in ameliorating psoriasis, by comparing the *in vitro* proliferation of fibroblasts grown from biopsy specimens of healthy and psoriatic skin. They found that magnesium bromide and magnesium chloride exhibited significantly more potent inhibitory effects on cell growth than did their corresponding potassium salts and sodium chloride, and that these effects were manifested in healthy as well as psoriatic fibroblasts³².

Moisturizing Action

In 1997, Ma'or et al. compared the cutaneous smoothing effects of three different liquid gels, one of which contained Dead Sea minerals. The formulations were applied to 20 mature women twice daily over 4 weeks, with computer-aided laser profilometry used to evaluate skin roughness before and after the treatment period.

At the conclusion of treatment, the gel containing 1% Dead Sea mineral solution was associated with a 41% reduction in skin roughness. A 28% reduction was

achieved with the use of the gel devoid of mineral additives, and a 10% reduction was seen with a control gel absent any anti-wrinkle ingredients³³.

Reducing Chemotherapy's Side Effects

In another recent study, researchers assessed the effectiveness of Dead Sea products on the side effects of radio-chemotherapy in 24 patients suffering from head and neck cancer. The control group consisted of 30 conventionally treated patients. The radio-chemotherapy patients were directed to use two products containing Dead Sea minerals - a mouthwash (Lenom, from Clinica Lenom Ltd.) and a moisturizing cream (Solaris) - three times daily for 1 week before, during, and up to 2 weeks following the conclusion of radiotherapy.

The investigators observed grade 1-2 mucositis in 13 patients treated with Dead Sea minerals (54%), with none exhibiting grade 3-4 mucositis. In the control group, 17 subjects (57%) had grade 1-2 mucositis, while grade 3-4 mucositis was noted in 4 (13%). In addition, grade 1-2 dermatitis was seen in 13 patients treated with Dead Sea minerals (54%), with none displaying grade 3-4 dermatitis, whereas grade 1-2 dermatitis was observed in 11 control patients (37%) and grade 3-4, in 5 (17%)³⁴⁻³⁵.

Anti-aging effect

Cellular and molecular characteristics of aged epidermal keratinocytes were analyzed in monolayer cultures and in skin by measuring their morphological, fluorometric and biochemical properties. This essential work, done by the team of Milner, shed light on the aging skin process and most precisely on its characterization in keratinocytes. The study, published in 2008, showed altered expression of 16 biochemical markers in aged cultured cells and in tissues, including caspases 1 and 3 and beta-galactosidases activities, p16, Ki67, 20S proteasome and others.

Effects of Dead Sea minerals were analyzed as a test case, on keratinocytes cultures and human skin. The authors reported that Dead Sea minerals stimulated proliferation and mitochondrial activity, decreased the expression of some aging markers and limit apoptotic damage after UVB irradiation³⁶.

Protective effect against UVB-induced stress

One year later, using Dermud™ (from Ahava Laboratories), a leave-on skin preparation containing DS water and mud, but also zinc oxide, aloe-vera extract,

pro-vitamin B5 and vitamin E, the same team tried to better objective any alteration in the biological effects induced by UVB radiation. The authors applied the cream on human skin organ cultures which were irradiated topically, and analyzed for mitochondrial activity (by MTT assay), apoptosis (by caspase 3 assay), cytokine secretion (by solid phase ELISA), overall antioxidant capacity and for uric acid content (by HPLC).

Topical application of Dermud™ decreased all the effects of irradiation significantly, showing a protective, anti-oxidant and anti-inflammatory effect, which was able to reduce the deleterious effects of irradiation on skin. Photodamage and photoaging, as well as oxidative stress and inflammation in skin pathologies, might be reduced by this product, concluded the authors³⁷.

Improvement of Atopic Dermatitis scores

The efficacy of TP, an emollient cream enriched with DS water in children with Atopic Dermatitis was recently assessed in a double-blind, randomized controlled study. 86 patients were assigned during the 12-week trial either to DS water rich cream twice daily, or to 2 controls: cream with a lower concentration of DS water and emollient without DS minerals. Efficacy was assessed every 2 weeks by SCORing Atopic Dermatitis (SCORAD) and many other objective and subjective scores (Investigator Global Assessment - IGA, Patient Global Assessment - PGA, Transepidermal Water Loss - TEWL, Stratum Corneum Hydration - SCH, affected Body Surface Area - BSA, Objective Severity Assessment of Atopic Dermatitis - OSAAD).

