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PERSPECTIVES

Thermal waters as cosmeceuticals: La Roche-Posay thermal spring water example

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Sophie Seite

La Roche-Posay Pharmaceutical Laboratories, Asnières, France

Abstract: The curative use of thermal spring water is well known, but further investigation of its biological properties and therapeutic benefits is necessary. This present article reports all available scientific data concerning La Roche-Posay Thermal Spring Water and provides a better understanding of the biological mechanism of action of this water in regard to its composition and physicochemical properties and its clinical benefits for patients. These data justify the use of this selenium-rich water as an active or "cosmeceutical" ingredient in topical formulations to increase quality of life and compliance in patients with chronic disease.

Keywords: thermal spring water, selenium, biological properties, curative use

Introduction

The curative use of thermal water has been mentioned since the Roman imperial period. The connection between thermal water sources and volcanic phenomena has always been clear. The quality of water and its temperature are related to the geological structure of the soil in which it flows. Thermal sources have been exploited in many countries, for example, France, where there are over 1200 thermal springs. Thermal spring waters can be classified into five major categories (bicarbonate, sulfate, sulfide, chloride, and weakly mineralized trace metal) and may be cold (less than 20°C or 68°F), warm (20°C–30°C or 86°F), or hot (up to about 100°C or 212°F). They are used in 12 therapeutic orientations, but the curative use of thermal spring waters has been totally empirical, and for years physicians generally have doubted their medical value. Use of modern scientific methods has been mandatory to evaluate precisely the biological properties of these waters and the therapeutic benefit for patients. For practical reasons, very few scientists have invested in this program. Thanks to private research, scientific literature is now available for some thermal spring waters which justify their widespread therapeutic use in the 21st century.

Composition and physicochemical properties

The physicochemical characteristics of mineral waters depend on the nature of the geologic materials through which the groundwater has moved. Common soluble minerals include calcium (Ca^{2+}), bicarbonate (CO_3H^-), silicates, iron compounds, sodium and magnesium salts, sulfur compounds, and metals. Trace elements, including selenium, as well as purity and pH are very important parameters to be considered. La Roche-Posay Thermal Spring Water (LRP-TSW), for example, has been extensively studied, and scientists have discovered that it is the product of a mixture of rain water percolating

Correspondence: Sophie Seité
La Roche-Posay Pharmaceutical Laboratories, 110 Avenue Henri Barbusse, 92602 Asnières Cedex, France
Tel +33 01 4688 6544
Fax +33 01 4688 2922
Email sophie.seite@loreal.com

very slowly through chalky and selenium-rich rocks from the very old Turonian period and located in the sand of the Cenomanian period. The composition of LRP-TSW is shown in Table 1. Selenium has a major role in thermal spring water. Selenium salts are toxic in large amounts, but trace amounts of the element are necessary for cell function, forming the active center of the glutathione peroxidase and thioredoxin reductase enzymes (which indirectly reduce certain oxidized molecules) and three known deiodinase enzymes (which convert one thyroid hormone to another). Intrinsically, its major properties are free radical scavenging and anti-inflammatory, as well as protection against toxic heavy metals. The mineral content of thermal spring water contributes to the skin comfort provided. If the physical sensation of freshness is not related to the mineral content, in contrast, the magnitude of softness and suppleness of the skin as well as skin comfort is greater with thermal spring water having a lower mineral concentration (ie, <1 g/L).[1] These properties are very important in patients affected by chronic dermatoses, such as atopic dermatitis and psoriasis, which are often associated with skin dryness and pruritus. Because of its weakly mineralized nature and silicate content, LRP-TSW is also called "l'eau de velours" (velvet water).

Thermal spring waters have been used widely in the treatment of inflammatory skin diseases for a long time, but their use has been largely empirical.[2] Considerable research has now been performed in order to further understand the mechanism of action of thermal spring waters (and their ingredients) and to investigate the precise clinical benefit for patients.

