Research Paper Medicine

Sulphurous Mud-Balneotherapy: an Possible Strategy for the Plaque Psoriasis

Maria Costantino	Association no profit F.I.R.S.Thermae (Interdisciplinary Training, Researches and spa Sciences), Via Marziale n. 21, CAP 80070 Bacoli (Naples), Italy Department of Medicine and Surgery, University of Salerno - Via Giovanni Paolo II n.132 , CAP 84084 Fisciano, Italy
Mariagrazia Bathilde Marongiu	Association no profit F.I.R.S.Thermae (Interdisciplinary Training, Researches and spa Sciences), Via Marziale n. 21, CAP 80070 Bacoli (Naples), Italy
Salvatore Iannotti	School of Counseling with a Psychosocial Genomic and Positive Psychological Approach (Istituto Mente Corpo) Via Abbamondi, 9 Solopaca Benevento-Italy
Amelia Filippelli	Association no profit F.I.R.S.Thermae (Interdisciplinary Training, Researches and spa Sciences), Via Marziale n. 21, CAP 80070 Bacoli (Naples), Italy Department of Medicine and Surgery, University of Salerno - Via Giovanni Paolo II n.132 , CAP 84084 Fisciano, Italy

KEYWORDS Plaque Psoriasis, Mud-balneotherapy, Oxidative Stress.

ABSTRACT

The aim of this observational pilot study was to evaluate effectiveness, safety and a possible antioxidant effect of sulphurous mud-balneotherapy in patients suffering from plaque psoriasis. The study was conducted on a sample of 58 subjects (50% women and 50% men) with a mean age of 52±13 years (age range 14-78 years) divided into 2 groups: A and B. The psoriatic patients of group A (n=33) was subjected to sulphurous mud-balneotherapy. In the patients of group B(n=25), composed of subjects with plaque psoriasis in pharmacological topical therapy, was associated the mud-balneotherapy carried out in the same way and modality in which it was made in the group A. After 2 weeks were assessed: the PASI index (Psoriasis Area and Severity Index), the impact of the treatments used on quality of life for psoriatic people tested by the DLQI questionnaire and plasma concentration of ROMs (by d-ROMs Test, Diacron-Grosseto-Italy). The data collected at the end of mud-balneotherapy (group A) as compared to basal values have shown a significant ($p<0.05$) reduction of PASI score, DLQI score and plasma [ROMs]. The association pharmacological topical therapy and sulphurous mud-balneotherapy (group B) induced a significant ($p<0.05$) decrease of DLQI score and plasma [ROMs] in greater percentage as compared to group A, whereas for PASI score in groups A and B was demonstrated significant equal reduction. In conclusion, the results of this study show that the sulphurous mud-balneotherapy can play an important role in the therapeutic strategy of plaque psoriasis to the benefit of an improved quality of life.

1. Introduction

Plaque Psoriasis is a chronic, inflammatory skin disease, non-contagious, and recurrent [1]. In the general Italian population it is estimated a prevalence of 2.8%, with a significant socio-economic impact according to a study of drug-economics, which considered the direct and indirect costs of the disease [2-5]. The Italian National Health Service spends on average about € 8371.61 for psoriatic patient, a figure that rises to € 11434.40 for the most severe cases [2-5]. Plaque psoriasis is characterized by an acceleration of keratinocytes tournover [1,6,7]. Normally, in fact, skin cells have an evolutionary cycle of about 28 days; in psoriatic subjects the cycle occurs in only 4-6 days. Clinically, this involves the appearance of erythematous plaques, papules and lesions that can be distributed in any part of the body; frequently affecting the visible parts like arms, back, chest, elbows, legs, hands, head and face. This leads to important consequences on the perception of body image, social relations, and, in general, on the quality of life [1,6,8,9]. Psoriasis has a multifactorial pathogenesis, in which predisposing genetic factors (the dysregulation of the immune system and the alteration of keratinocytes), and environmental trigger factors (such as local trauma, typically streptococcal infections, emotional stress, drugs β-blockers, lithium, antimalarials, NSAIDs, progesterone, estrogen at high doses, smoke, etc.) interact with each other by triggering a specific immune response mediated by T lymphocytes [10-13]. Various studies have also shown the importance of oxidative stress in the induction of psoriasis by increased production of free radicals and / or decreased function of the endogenous antioxidant defenses of the organism [14-17]. In people with psoriasis has been described the establishment of an oxidative environment both at a systemic level and at the local level of plaques, a condition due to a massive release of reactive oxygen species (ROS) by neutrophils [14]. Still in psoriasis, as well as in other inflammatory diseases of the skin, antioxidant defenses are greatly reduced. In fact, we find lower levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), ascorbic acid in people with psoriatic skin compared to that of normal subjects [17]. A recent study [18] in patients with psoriasis has shown, increased protein glycation and stimulation of the immune system in response to glycation end products. The research found, in patients with psoriasis in the ac-