TP was the most effective regarding TEWL, SCH and OSAAD. The authors reported that the study clearly showed the benefits of the DS minerals enriched emollient as a leave-on emulsion, in term of skin barrier function. They recommended this product as an effective treatment for AD skin in acute phases and for maintenance therapy³⁸.

MUD TREATMENT AND DEAD SEA MUD

Fangotherapy - the use of mud, peat, and clay for healing purposes - gained popularity in the early 1800's in Europe where it was, and still is, used to treat a variety of musculoskeletal and skin conditions. While only few double-blind studies are available in order to evaluate their efficacy these treatments have been used extensively on such conditions as rheumatic diseases including fibromyalgia and muscular pain³⁹⁻⁴⁰, endocrine diseases and immune system disorders⁴¹⁻⁴²⁻⁴³, respiratory diseases⁴⁴, a variety of skin diseases: acne⁴⁵, dermatitis⁴⁶, psoriasis⁴⁷, and even in gynecology⁴⁸. As well, numerous cosmetic companies developed products containing mud as unique or major component. Here also, only few publications deal with

the specific properties of the mud, while most of them correlate its effects to the mineral content.

A limitation of this thermal treatment is the possibility that hot applications could induce a disease flare, but beneficial effects of baths and mud packs in patients affected with inflammatory rheumatic diseases, especially ankylosing spondylitis and rheumatoid arthritis, have been reported⁴⁹⁻⁵⁰⁻⁵¹ and do not confirm the hesitations to use them even in unstable disease.

Very recently, a systemic review presented the level of evidence for the claims of therapeutic effects of Dead Sea treatments in several rheumatologic diseases and as well as for the safety of such treatments. The authors concluded on a good safety profile and on a proven scientific evidence for their beneficial effects. This work included papers dealing with fangotherapy, clearly indicating a potential use in any inflammatory joint disease, in acute or chronic phase⁵².

Dermal properties of Mud

Many types of clay are commercially available from different soils and environments around the world. All commercially available clay has the same basic properties, but clays from marine sediments or from areas around hot springs usually have higher mineral contents than other clays (for example Dead Sea mud).

All types of fango have heat-retention properties and can be warmed up and applied to the skin to stimulate and improve circulation. This aids nutrient and waste exchange, opens follicles, and improves the elasticity of skin. Apart from the common effect of increased circulation, clay, mud, and peat each have different therapeutic properties and uses, all connected to their incorporated minerals.

One interesting study showed clearly this issue, using in a double-blind randomized clinical trial mineral-deleted mud pack as placebo. These mud packs, completely emptied from their minerals, were used by patients suffering from Osteoarthritis, and heated before being applied on the knees, as the natural black mud packs. The significant differences in improvement between the two groups showed clearly that the heating process was not the responsible for the beneficial effect of the mud application, but the presence of minerals in the mud⁵³.

Clay is highly absorbent and is used to draw impurities and moisture from the surface of the skin. This drawing action simulates circulation and lymphatic flow and purifies the skin, to cure wounds, soothe irritations, as a method of cleansing the skin⁵⁴. Clay minerals, used in aesthetic medicine and in cosmetic products, as active principles or excipients, and in geotherapy, pelotherapy and paramuds, are often presented, after drying slightly on the skin, as capable to aid natural exfoliation and improve skin texture. Despite these well accepted axioms and some interesting studies on this topic, we did not find an enough well-built body of evidence for such properties.

Clays readily suspend to form an emulsion in water or other liquid substances. This property is useful in cosmetics as clay helps to hold other substances together and prevent separation. Clay is regularly used as an emollient and colorant in powders, liquid foundations, lotions, and skin masks. Recently, in order to develop a Dead Sea Minerals (DSM) based drug delivery system for topical therapy of skin diseases, polymeric nanoparticles based on Poly (maleic anhydride-alt-butyl vinyl ether) 5% grafted with monomethoxy poly(ethyleneglycol) 2000 MW (PEG) and 95% grafted with 2-methoxyethanol (VAM41-PEG) loaded with DSM were prepared by means of a combined mini-emulsion/solvent evaporation process. The resulting nano-particles were characterized in terms of dimension, morphology, biocompatibility, salt content and release⁵⁵.