Biological properties of LRP-TSW

Antiradical properties

Oxidative damage reduces cell survival, increases membrane lipid peroxidation, and modifies selenium-glutathione peroxidase activity. Human skin fibroblasts cultured in three different media, ie, medium 1 (control with demineralized water), medium 2 (demineralized water supplemented with selenium at the same concentration as in LRP-TSW), and medium 3 (reconstituted with LRP-TSW instead of demineralized water) did not have the same resistance to stress induced by exposure to ultraviolet B (0.2 J/cm² for three consecutive days) or by hydrogen peroxide (1.5×10^{-4} M). Better resistance with higher cell survival was noticed for cells cultured in medium 3 in comparison with those cultured in medium 1 after oxidative stress (hydrogen peroxide) and in particular after exposure to ultraviolet B. Interestingly, selenium-glutathione peroxidase and superoxidase dismutase activity was higher in fibroblasts cultured in medium containing LRP-TSW (medium 3) than in fibroblasts cultured in the other media. LRP-TSW also contains copper and zinc, which may partly explain the beneficial effects observed because most of the superoxidase dismutase activity in the skin is due to copper and zinc superoxidase dismutase.[3]

Furthermore, after exposure to increasing ultraviolet B doses (50 to 200 mJ/cm²), human keratinocytes cultured in medium containing LRP-TSW showed better resistance with better cell survival (ultraviolet B dose required to kill 50% of the cells [IC_{50}] 80 ± 13 mJ/cm² versus 150 ± 33 mJ/cm²) and a reduction (by a factor 2) in interleukin 1α cytokine release in comparison with cells cultured in medium containing demineralized water.[4]

The effect of selenium on lipid peroxidation has also been studied in cultured human skin fibroblasts. Immediately after exposure to ultraviolet A (365 nm, 36 J/cm²), a decrease in lipoperoxide content in the cell culture supernatant was noticed upon quantification of thiobarbituric acid reactive substances, an index of lipid peroxidation and oxidative stress.[5] A reduction by a factor of 1.8 and 1.7, respectively, was noticed if the cells were cultured in a medium containing 2% fetal calf serum and supplemented with selenium (medium 2) or in LRP-TSW (medium 3) compared with control medium containing demineralized water (medium 1, Table 2). Together, selenium-glutathione peroxidase activity (Table 2) and cell viability were significantly increased.[6]

Immunomodulatory and anti-inflammatory properties

The effect of LRP-TSW on the migratory and stimulatory capacities of human epidermal Langerhans cells sensitized with trinitrobenzenesulfonic acid 5 mM has been studied.[7,8] Without any effect on cell viability, the number of migrating Langerhans cells cultured in a medium reconstituted with LRP-TSW was significantly lower than in a medium containing demineralized water (relative migration index = number of migrating Langerhans cells in medium with LRP-TSW/number of migrating Langerhans cells in control

Table 1 Physicochemical analysis of La Roche-Posay thermal spring water

pH	7	Silicate	31.6 mg/L
Temperature	13°C	Magnesium	4.4 mg/L
Resistance	1540 Ω	Strontium	0.3 mg/L
Dry residues	595 mg/L	Selenium	0.053 mg/L
Bicarbonate	387 mg/L	Zinc	<0.005 mg/L
Calcium	149 mg/L	Copper	<0.005 mg/L

Table 2 Effect of selenium and La Roche-Posay thermal spring water on lipid peroxidation and selenium-glutathione peroxidase activity in human skin fibroblasts exposed to ultraviolet A

	TBARS (nmol/mg)	Se-GSH·Px (mU/mg)
Donor 1		
Medium 1	3.06 ± 0.23	10.5 ± 2.1
Medium 2	1.40 ± 0.15*	46.8 ± 1.6*
Medium 3	1.10 ± 0.01*	48.2 ± 1.9*
Donor 2		
Medium 1	1.30 ± 0.02	29.8 ± 1.4
Medium 2	0.89 ± 0.09*	39.8 ± 0.9*
Medium 3	1.09 ± 0.02*	41.7 ± 2.9*
Donor 3		
Medium 1	3.06 ± 0.05	12.3 ± 1.6
Medium 2	1.70 ± 0.09*	45.0 ± 2.1*
Medium 3	2.09 ± 0.14*	45.8 ± 1.6*