tive phase of the disease, a significantly higher concentration of AGE-peptides (substances resulting from the processes of glycation with malicious action on cell permeability) and antibodies against carboxymethyllysine (anti-CML) and carboxyethyllysine (anti-CEL) compared to healthy controls. Currently for the treatment of plaque psoriasis [6,19-23] are available: topical medications for mild to moderate cases of psoriasis (with corticosteroids, vitamin D3 analogues, Salicylic acid, dithranol etc.); phototherapy which is useful in moderately severe psoriasis unresponsive to topical therapy alone; systemic pharmacological therapeutic aids reserved for the most severe and extended forms of psoriasis including the use of oral or parenteral administration of immunosuppressive drugs such as methotrexate or cyclosporine, retinoids, etc., and in cases of contraindication or ineffectiveness of the latter can be used in these severe forms biologic drugs such as adalimumab, etanercept, infliximab, etc.. Recent research has shown that interventions through therapeutic hypnosis (the Ultradian Healing Response) and meditation (the Relaxation Response) reduces stress and promotes healing on the molecular-genomic level [24-30]. From the literature the importance of the "***crenotherapy***" (from the greek crené-source) or "***spa Medicine"*** is deduced in numerous dermatologic affections. Spa Medicine uses natural mineral waters, with different modes of use and applications [6,31,32]. In the field of dermatology spa Medicine comprising the use of mineral water in the form of balneotherapy and/or mud-bath therapy seems to give, in mild to moderate cases of psoriasis, satisfactory results [6,33-40] with improvement of the clinical and psychological symptoms of the patients', and good compliance and tolerability with rare adverse effects, which is useful in the treatment of chronic diseases such as psoriasis. Literature data [41-47] show a possible antioxidant effect of mineral waters, in particular those sulphurous [41,42,44-47]. A personal research [41] has highlighted, in healthy rats, the ability of the drinking therapy with sulphurous mineral water to significantly reduce the plasma concentration of reactive oxygen metabolites ([ROMs]) versus tap water; moreover other studies [42,43] have shown a protective effect induced by sulphurous mineral water against oxidative DNA damage in inflammatory respiratory diseases due to the reducing properties of the sulfhydryl groups in it. In retrospective studies [44,45] the sulphurous mineral waters have demonstrated antioxidant effect and positive action on the oxidative defense mechanism in rabbits and rats. Therefore, considering that studies regarding the effectiveness and safety of mineral water used in the form of mud-balneotherapy in plaque psoriasis are still insufficient [37,39]; considering the data of the literature that highlight the important role of oxidative stress in psoriasis and considering the possible antioxidant action of sulphurous mineral waters as demonstrated by various researches, the purpose of this pilot observational study was to evaluate effectiveness, safety and a possible antioxidant effect of mud-balneotherapy with sulphurous mineral water, alone or in association with pharmacological topical treatment, in subjects suffering from plaque psoriasis, the most common clinical form of psoriasis.

2. Materials and Methods

In our pilot observational study was considered a sample of 58 patients suffering from plaque psoriasis. Informed consent was obtained from all subjects and the research project was based on the guidelines of the Declaration of Helsinski. The subjects of the test sample, included 29 (50%) female and 29 (50%) male, with a mean age of 52±13 (age range: 14-78 years), who presented themselves to our observation with a diagnosis made by specialist. The enrolled psoriatic subjects were divided into 2 groups respectively called A and B whose characteristics-Descriptive statistics are reported in Table 1.

The patients in group A (n=33) were subjected, in the morning and preferably on an empty stomach, to a cycle mud-balneotherapy using sulphurous mineral waters in Italian spas (Telese spa in Telese Terme-Benevento and Rosapepe spa in Contursi Terme-Salerno). The application of mud on the body was done to the skin of the area(s) to be treated at a temperature of 35°C. The duration of each application was 10-12 minutes. At the end of the session, patients received, after a cleansing shower with normal water, a bath at a temperature between 36-37°C for a duration of 15 minutes. Subsequently, the patient has gone in individual cabin where, suitably covered, has rested for 20-30 minutes lying down or reclined. This stage of treatment is called "reaction". The subjects in group B (n=25) carried out a pharmacological topical treatment with drugs usually used in psoriatic disease (clobetasol, flumethasone, momethasone, betamethasone, calcipotriol, calcitriol, tacalcitol, hydrating cream) prescribed by their general practitioner or by specialist in dermatology. In addition the pharmacological treatment was associated with a cycle sulphurous mud-balneotherapy carried out as in group A.

After two weeks of treatment in each patient of the two groups identified (A and B) were detected the following parameters:

a) ADVERSE EVENTS

b) PASI index (Psoriasis Area and Severity Index) [48], used clinically to assess the severity of psoriatic disease.

c) Impact of the therapeutic cycle considered on the QUALITY OF LIFE of the subjects examined by the administration of the questionnaire "Dermatology Life Quality Index" (DLQI), used by Finlay also at the spa [49,50]. The DLQI is a specific questionnaire comprising 10 questions through which it is possible to analyze the problems related to therapies for psoriasis, psoriasis interference with daily activities and relationships. The DLQI ranges from a minimum score of 0 (no interference of the disease) to a maximum score of 30 (maximum involvement of the disease on quality of life). The higher the score worse the quality of life of the subject.