Safety profile of mud was assessed by several publications like for example for the Dead Sea mud, which was found to be free of any special enrichment of 12 toxic trace elements, and safe for the consumer as well as its derivative products⁵⁶. Moreover, a detailed microbial and chemical analysis of Dead Sea mineral mud compounded in dermatological and cosmetic preparations was performed by Ma'or and colleagues. Surprisingly, they found low numbers of colony-forming microorganisms in the mud. Antibacterial properties of Dead Sea mud were found on many species, even after sterilization by gamma irradiation, and thought probably owing to chemical and/or physical phenomenon⁵⁷.

Importance of Sulfur in Mud: the Dead Sea Mud

While mud, like clay, is mainly mineral in origin, it contains 2–4 percent organic substances, which play an important role in mud's therapeutic use. Mud softens skin's texture and some minerals may be absorbed from the mud into skin, although the evidence for this is still inconclusive. Therapeutic mud is matured or ripened in natural mineral water, as for Dead Sea mud. The maturing process for each mud may be slightly different, but generally involves the oxidation and reduction of the mud over a period up to twelve months long – or to thousands years⁵⁶. The process of maturing mud, characterized by changes in its chemical composition and appearance should be carefully checked.

Sulfur is perhaps the most important component of therapeutic mud and occurs naturally in proximity to volcanoes and hot springs. Sulfur baths have been researched as a means of reducing oxidative stress on the body and decreasing inflammation³⁹. Among rheumatology, sulfur-rich mineral and mud baths were advocated as useful adjuvant in the treatment of fungal infections, scabies, psoriasis, eczema, and acne⁵⁸. As well, sulfur is thought to exert beneficial anti-inflammatory, keratoplastic and antipruriginous effects on skin¹⁴.

One of the most popular types of sulfur-containing therapeutic mud is obtained from the Dead Sea region in Israel. It is believed to be derived from older sediments or the red-brown soils that are swept into the sea during the winter time. Sediment

precipitations in the Dead Sea were investigated since long⁵⁹ and are continuously monitored⁶⁰ allowing a precise analysis of the water and its components.

Dead Sea black mud is a homogeneous mixture of Dead Sea minerals and organic materials. It is believed to help in decreasing some of skin diseases and rheumatism pains and to rejuvenate skin cells. This world-wide best seller is used at the Dead Sea in two main indications: for musculo-skeletal pain of any origin and in cosmetic procedures through a variety of treatments (facial peeling and mask and body applications).

This mud has the ability to stay warm and moist for up to an hour, thus stimulating circulation and clearing skin of dead epidermal cells⁴⁶. Lately, it becomes largely used in the spas at the Dead Sea, in combination with other natural products like aloe-vera and aromatic oils. Patients – or healthy tourists – apply the mud twice a day at the sea shore and leave it on their skin and/or their painful muscles or joints for 20 minutes. The more sophisticated procedures take place in the spa: envelopments (wrap) associated to medical massage and physiotherapy and cosmetic treatments. Many of the satisfied users will buy it on the spot for further utilization at home, or seek for restock after their return, back home.

CONCLUSIONS

Minerals and mud are used for therapeutic purposes, with some beneficial effect on health, in pharmaceutical formulations, spas and aesthetic medicine. The therapeutic effects of mineral waters at various spas, and at the Dead Sea in particular, have been well established. Research on Dead Sea mud supports its use in the treatment of psoriasis and atopic dermatitis but most of the studies related its anti-inflammatory properties in rheumatology and musculo-skeletal diseases. Recently more studies focused on the possible positive effects of the Dead Sea minerals on the skin barrier and function. Nevertheless, such results do not explain the popularity of numerous skin products that contain Dead Sea mineral ingredients.

It remains unclear how effective products touted for harnessing the curative powers of the Dead Sea are in conferring similar benefits. These products likely do no harm and, given the host of other ingredients, probably at least contribute to moisturizing the skin. However, more research is necessary to establish their mechanism of action and evaluate their efficacy in cosmetic medicine.

Although the Dead Sea may be biologically dead, it maintains its historical ability to nourish the mind and body through its therapeutic qualities. Life may not be sustainable within its waters, but it most certainly thrives along its shores... and surely keeps on all around the world through its natural products.