Notes: Data are normalized to cell protein content and are shown as the mean ± standard deviation of triplicate measurements for each donor. TBARS were measured in the supernatant after ultraviolet A exposure. Data for a given donor were determined from the same cell culture. *$P < 0.05$ versus medium 1.
Abbreviations: TBARS, thiobarbituric acid reactive substances; Se-GSH·Px, selenium-glutathione peroxidase.

medium = 0.5 ± 0.3 [mean of eight donors]). A significant downregulation of both HLA-DR (by 25%) and certain costimulatory molecules expressed at the Langerhans cell surface, such as B7-2 (by 35%) and intercellular adhesion molecule 1 (by 25%) were noticed after 3 days of culture in medium containing LRP-TSW compared with the control medium. It is worth noting that these molecules play a role in the initiation of the signal transduction cascade, resulting in T lymphocyte proliferation. However, when added to a mixed epidermal cell-lymphocyte culture, LRP-TSW did not affect the allostimulatory activity of human Langerhans cells.[8]

Furthermore, the modulatory effects of media containing either selenium or strontium salts as well as LRP-TSW were evaluated using a reconstructed normal or inflammatory skin model (biopsies of healthy skin or skin with atopic dermatitis, respectively) for production of cutaneous inflammatory cytokines (interleukins 1α and 6 and tumor necrosis factor alpha). Whatever the medium, after 10 days of culture, the production of these three cytokines, determined using an enzyme-linked immunosorbent assay, was lower in the reconstructed inflammatory skin than in the control (Figure 1). The combined immunohistochemical and enzyme-linked immunosorbent assay techniques showed a selective inhibitory effect of selenium salts on production of interleukin 1α, which was less evident with strontium salts (Figure 1A). However, for tumor necrosis factor alpha, the inhibitory effect was greater with strontium salts (Figure 1C). Nevertheless, the most important modulating effect of both selenium and strontium salts was decreased interleukin 6 production, both at the intracellular and extracellular levels (Figure 1B).[9,10]

Anticarcinogenic properties

Compared with an untreated group (group 1) as well as a demineralized water-containing cream-treated group (group 2), a dramatic reduction in the number of ultraviolet B-induced skin tumors along with an increased lag time until first tumor appearance was seen in a group treated with a cream containing LRP-TSW (group 3) before chronic exposure to ultraviolet B (Figures 2A and B). Moreover, for group 1, malonedialdehyde formation (an indicator of lipid peroxidation) was amplified by two-fold after 11 weeks of ultraviolet B exposure, without any significant changes in selenium-glutathione peroxidase activity. In contrast, in group 3, some malonedialdehyde formation was noticed during the 25-week ultraviolet B exposure period, and a significant increase in selenium-glutathione peroxidase activity was noted.[11]

Anti-inflammatory properties

Sodium lauryl sulfate is a well known irritant. Increased cutaneous blood flow assessed by laser Doppler velocimetry was noticed when sodium lauryl sulfate 0.75% was applied under occlusive conditions for 24 hours on the ventral forearm in 10 volunteers. This increased blood flow was reduced by 46% ($P < 0.001$ versus untreated areas) when volunteers were pretreated with a gel containing LRP-TSW twice a day for 4 days prior to sodium lauryl sulfate exposure, whereas a decrease of only 15% was observed in areas pretreated with a gel containing demineralized water.[12]

Protection against ultraviolet B-induced skin damage in humans

A double-blind randomized study was performed in 10 men and women with skin type II and III in order to assess the ability of a cream containing LRP-TSW versus the same cream containing demineralized water to protect against ultraviolet B-induced erythema and formation of sunburn cells. The creams were applied once a day at 2 mg/cm² for 7 days on 10 × 10 cm areas. After determination of the individual minimal erythema dose, all treated areas were exposed to increasing ultraviolet B doses varying from an individual minimal erythema dose of 0.76–1.69 (with a 1.25 progression) and 24 hours later, colorimetric assessment of redness/erythema (a*) was performed on each area and biopsies were taken for counting of sunburn cells in paraffin-embedded skin sections after hematoxylin-eosin-saffron staining.