d) PLASMA CONCENTRATION OF REACTIVE OXYGEN METABOLITES ([ROMs]): measured by the d-ROMs test (Diacron, Grosseto, Italy) performed with dedicated analytical system (FREE System- Florence Spectrophotometer Slim SEAC) on peripheral capillary blood. The d-ROMs is a spectrophotometric test used to determine the concentration of ROMs, primarily hydroperoxides (ROOH) generated in cells from the attack of oxidative reactive oxygen species (ROS) on various biochemical substrates (carbohydrates, lipids, amino acids , proteins, nucleotides, etc.) [51,52]. The ROMs are relativily more stable than reactive oxygen species (ROS) and therefore more easily detected and quantified by analytical procedures [51]; moreover ROMs can be considered markers of early oxidative damage for the generation of two highly reactive prooxidants radicals, the alkoxyl and alkylperoxyl, which in turn promote the oxidative cascade [51,53]. The detailed description of the technique of relief is in Costantini and Dell'Omo [54,55]. The results of d-ROMs test were expressed in arbitrary units called "Carratelli Units" (CARR.U.), where 1 CARR.U corresponds to 0.08 mg of H_2O_2 / 100mL (48,49). It should be noted that in healthy subjects the plasma concentration of ROMs comprises a range of 250-300 CARR.U. [51,52].

2.1 Statistical Analysis

The general characteristics of the population included in the study were analyzed using descriptive techniques. In all the evaluations carried out the data obtained were expressed as the arithmetic mean ± standard deviation (SD). The results were compared with Student's "t" test, normally distributed data and with the Wilcoxon-Mann-Whitney test in data with non-normal distribution. P values ≤ 0.05 were considered statistically significant [56].

3. Results

3.1 Adverse events

The collected data showed in psoriatic patients treated in sulphurous mud-balneotherapy, alone (group A) or in combination with drug therapy (group B), good local and systemic tolerability with absence of mortality; not increase of itch; absence of nausea, malaise, vomiting, dizziness, diarrhea, head-

ache, dry mouth. In one subject in group A was observed dizziness mild and of short duration in second day of treatment.

3.2 PASI index

At the end treatment, in groups A and B, a significant ($p<0.05$) reduction PASI score (group A: 10±9→5±5 - group B: 8±8→4±4) (Table 2) is observed in comparison to the basal values. The comparison between the mean values of PASI score in group B versus group A detected after treatment showed decrease found not significant ($p>0.05$) (Figure 1).

3.3 Impact on quality of life

In Figure 2 are reported the mean values±SD of the maximum score of the questionnaire DLQI detected in the two groups of subjects with psoriasis considered before and after treatment. The analysis of the data showed a significant ($p<0.05$) reduction of the total score DLQI in the treated groups (group A: 5.4±4.3→3.3±3.1 and group B: 6.8±3.9→3.8±2.5) at the end treatment versus basal values (Figure 2). The comparison between the mean values of the DLQI score in group B versus group A measured after treatment demonstrated not significant variation ($p>0.05$) (Figure 3).

3.4 Effects on plasma concentration of reactive oxygen metabolites ([ROMs])

At the end treatment, in groups A (sulphurous mud-balneotherapy only: 404CARR.U.±68→363±54) and B (association sulphurous mud-balneotherapy + pharmacological topical therapy: 351CARR.U.±47→300.CARR.U.±46) a significant ($p<0.05$) reduction of plasma [ROMs] is observed in comparison to the basal values (Table 3). The comparison between the mean values of the [ROMs] measured after treatment in group B versus group A demonstrated significant ($p<0.05$) reduction (Figure 4).

4. Discussion

Plaque psoriasis, the most common clinical form of psoriasis, is an inflammatory, chronic, immune-mediated disease. It affects about 90% of patients with psoriasis and 20-30% of cases are of a moderate-to-severe degree. In light of current scientific knowledge it is clear that genetic predisposing factors and environmental triggers interacting with each other would be able to induce an enormous acceleration of the replacement of epidermal cells in addition to vascular inflammation and hyperplasia. It was also shown a close correlation between oxidative stress and inflammation in psoriasis [14,15]. Further studies are required to know whether proper management of oxidative stress at mild stage can help to reduce the progression of the disease (57). At present for this chronic condition, there is no definitive cure. However, there are several methods, classic and innovative to try to control it. The therapeutic drug modalities as well as treatments with ultraviolet light, used alone or in combination, while giving often, but not always, good results, are not well accepted by patients for the unwanted side effects following a prolonged use, which is just what it needs to be done in chronic disease as psoriasis. In fact, the majority of subjects with psoriasis declares that it would be desirable the availability of treatments presenting not only effectiveness, but also good compliance and an acceptable safety profile. In this respect the mud therapy and/or balneotherapy with mineral water can be very useful with satisfactory results [6,36-39,58,59] even though studies, above in regard mud-balneotherapy, are few [6,37,39,40,58]. On the basis of the above considerations and literature data that have shown the important role played by oxidative stress in psoriasis as well as a possible antioxidant effect of sulphurous mineral waters, this pilot observational study has been prepared with the aim to evaluate the effectiveness and a possible antioxidant action of sulphurous mud-balneotherapy in patients suffering from plaque psoriasis.

"Short-term" results of the study showed effectiveness of sulphurous mud-balneotherapy (group A) demonstrated by a significant ($p<0.05$) reduction of clinical parameters considered: itching, erythema and scaling of the psoriatic patches as shown by the decrease in PASI-score (Table 2) at the end of treatment versus basal values. It should be noted that the PASI is used clinically to assess the severity of psoriatic disease and therefore the effectiveness of the treatments carried out. Clinical improvement, in addition, also induced a significant ($p<0.05$) improvement of social life and relationships of these subjects as demonstrated by the reduction in the DLQI score at the end of treatment versus basal values, thus resulting in reduced interference of the disease with daily activities and interpersonal relationships (Figure 2) (60). In agreement with literature data our study shows a possible antioxidant effect of sulphurous mineral water used in the form of mud-balneotherapy as demonstrated by significant ($p <0.05$) reduction of plasmatic values of [ROMs] at the end of treatment as compared to basal values (Table 3).