REFERENCES

1. Shani J, Seidl V, Hristakieva E, Stanimirovic A, Burdo A, Harari M. Indications, contraindications and possible side-effects of climatotherapy at the Dead Sea. *Int J dermatol.* 1998; 37:717-8.
2. Abels DJ, Kipnis V. Bioclimatology and balneology in dermatology: a Dead Sea perspective. *Clin Dermatol.* 1998; 16(6):695-8.
3. Harari M, Czarnowicki T, Fluss R, Ruzicka T, Ingber A. Patients with early-onset psoriasis achieve better results following Dead Sea climatotherapy. *J Eur Acad Dermatol Venereol.* 2012; 26(5):554-9.
4. Ben-Amitai D, David M. Climatotherapy at the Dead Sea for pediatric-onset psoriasis vulgaris. *Pediatr Dermatol.* 2009; 26(1):103-4.
5. Halverstam CP, Lebwohl M. Nonstandart and off-label therapies for psoriasis. *Clin Dermatol.* 2008; 26(5):546-53.
6. Harari M, Novack L, Barth J, David M, Friger M, Moses SW. The percentage of patients achieving PASI 75 after 1 month and remission time after climatotherapy at the Dead Sea. *Int J dermatol.* 2007; 46(10):1087-91.
7. Harari M, Dreier J, Czarnowicki T, Ruzicka T, Ingber A. SCORAD 75: a new metric for assessing treatment outcomes in atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2011 Nov 10. doi: 10.1111/j.1468-3083.2011.04331.x.
8. Harari M, Shani J, Seidl V, Hristakieva E. Climatotherapy of atopic dermatitis at the Dead Sea: demographic evaluation and cost-effectiveness. *Int J Dermatol.* 2000; 39(1):59-69.
9. Czarnowicki T, Harari M, Ruzicka T, Ingber A. Dead Sea Climatotherapy for Vitiligo: a retrospective study of 436 patients. *J Eur Acad Dermatol Venereol.* 2011; 25(8):959-63.
10. Kushelevsky AP, Harari M, Kudish AI, Hristakieva E, Ingber A, Shani J. Safety of solar phototherapy at the Dead Sea. *J Am Acad Dermatol.* 1998; 36(3):447-52.
11. Kudish AI, Harari M, Evseev EG. The measurement and analysis of normal incidence solar UVB radiation and its application to the photoclimatotherapy protocol for psoriasis at the Dead Sea. *Photochem Photobiol.* 2011; 87(1):215-22.
12. Ultraviolet radiation properties as applied to photoclimatotherapy at the Dead Sea. *Int J Dermatol.* 2003; 42(5):359-65.
13. Abels DJ, Even-Paz Z, Efron D. Bioclimatology at the Dead Sea in Israel. *Clin Dermatol.* 1996; 14(6):653-8.
14. Matz H, Orion E, Wolf R. Balneotherapy in dermatology. *Dermatol Ther.* 2003; 16(2):132-40.
15. Carpio-Obeso MP, Shorr M, Valdes-Salas B. Desert ecosystems: similarities, characteristics, and health benefits. *Rev Environ Health.* 199; 14(4):257-67.