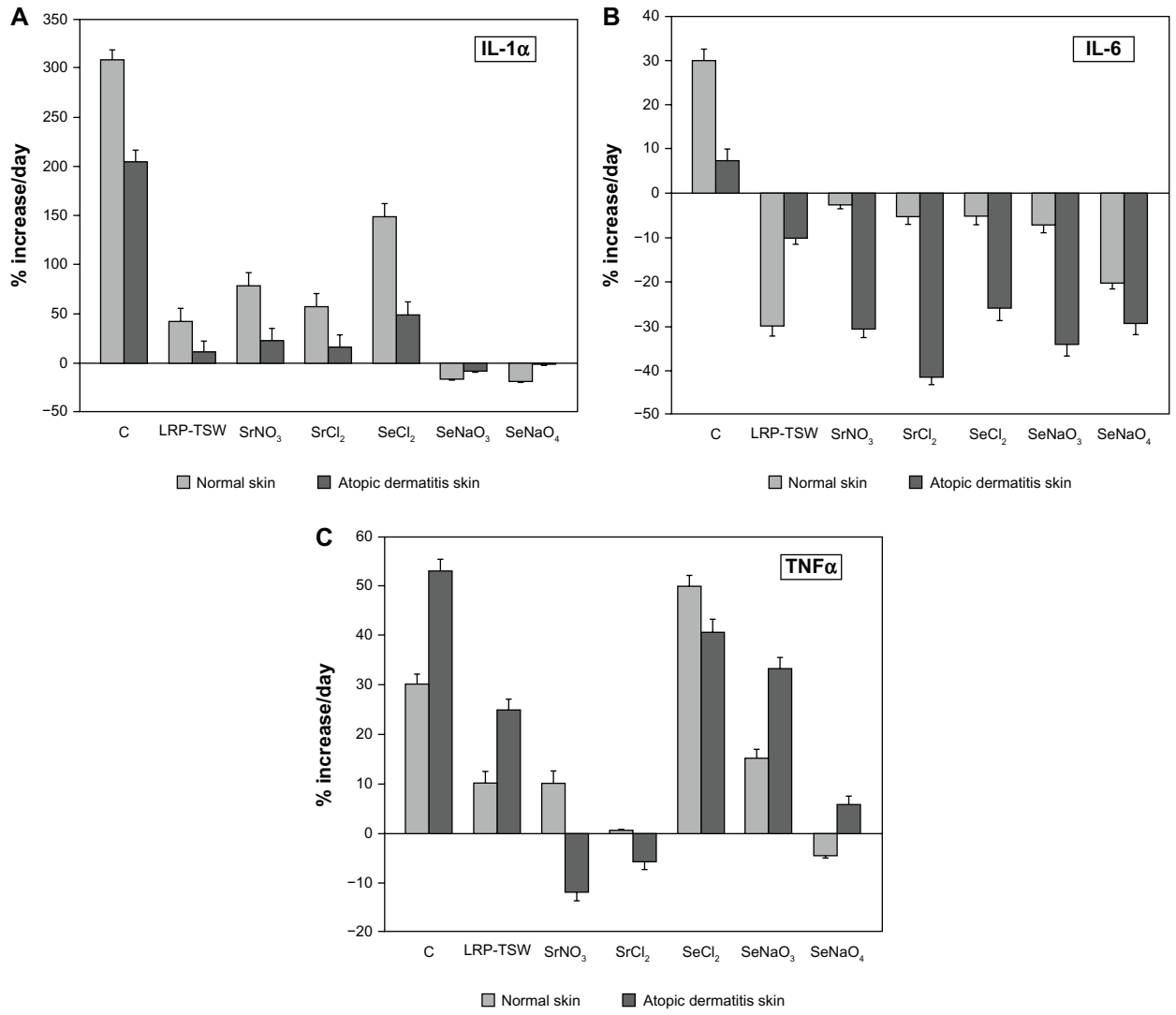

Figure 1 (**A**–**C**) Modulation of cytokine concentrations in supernatants of control and inflammatory reconstituted skin cultured in media containing different salts, demineralized water, or La Roche-Posay thermal spring water.[10]
Note: Results are expressed as the percentage increase according to expression on days 10–14 × 100/day 10.
Abbreviations: C, control medium with demineralized water; IL, interleukin; $SrNO_3$, strontium nitrate; $SrCl_2$, strontium chloride; $SeCl_2$, selenium chloride; $SeNaO_3$, sodium selenate; $SeNaO_4$, sodium selenite; TNF, tumor necrosis factor.

Neither the LRP-TSW cream nor the demineralized water cream provided significant protection against erythema, but the number of sunburn cells per square centimeter of epidermis was significantly reduced ($P = 0.04$) in areas pretreated with the cream containing LRP-TSW versus the same cream containing demineralized water.[13]

Therapeutic properties of LRP-TSW

Clinical therapeutic uses for thermal spring water include many chronic inflammatory diseases, such as atopic dermatitis (eczema), psoriasis, wound healing, burn scars, and pruritus, as well as rosacea-like dermatosis and ichthyosis, all of which have been widely described.[2]

Psoriasis vulgaris

A clinical study was performed in 92 patients with moderate psoriatic plaques and undergoing balneotherapy at the La Roche-Posay care center. Balneotherapy included a generalized high pressure filiform shower (15 bars for 4 minutes, with low pressure pulverization on facial lesions for 5 minutes if necessary) and a 20-minute bath at 35°C every day for 3 weeks. Patients also drank one liter of LRP-TSW per day. Assessment parameters included clinical evaluation using the Psoriasis Area Severity Index (PASI)[14] and measurement of plasma selenium levels. After 3 weeks of balneotherapy, the PASI was reduced by 47% ± 4% (from 5.5% ± 0.5% to 2.9% ± 0.3%, $P < 0.001$). Interestingly, 8% of patients were completely cleared of psoriasis and