The association pharmacological topical therapy and sulphurous mud-balneotherapy (group B) induce a significant ($p<0.05$) reduction of parameters considered (PASI, DLQI and plasma [ROMs]) at the end treatment versus basal values (Tables 2-3, Figure 2). In group B the percentage reduction of parameters: DLQI (-44%) and plasma [ROMs] (-15%) was highest compared to that observed in group A (mud-balneotherapy only DLQI -39%; plasma [ROMs]: -10%), whereas percentage reduction of parameter PASI score was egual to that observed in group A (PASI score -50%). After treatment the comparison of data collected in group B versus group A showed that mud-balneotherapy and topical drug treatment (group B) induces a significant decreased plasma [ROMs].

In our study it was sulphurous mineral water used in a mud-balneotherapy treatment. The sulphurous mineral waters containing bivalent sulfur and its compounds (hydrogen sulfide, sulfhydryl ion), chlorides and sodium, bicarbonate, calcium and magnesium, are able to perform many important therapeutic effects which can be summarized as: ***exfoliating and keratolytic action*** on the stratum corneum resulting in peeling effect (sulfhydryl ion is able to reduce, and therefore to split, the disulfide bonds of cystine, which take aggregated molecules of keratin, freeing the two molecules of cysteine) [6,31,40,61]; ***anti-inflammatory and immunomodulatory action*** (by stimulation of the reticuloendothelial system; by reduction of release of pro-inflammatory cytokines, that significantly contribute to pathological psoriatic damage as interleukin 8, by hydrogen sulfide; in vitro studies have shown a dose-dependent inhibitory effect of mineral waters such as "sulphureous" on blastization and proliferation of T lymphocytes obtained from the peripheral blood of both normal subjects and patients with chronic inflammatory syndromes of the upper respiratory tract as well as articular and peri-articular);

stimulation of cutaneous tropism [40,62-65].

The bicarbonate ions are able to normalize the cutaneous pH generally impaired in the presence of exudative-degenerative processes which helps to reduce the itching and skin irritation; Add to that the moisturizing cutaneous action of magnesium as well as its ability to help the maturation and differentiation of keratinocytes and the disinfectant action of chlorides [66-68].

The pressure and temperature of the bath stimulate the blood vessels bringing a general feeling of improved well-being to the whole body [61,69].

Moreover, in agreement with literature data [57], which reveals that the proper management of oxidative stress in psoriasis may help decrease the progression of the disease, our research has shown that the use of sulphurous mud-balneotherapy may be an effective strategy in this disease for the antioxidant effect observed.

5. Conclusion

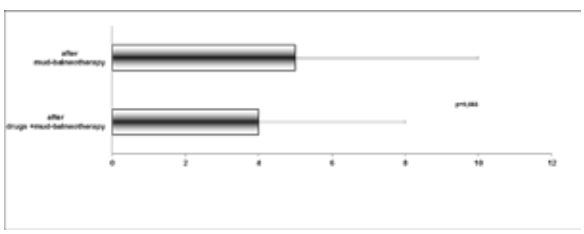
In conclusion the results of our study show that in a chronic disease such as plaque psoriasis of mild to moderate degree, the sulphurous mud-balneotherapy (which uses natural substances with limited unwanted adverse events; good local and

systemic tolerability; positive compliance; a possible antioxidant effect; reduction of PASI index and DLQI score) may be a viable alternative or a adjunctive therapy to pharmacological topical treatments, steroids in the first place, both to give a break to drug and/or reduce the drug dosage. In fact in long term treatment it is necessary to balance the benefits with the risks of potential adverse events of protracted drug therapy. Therefore the use of sulphurous mud-balneotherapy should be taken into due account in the treatment strategies for diseases that require prolonged use of drugs, so that doses and frequency of administration can be reduced. Recently the WHO (World Health Organization) has included spa therapy among the strategies and goals of traditional medicine [70].

Conflict of Interests

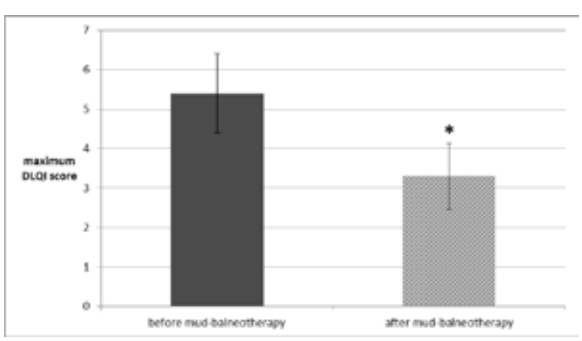
The authors declare that there is no conflict on interests regarding the publication of this paper.