16. Harari M, Barzilai R, Shani J. Magnesium in the management of asthma: critical review of acute and chronic treatments, and Deutsches Medizinisches Zentrum's (DMZ's) clinical experience at the Dead Sea. *J Asthma*. 1998; 35(7):525-36.
17. Cordray S, Harjo JB, Miner L. Comparison of intranasal hypertonic Dead Sea saline spray and intranasal aqueous triamcinolone spray in seasonal allergic rhinitis. *Ear Nose Throat J*. 2005; 84(7):426-30.
18. Proksh E, Nissen HP, Bremgartner M, Urquhart C. Bathing in a magnesium-rich Dead Sea salt solution improves skin barrier function, enhances skin hydration, and reduces inflammation in atopic dry skin. *Int J Dermatol*. 2005; 44(2):151-7.
19. Even-Paz Z, Shani J. The Dead Sea and psoriasis. Historical and geographical background. *Int J Dermatol*. 1989; 28(1):1-9.
20. Halevy S, Sukenik S. Different modalities of spa therapy for skin diseases at the Dead Sea area. *Arch Dermatol*. 1998; 134(11):1416-20.
21. Hodak E, Gotlieb AB, Segal T et al. Climatotherapy at the Dead Sea is a remittive therapy for psoriasis: combined effects on epidermal and immunologic activation. *J Am Acad Dermatol*. 2003; 49(3):451-57.
22. Moses SW, David M, Goldhammer E, Tal A, Sukenik S. The Dead Sea, a unique natural health resort. *Isr Med Ass J*. 2006; 7:483-8.
23. Denda M, Katagiri C, Hirao T, Maruyama N, Takahashi M. Some magnesium salts and a mixture of magnesium and calcium salts accelerate skin barrier recovery. *Arch Dermatol Res*. 1999; 291(10):560-3.
24. Schempp CM, Dittmar HC, Hummler D, et al. Magnesium ions inhibit the antigen-presenting function of human epidermal Langerhans cells in vivo and in vitro. Involvement of ATPase, HLA-DR, B7 molecules and cytokines. *J Invest Dermatol*. 2000; 115(4): 680-6.
25. Iwata M, Takebayashi T, Ohta H, Alcade RE, Itano Y, Matsumura T. Zinc accumulation and metallothionein gene expression in the proliferating epidermis during wound healing in mouse skin. *Histochem Cell Bio*. 1999; 112(4):283-90.
26. Deters A, Shnetz M, Schmidt M, Hensel A. Effect of zinc histidine and zinc sulfate on natural human keratinocytes. *Forsh Komplementarmed Klass Naturheillkd*. 2003; 10(1):19-25.
27. Nissenbaum A, Rullkotter, Yechieli Y. Are the curative properties of "Black Mud" from the Dead Sea due to the presence of bitumen (Asphalt) or other types of organic matter? *Environ Geochem Health*. 2002; 24(4):327-35.
28. Diezel W, Schulz E, Laskowski J et al. Magnesium ions: topical application and inhibition of the croton oil-induced inflammation. *Zschr Hautkrh*. 1994; 69:759-60.

29. Shani J, Barak D, Levi D et al. Skin penetration of minerals in psoriatics and guinea-pigs bathing in hypertonic salt solutions. *Pharmacol Res Commun.* 1985; 17(6):501-12.
30. Shani J, Livshitz T, Roberrecht H, Van Grieken R, Rubinstein N, Even-Paz Z. *Pharmacol Res Commun.* 1985; 17(5):479-88.
31. Shani J, Sharon R, Koren R, Even-Paz Z. Effect of dead-Sea brine and its main salts on cell growth culture. *Pharmacology.* 1987; 35(6):339-47.
32. Levi-Schaffer F, Shani J, Politi Y, Rubinchik E, Brenner S. Inhibition of proliferation of psoriatic and healthy fibroblasts in cell culture by selected Dead-sea salts. *Pharmacology.* 1996; 52(5):321-8.
33. Ma'or Z, Yehuda S, Voss W. Skin smoothing effects of Dead Sea minerals: comparative profilometric evaluation of skin surface. *Int J Cosmet Sci.* 1997;19(3):105-10.
34. Matceyevsky D, Hahoshen NY, Vexler A, Noam A, Khafif A, Ben-Yosef R. Assessing the effectiveness of Dead Sea products as prophylactic agents for acute radio-chemotherapy-induced skin and mucosal toxicity in patients with head and neck cancers: a phase II study. *Isr Med Assoc J.* 2007; 9(6):439-42.
35. Harari M, Ingber A, Ruzicka T. Assessing the effectiveness of Dead Sea products. *Isr Med Assoc J.* 2007; 9(9):692-3.
36. Soroka Y, Ma'or Z, Leshem Y, Verochovsky L, Neuman R, Bregegere FM, Milner Y. Aged keratinocyte phenotyping: morphology, biochemical markers and effects of Dead Sea minerals. *Exp Gerontol.* 2008; 43(10):947-57.
37. Portugal-Cohen M, Soroka Y, Ma'or Z, Oron M, Zioni T, Bregegere FM, Neuman R, Kohen R, Milner Y. Protective effects of a cream containing Dead Sea minerals against UVB-induced stress in human skin. *Exp Dermatol.* 2009; 18:781-8.
38. Portugal-Cohen M, Oron M, Merrik E, Ma'or Z, Ben-Amitai D, Yogev H, Zvulonov A. A Dead Sea water-enriched body cream improves skin severity scores in children with Atopic Dermatitis. *J Cosmet Dermatol Sci Appl.* 2011; 1:71-8.
39. Ekmekcioglu C et al. Effect of sulfur baths, peroxide concentrations and lipids levels in patients with degenerative Osteoarthritis. *Complement Class Nat Med.* 2002; 9:216-20.
40. Kristof O et al. Analgesic efficacy of the serial application of a sulfurated mud bath at home. *Forsh Komplementarmed Klass naturheilkd.* 2000; 7:233-6.
41. Beer M et al. The effect of peat components on endocrine and immunological parameters and on trace elements. *Clin Lab.* 2001; 47:161-7.
42. Vvgodner EB, Serebriakow SN, Bobkova AS. Non-medicinal methods of correction of immune disorders in peptic ulcer patients. *Ter Arkh* 1991; 63:78-81.