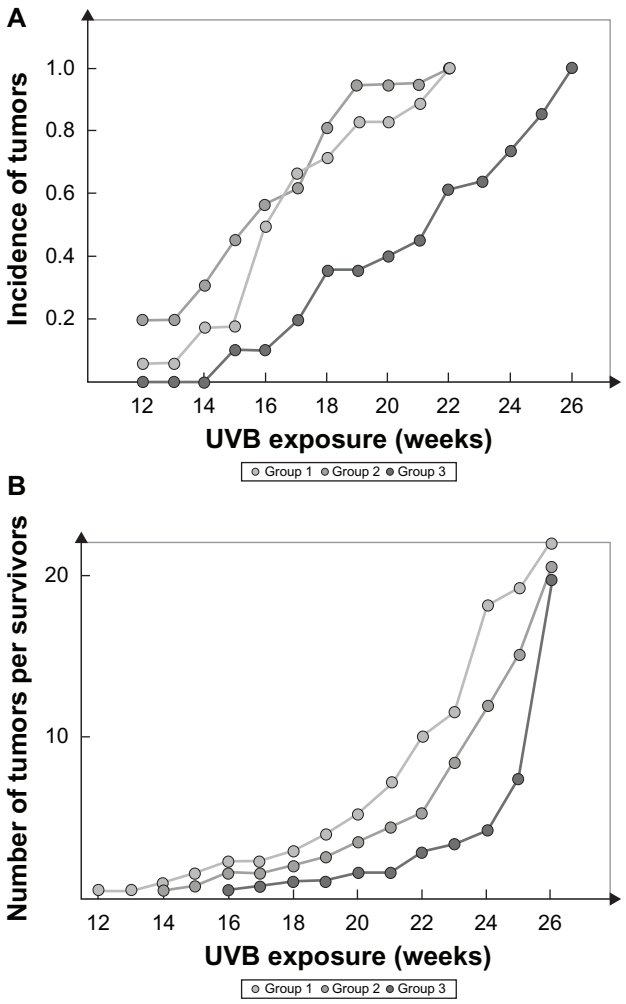

Figure 2 Protective effect of La Roche-Posay thermal spring water on the incidence of skin tumors (**A**) and on number of tumors per survivors (**B**) following repeated ultraviolet B exposure.[11]

48% were improved by more than 50%. Men responded significantly better than women ($P < 0.01$). Before therapy, the mean selenium plasma level measured in the psoriatic patients was significantly lower (77.1 ± 2.1 mg/L) than that in an aged-matched and gender-matched normal healthy control population (100 ± 4 mg/L). At the end of balneotherapy, a significant ($P < 0.01$) increase in mean selenium plasma levels (90.4 ± 2.7 mg/L, $P < 0.01$) was noticed and found to be correlated with the reduction in PASI (4, $r_s = 0.31$).[15]

Scars

Scars are a recognized treatment indication at the La Roche-Posay care center, and thermal spring water induces accelerated healing, softens the outer skin layer, and reduces itching and vasomotor pains. Two cases showing encouraging results from the use of LRP-TSW spray in the treatment of scars following pediatric plastic surgery have been described by Soupre et al (unpublished data) in which LRP-TSW spray softened the inflammatory appearance of scars, reduced itching, facilitated elimination of crusts, and prevented formation of new crusts, thereby offering a nontraumatic method of preventing wound infection induced by frequent washing.

Noninfectious blepharitis

Blepharitis is one of the most frequent ocular pathologies, and involves inflammation of the palpebral margin.[16] One study has evaluated the therapeutic effect of LRP-TSW versus an isotonic 0.1% zinc sulfate solution in this condition,[17] and included two groups of 30 and 29 volunteers, respectively, with seborrheic blepharitis, anterior blepharitis, and/or posterior blepharitis with conjunctival irritation. Each solution was applied twice a day to both eyes using a compress for 4 weeks. The LRP-TSW and zinc sulfate solution were well tolerated by patients who had inflammatory palpebral edge pathologies with no signs of functional irritation, no potential for irritation of the conjunctiva and cornea, a lower lacrimal pH, and preservation of the lacrimal lipid layer. Both solutions also corrected the pathogenic cycle, along with lipid reduction at the palpebral edge, a reduction in diameter of the Meibomian glands, and preservation of the conjunctival saprophyte flora.

Conclusion

Thermal spa waters have been used for years in both spa and aerosol form, with very good results in patients suffering from a range of conditions, in particular, chronic inflammatory skin diseases. Some recent publications have led to a better understanding of their mechanisms of action. For example, LRP-TSW has demonstrated a protective action against both the short-term and long-term deleterious effects of radical oxygen species induced by, eg, ultraviolet exposure (ie, antioxidant, immunomodulating, and anticarcinogenic effects), and has also shown an anti-inflammatory and anti-irritant potential. Although there is still progress to be made, extensive research performed by a few companies has given us a good rationale based on the evidence-based medicine concept of prescribing for including thermal spring waters in the therapeutic arsenal in order to improve patient quality of life. The evidence to date justifies the use of selenium-rich thermal spring water as an active ("cosmeceutical") ingredient in topical formulations.

Disclosure

Sophie Seité is employee of La Roche-Posay Pharmaceutical Laboratories.

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