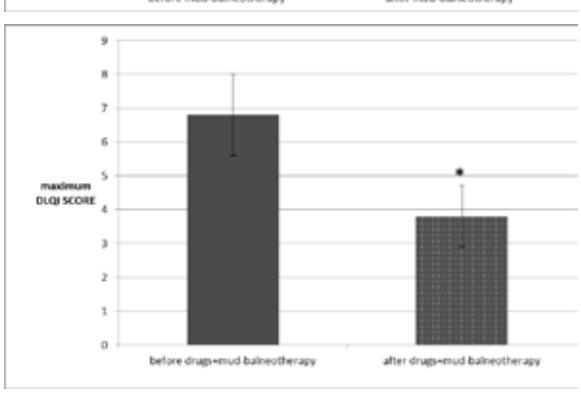
Figure 1 - Comparison between the mean values±SD of PASI score detected after treatment in group B (drugs+mud-balneotherapy) *versus* group A (mud-balneotherapy).



Student's' t test unpaired *p<0.05 - **p<0.01

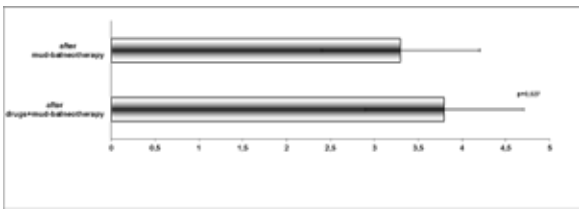
Figure 2 – Comparison of mean values±SD of maximum score of DLQI questionnaire detected at the end treatment vs baseline in two groups (A and B) of psoriatic subjects considered.





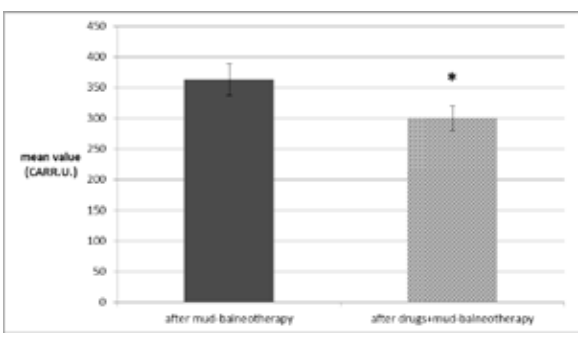
Wilcoxon Signed-Ranks test for paired samples *p<0.05 - **p<0.01

Figure 3 –Comparison between the mean values±SD of maximum DLQI-score detected after treatment in group B (drugs+mud-balneotherapy) versus group A (mud-balneotherapy).



Mann-Whitney test for independent samples *p<0.05 - **p<0.01

Figure 4 - Comparison between the mean values±SD of plasmatic reactive oxygen metabolites ([ROMs]), expressed in CARR.U., detected after treatment in group B (drugs+mud-balneotherapy) *versus* group A (mud-balneotherapy).



Student's' t test unpaired *p<0.05 - **p<0.01

Table 1 - Generality of the two groups of psoriatic patients (A and B) considered: descriptive statistics.

NUMBER OF CASES	GROUP A N=33	GROUP B N=25
AGE (years)		
Mean ±DS	52±13	52±14
Median	52	55
Minimum	20	14
Maximum	78	73
SEX		
male (%) females (%)	16 (48%) 17 (52%)	13 (52%) 12 (48%)

Table 2 – Comparison of mean values±SD of PASI score detected at the end treatment *vs* baseline in two groups (A and B) of psoriatic subjects considered .

Group	PASI score (mean±SD) before treatment	PASI score (mean±SD) after treatment
A(cycle mud balneotherapy)	10 ± 9	5 ± 5 **
B (pharmacological topical treatment + cycle mud-balneotherapy)	8 ± 8	4 ± 4 **

Student's t test paired *p<0.05 - **p<0.01

Table 3 – Comparison of mean values±SD of plasmatic reactive oxygen metabolites ([ROMs]), expressed in CARR.U., obtained before and after treatment with sulphurous mud-bath therapy alone (group A) or in association with pharmacological topical therapy (group B) in psoriatic subjects observed.

GROUP CONSIDERED	[ROMs] (mean± SD) before treatment	[ROMs] (mean± SD) after treatment	Student's' t test paired *p<0.05 - **p<0.01
A (mud-balneotherapy)	404 CARR.U.±68	363 CARR.U.±54*	p=0.016
B (pharmacological topical treatment +cycle mud balneotherapy)	351 CARR.U.±47	300 CARR.U.±46*	p=0.035