43. Bellometti S, Galzigna I. Function of the hypothalamic adrenal axis in patients with fibromyalgia syndrome undergoing mud-pack treatment. *Int J Pharmacol Res.* 1999; 19:27-3.
44. Ivanov EM, Shakinova OV, Zhuravskaia NS. Ultraviolet radiation of blood and peloid therapy of patients with chronic bronchitis. *Vopr Kurortol Fizigter Lech Fiz Kult.* 2001; 4:13-7.
45. Israfilova SG. Experience in the multi-nodal therapy of acne, including volcano mud applications and cosmetic procedures. *Vestn deramtol Venereol.* 1989; 2:56-7.
46. Comacchi C, Hercegova J. A single mud treatment induces normalization of stratum corneum, corneum hydratation, transepidermal water loss, skin surface pH, and sebum content in patients with seborrheic dermatitis. *J Eur Acad Dermatol Venereol.* 2004; 18:372-4.
47. Delfino M et al. Experimental study on the efficacy of thermal muds of Ischia Island combined with balneotherapy in the treatment of psoriasis vulgaris with plaques. *Clin Ter.* 2003; 154:167-71.
48. Artymuk NV, Kira EF, Kondratieva TA. Intravaginal gel prepared from dead Sea peloid for treating luteal-phase defect. *Int J Gynaecol Obstet.* 2010; 108(1):72-3.
49. Tishler M, Brostovski Y, Yaron M. Effect of spa therapy in Tiberias on patients with ankylosing spondylitis. *Clin Rheumatol.* 1995; 14(1): 21-5.
50. Codish S, Dobrovinsky S, Abu-Shakra M, Flusser D, Sukenik S. Spa therapy for ankylosing spondylitis at the Dead Sea. *Isr Med Assoc J.* 2005; 7(7):443-6.
51. Codish S, Abu-Shakra M, Flusser D, Friger M, Sukenik S. Mud compresses therapy for the hands of patients with rheumatoid arthritis. *Rheumatol Int.* 2005; 25(1):49-54.
52. Katz U, Shoenfeld Y, Zakin V, Sherer Y, Sukenik S. Scientific evidence of the therapeutic effects of Dead Sea treatments: a systematic review. *Semin Arthritis Rheumatol.* 2012 Apr 11. doi:10.1016/j.semarthrit.2012.02.006
53. Flusser D, Abu-Shakra M, Friger M, Codish S, Sukenik S. Therapy with mud compresses for knee osteoarthritis: comparison of natural mud preparations with mineral-depleted mud. *J Clin Rheumatol.* 2002; 8(4):197-203.
54. Carretero MI, Clay minerals and their beneficial effects upon human health. A review. *Applied Clay Sci.* 2002; 21:155-63.
55. Dessy a, Kubowicz S, Alderighi M, Bartoli C, Piras AM, Schmid R, Chiellini F. Dead Sea minerals loaded polymeric nanoparticles. *Colloids Surf B Bio-interfaces.* 2011; 87(2):236-42.
56. Abdel-Fattah A, Pingitore NE Jr. Low levels of toxic elements in Dead Sea black mud and mud-derived cosmetic products. *Environ Geochem Health.* 2009; 31(4):487-92.

57. Ma'or Z, Henis Y, Alon Y, Orlov E, Sorensen KB, Oren A. Antimicrobial properties of Dead Sea black mineral mud. *Int J Dermatol.* 2006; 45(5):504-11.
58. Leslie KS, Millington GWM, Levell NJ. Sulfur and skin: from Satan to Saddam. *J Cosmet Dermatol.* 2004; 3:94-98.
59. Bentor YK. Some geochemical aspects of the Dead Sea and the question of its age. *Geochimica Cosmochimica Acta.* 1961; 25(4):239-40.
60. Gertman I, Hecht A. The Dead Sea hydrography from 1992 to 2000. *J Marin Sys.* 2002; 35(2-4):169-181.