REFERENCES

[1] A. Alessi and R. Caputo, "Dermatologia e malattie a trasmissione sessuale," Raffaello Cortina Editore, Milano, 1999. | [2] L. Naldi, "Epidemiology of psoriasis," Current Drug Targets, Inflammation & Allergy, vol.3, pp. 121-8, 2004. | [3] L. Naldi, P. Colombo, E.B. Placchesi, R. Piccitto, L. Chatenoud, and C. La Vecchia, "PraKtis Study Centers. Study design and preliminary results from the pilot phase of the PraKtis study: self-reported diagnoses of selected skin diseases in a representative sample of the Italian population," Dermatology, vol. 208, pp. 38-42, 2004. | [4] G.L. Colombo, G.F. Altomare, K. Peris, P. Martini, G. Quarta, M. Congedo, A. Costanzo, A. Di Cesare, E. Lapucci, and S. Chimenti, "Moderate and severe plaque psoriasis: cost-of-illness study in Italy," Therapeutics and Clinical Risk Management, vol. 4, no.2, pp. 559–568, 2008. | [5] L.R. Braathen,"Cost of caring for hospital-based patients in dermatology in Europe," Journal of the European Academy of Dermatology and Venereology, vol. 15, pp. 292, 2001. | [6] M. Costantino,"Percorsi terapeutici termali nel trattamento della psoriasi," Ed. UNI-service, Trento, 2011. | [7] M.A. Lowes, A.M. Bowcock, and J.G. Krueger, "Pathogenesis and therapy of psoriasis," Nature, vol. 445, no. 7130, pp. 866-73, 2007. | [8] F. Sampogna, F. Sera, D. Abeni, et al., "Measures of clinical severity, quality of life, and psychological distress in patients with psoriasis: a cluster analysis," Journal of Investigative Dermatology, 2004; 122:602-7. | [9] L. Naldi and D. Gambini, "The clinical spectrum of psoriasis," Clinics in Dermatology, vol. 25, no. 6, pp. 510-8, 2007. | [10] F. Capon, P. Di Meglio, J. Szaub, N.J. Prescott, C. Dunster, L. Baumber et al., "Sequence variants in the genes for the interleukin-23 receptor (IL23R) and its ligand (IL12B) confer protection against psoriasis," Human Genetics, vol.122, no. 2 pp. 201–206, 2007. | [11] F. Capon, S. Semprini, S. Chimenti, G. Fabrizi, G. Zambruno, S. Murgia, C. Carcassi, M. Fazio, R. Mingarelli, B. Dallapiccola, and G. Novelli, "Fine mapping of the PSORS4 psoriasis susceptibility region on chromosome 1q21," Journal of Investigative Dermatology, vol. 116, no.5, pp. 728-730, 2001. | [12] P. Borgiani, L. Vallo, M.R. D'Apice, E. Giardina, S. Pucci, F. Capon, S. Nisticò, S. Chimenti, F. Pallone, and G. Novelli, "Exclusion of CARD15/NOD2 as a candidate susceptibility gene to psoriasis in the Italian population," European Journal of Dermatology, vol.12, no. 6, pp. 540-2, 2002. | [13] A.M. Bowcock and W.O. Cookson, "The genetics of psoriasis, psoriatic arthritis and atopic dermatitis," Human Molecular Genetics, vol.13, suppl. 1, pp. R43–R55, 2004. | [14] P.K. Dipali, N.S. Adinath, D.A. Rajesh et al., "Role of Oxidative Stress in Various Stages of Psoriasis," Indian Journal of Clinical Biochemistry, vol. 25, no. 4, pp. 388–392, 2010. | [15] A. Wozniak, G. Drewa, E. Krzyzynka-Malinowska et al., "Oxidant-antioxidant balance in patients with psoriasis," Medical Science Monitor, vol. 13, no. 1, pp. R 30–R 33, 2007. | [16] W.A. Pryor, J.P. Stanley, and E. Blair, "Autoxidation of polyunsaturated fatty acids: II. A suggested mechanism for the formation of TBA-reactive materials from prostaglandin-like endoperoxides," Lipids, vol. 11, no. 5, pp. 370-9, 1976. | [17] S. Briganti and M. Picardo, "Antioxidant activity, lipid peroxidation and skin diseases—what's new?" Journal of the European Academy of Dermatology and Venereology, vol.17, pp. 663–669, 2003. | [18] A. Damasiewicz-Bodzek and T.Wielkoszynski, "Advanced protein glycation in psoriasis," Journal of the European Academy of Dermatology and Venereology, vol. 26, no. 2, pp. 172-9, 2012. | [19] L. Naldi and C.E.Griffiths, "Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks," British Journal of Dermatoly, vol.152, pp. 597-615, 2005. | [20] P. Gisondi and G. Girolomoni, "Aggiornamento sui trattamenti biologici della psoriasi," Giornale Italiano di Dermatologia e Venereologia, vol 142, Suppl. 1, pp. 1–11, 2007. | [21] D. Pathirana, A.D. Ormerod, P. Saiag et al., "European S3-Guidelines on the systemic treatment of psoriasis vulgaris," Journal of the European Academy of Dermatology and Venereology, vol. 23, Suppl. 2, pp. 5- 70, 2009. | [22] A.B. Gottlieb, R.G. Langley et al., "A randomized, doubleblind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis," British Journal of Dermatology, vol. 167, no. 3, pp. 649-57, 2012. | [23] Nuove linee guida Psoriasi ADOI. 2013-2016. Il Trattamento della psoriasi nell'adulto. Linee guida 25 SNLG-ISS http://www.snlg-iss.it | [24] J. Dusek, H. Hasan, A. Wohlhueter, M. Bhasin, L. Zerbini, M, Joseph, H. Benson, and T. Libermann, "Genomic Counter-Stress Changes Induced by the Relaxation Response," PLoS ONE, vol. 3, no. 7, pp. e2576, 2008. | [25] P. Lichtenberg, R. Bachner-Melman, I. Gritsenko, and R. Ebstein, "Exploratory association study between catechol-Omethyltransferase (COMT) high/low enzyme activity polymorphism and hypnotisability," American Journal Medical Genetics, vol. 96, pp. 771-774, 2000. | [26] P. Lichtenberg, R. Bachner-Melman, R. Ebstein, and H. Crawford, "Hypnotic susceptibility: multidimensional relationships with Cloninger's Tridimensional Personality Questionnaire, COMT polymorphisms, absorption, and attentional characteristics," International Journal Clinical of Experimental Hypnosis, vol. 52, pp. 47-72, 2004. | [27] E.R. Rossi, "The Psychobiology of Gene Expression: Neuroscience and Neurogenesis in Therapeutic Hypnosis and the Healing Arts," NewYork, W. W. Norton Professional Books, 2002. | [28] E.R. Rossi, "The Breakout Heuristic: The New Neuroscience of Mirror Neurons, Consciousness and Creativity in Human Relationships: Selected Papers of Ernest Lawrence Rossi," Phoenix, Arizona: The Milton H. Erickson Foundation Press, 2007. | [29] E. Rossi, S. Iannotti, M. Cozzolino et al., "A Pilot Study of Positive Expectations and Focused Attention via a NewProtocol for Optimizing Therapeutic Hypnosis and Psychotherapy Assessed with DNA Microarrays: The Creative Psychosocial Genomic Healing Experience," Sleep and Hypnosis, vol.10, no. 2, pp. 39-44, 2008. | [30] D. Atkinson, S. Iannotti, M. Cozzolino et al., "A New Bioinformatics Paradigm for the Theory, Research, and Practice of Therapeutic Hypnosis," American Journal of Clinical Hypnosis, vol. 53, pp. 27-45, 2010. | [31] G. Nappi, "Medicina e Clinica Termale," Ed. Selecta Medica, Pavia, 2001. | [32] Messina, F. Grossi, " Elementi di Idrologia Medica," Ed. SEU, Roma, 1984. | [33] H. Matz, E. Orion, and R.Wolf, "Balneotherapy in dermatology," Dermatologic Therapy, vol. 16, pp. 132-140, 2003. | [34] I. Bacle, S. Meges, C. Lauze, P. Macleod, and P. Dupuy, "Sensory analysis of four medical spa spring waters containing various mineral concentrations," International Journal of Dermatology, vol. 38, pp. 784-786, 1999. | [35] N. Riyaz and F.R. Arakkal, "Spa Therapy in Dermatology," Indian Journal of Dermatology, Venereology and Leprology, vol. 77, no. 2, pp. 128-34, 2011. | [36] A. Peroni, P. Gisondi, M. Zanoni et al., "Balneotherapy for chronic plaque psoriasis at Comano spa in Trentino, Italy," Dermatologic Therapy, vol. 21, Suppl. 1, pp. S31-8, 2008. | [37] M. Costantino, G. Nappi, E. Contaldi, and E. Lampa, "Efficacia della fangobalneoterapia sulfurea nella psoriasi: studio clinico-sperimentale," Medicina Clinica e Termale, vol. 58, pp. 127-137, 2005. | [38] G. Borroni, V. Brazzelli, L. Fornara, R. Rosso, M. Paulli, C. Tinelli, and O. Ciocca, "Clinical, pathological and immunohistochemical effects of arsenical-ferruginous spa waters on mild-to-moderate psoriatic lesions: a randomized placebo-controlled study," International Journal of Immunopathology and Pharmacology, vol. 26, no. 2, pp. 495-501, 2013. | [39] M. Delfino, N. Russo, G. Migliaccio, and N. Carraturo, "Experimental study on efficacy of thermal muds of Ischia Island combined with balneotherapy in the treatment of psoriasis vulgaris with plaques," La Clinica Terapeutica, vol. 154, no. 3, pp. 167-71, 2000. | [40] M. Costantino and A. Filippelli, "Impact of spa therapy with sulphureous mineral water on quality of life and psychological distress in chronic plaque psoriasis," Clin Ter vol. 165(4), pp e277-284, 2014. | [41] M. Costantino, G. Giuberti, M. Caraglia et al., "Possibile antioxidant role of SPA therapy with chlorine-sulphur-bicarbonate mineral water," Amino Acids, vol. 36, no. 2, pp.161-165, 2009. | [42] P.C. Braga, C. Ceci, L. Marabini, and G. Nappi, "The antioxidant activity of sulphureous thermal water protects against oxidative DNA damage: a comet assay investigation," Drug Research, vol. 63, no. 4, pp. 198-202, 2013. | [43] F. Joly, J.E. Branka, and L. Lefeuvre, "Thermal water from Uriage-les-Bains exerts DNA protection, induction of catalase activity and claudin-6 expression on UV irradiated human skin in addition to its own antioxidant properties,"Journal of Cosmetics,Dermatological Sciences and Applications, vol. 4, pp. 99-106, 2014. | [44] M.C. Albertini, V. Sammartino, F. Canestrari et al., "Effets antioxydants du traitement hydromineral avec une eau sulfurée chez le lapin," La Presse Thermale et Climatique, vol.133, pp.124–127, 1996. | [45] M.C. Albertini, F. Canestrari, V. Sammartino et al., "Rat abreuvé d'eau sulfurée: évaluation du stress oxidatif," La Presse Thermale et Climatique, vol. 136, pp.31–35, 1999. | [46] V. Coiro, G. Jotti Saccani, A. Bellarmino et al., "Effetti della terapia idropinica con acqua sulfureo-solfato calcica di Tabiano sullo stress ossidativo nel diabete mellito," Progress in Nutrition, vol. 6, no.3, pp.169-177, 2004. | [47] S. Benedetti, S. Pagliarani, F. Benvenuti et al., "Antioxidative effects of sulphurous water from Macerata Feltria thermal resort in patients with osteoarthritis," Progress in nutrition, vol. 9, no. 1, pp. 1–7, 2007. | [48] T. Frederiksson and U. Pettersson, "Severe psoriasis- oral therapy with a new retinoid," Dermatologica, vol.157, pp. 238-244, 1978. | [49] A.Y. Finlay and G.K. Khan, "Dermatology life quality index: a simple practical measure for routine clinical use," Clinical and Experimental Dermatology, vol. 19, pp. 210-16, 1994. | [50] A.Y. Finlay, E. Myon, R. Martini et al., "Impact of thermal SPA on children's quality of life," Journal of the European Academy of Dermatology and Venereology, vol. 18, Suppl. 2, pp. 310, 2004. | [51] E.L. Iorio, "The d-ROMs test and the evaluation of oxidative stress," Diacron International, 2004, Pistoia, Italy. | [52] A. Alberti, L. Bolognini, D. Macciantelli, and M. Carratelli, "The radical cation of N,N-diethyl-para-phenylendiamine: a possibile indicator of oxidative stress in biological samples," Research on Chemical Intermediates, vol. 26, no. 3, pp. 253-67, 2000. | [53] A. Bonisoli-Alquati, T.A. Mousseau, A.P. Moller, M. Caprioli, and N. Saino, "Increased oxidative stress in barn swallows from the Chernobyl region," Comparative Biochemistry and Physiology, Part A 155, pp. 205–210, 2010. | [54] D. Costantini and G. Dell'Omo, "Effects of T-cell-mediated immune response on avian oxidative stress," Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology, vol. 145, pp. 137–142, 2006. | [55] D. Costantini, "Oxidative stress in ecology and evolution: lessons from avian studies," Ecology Letters, vol.11, no. 11, pp.1238–1251, 2008. | [56] L. Lison, "Statistica applicata alla biologia sperimentale," Edizioni Ambrosiana, Milano, 1989. | [57] K.H. Basavaraj, P. VasuDevaraju, and K.S. Rao, "Studies on serum 8-hydroxy guanosine (8-OHdG) as reliable biomarker for psoriasis," Journal of the European Academy of Dermatology and Venereology, vol. 27, no.5, pp. 655-7, 2013. | [58] M. Costantino and E. Lampa, "Psoriasis and mud bath therapy: clinical-experimental study," La Clinica Terapeutica, vol.156, pp. 145-149, 2005. [59] S. Mazzulla, R. Chimenti, S. Sesti, S. De Stefano, M. Morrone, and G. Martino, "Effects of sulphurous bioglea on psoriasis," La Clinica Terapeutica, vol. 155, no.11-12, pp. 499-504, 2004. | [60] J. De Korte, M.A.G. Sprangers, F.M.C. Mombers, and J.D. Bos, "Quality of life in patients with psoriasis: A systematic literature review," Journal of Investigative Dermatology Symposium Proceedings, vol.9, no. 2, pp. 140-147, 2004. | [61] S. Nunes and B.M. Tamura, "A historical review of mineral water," Surgical and Cosmetic Dermatology , vol. 4, no. 3, pp. 252-8, 2012. | [62] P. Mirandola, G. Gobbi, C. Micheloni et al., "Hydrogen sulfide inhibits IL-8 expression in human keratinocytes via MAP kinase signalling," Laboratory Investigation, vol. 91, no.8, pp.1188-94, 2011. | [63] S. Valitutti, F. Costellino, and P. Musiani, "Effect of sulphureous (thermal) water on T lymphocytes proliferative response," Annals of Allergy, vol. 65, no. 6, pp. 463-468,1990. | [64] E. Tsoureli-Nikita, G. Menchini, I. Ghersetich, et al., "Alternative treatment of psoriasis with balneotherapy using Leopoldine spa water," Journal of the European Academy of Dermatology and Venereology, vol.16, no.3, pp. 260-2, 2002. | [65] I. Ghersetich, D. Freedman, and T. Lotti, "Balneology today," Journal of the European Academy of Dermatology and Venereology, vol.14, pp. 346-348, 2000. | [66] R. Verdolini, L. Bugatti, G. Filosa et al., "Old fashioned sodium bicarbonate baths for the treatment of psoriasis in the era of futuristic biologics: an old ally to be rescued," Journal of Dermatological Treatment, vol. 16, no.1, pp. 26-30,2005. | [67] E. Proksch, H.P. Nissen, M. Bremgartner et al., "Bathing in a magnesium-rich Dead Sea salt solution improves skin barrier function, enhances skin hydration, and reduces inflammation in atopic dry skin," International Journal of Dermatology, vol. 44, no. 2, pp.151-7, 2005. | [68] C.M. Schempp, H.C. Dittmar, D. Hummler 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," Journal of Investigative Dermatology, vol.115, no.4, pp. 680-6, 2000. | [69] A. Scalabrino, A. Galassi, F. Pierallini et al., "A single mud-bath treatment induces increased levels of circulating endogenous opioids." Current International, vol. 2, pp. 5-11, 1994. | [70] WHO (OMS), WHO Traditional Medicine Strategy 2014 -2023, OMS Ginevra 2013, online adress: http://apps.who.int/iris/handle/10665/92455 | |