Journal of Traditional and Complementary Medicine 10 (2020) 320–326

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Review article

Sulphate mineral waters: A medical resource in several disorders

Maria Costantino [a, b, *], Viviana Izzo [a], Valeria Conti [a], Valentina Manzo [a], Antonella Guida [c], Amelia Filippelli [a, b]

[a] Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Via S. Allende, 84081, Baronissi, SA, Italy
[b] Association non-profit F.I.R.S.Thermae (Interdisciplinary Training, Researches and spa Sciences) in Italian National Register of Research of MIUR, Naples, Via marziale 21, 80070, Bacoli, NA, Italy
[c] General Directorate Health Protection, Campania Region, Centro Direzionale is C3, 80143, Naples, Italy

ARTICLE INFO

Article history:
Received 5 January 2019
Received in revised form
5 April 2019
Accepted 21 April 2019
Available online 22 April 2019

Keywords:
Sulphate anion
Spa therapy
Spa medicine
Chronic disorders
Complementary therapy

ABSTRACT

Based on their chemical composition, salus per aquam (spa) mineral waters (or medical mineral waters) can be classified as sulphurous, sulphate, bicarbonate etc. Sulphate mineral waters where the predominant element is sulphate anion SO_4^{2-}, are frequently used in clinical therapy. In this review, we describe and analyze the current scientific knowledge concerning the therapeutic effect of sulphate mineral waters in the treatment of several disorders.

Moreover, we underline how important is to integrate spa treatments with other therapeutic approaches to meet the various needs that can arise during a specific pathological state.

1. Introduction

Salus peraquam (spa) Medicine, also referred to as *Crenotherapy*, uses spa mineral waters (or medical mineral waters), with a documented medical effect, to treat several diseases. Spa mineral waters are among the first medications used by humans. With the advancement of scientific knowledge, their positive pharmacological effects (correlated to their chemical properties) has been detailed, leading to the definitive clinical validation of the use of spa mineral waters in medical practice. Similarly to common drugs, spa mineral waters induce, through a predominantly chemical stimulus, a response in the living organism.[1] However, unlike the drug, which generally corresponds to a single active chemical identity, spa mineral water are a complex combination in solution of anions, cations and trace elements that altogether participate in creating a unique "pharmacological" composition.[1] In addition to their chemical properties (e.g. fixed residue at 180 °C, sulphydrometric grade, etc.), spa mineral waters are also identified by physical properties such as temperature at source, osmolarity, radioactivity and pH, which might contribute to the therapeutic action of the waters themselves.[1]

In Italy, the reference for classification of spa mineral waters is represents by Marotta and Sica,[2,3] this classification takes into account temperature, fixed residue and chemical composition. Based on this classification, which considers firstly the prevalent anion and secondly the prevalent cation, spa mineral waters can be classified as sulphurous, sulphate, bicarbonate, sodium-chloride, ferrous arsenic waters etc. This classification is useful to recognize the health properties of each type of water.

The aim of this review is to summarize the current scientific knowledge concerning the therapeutic effects of sulphate mineral waters (SMWs) in the treatment of gastroenteric, musculoskeletal, skin and respiratory disorders.

2. Classification, characteristics and administration methods of sulphate mineral waters

Chemical composition of spa mineral waters is widely determined by the type of the rock from which they originate. However, depending on the geochemical processes, similar types of rock can

* Corresponding author. Via S. Allende,1, 84081, Baronissi, SA, Italy.
E-mail addresses: mcostantino@unisa.it, mariacostantino@firsthermae.org (M. Costantino), vizzo@unisa.it (V. Izzo), vconti@unisa.it (V. Conti), vmanzo@unisa.it (V. Manzo), antonella.guida@regione.campania.it (A. Guida), afilippelli@unisa.it (A. Filippelli).

Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

https://doi.org/10.1016/j.jtcme.2019.04.004

List of abbreviations:

Spa	salus per aquam
SMWs	sulphate mineral waters
CO2	carbon dioxide
mg/L	milligrams/Liter
SO42	sulphate anion
AQP3	aquaporin 3
CCK	cholecystokinin
CCl4	carbon tetrachloride
QoL	quality of life
SKH1	hairless mice with atopic dermatitis
DNCB	2,4-dinitrochlorobenzene
PASI index	Psoriasis Area and Severity Index
ROS	Reactive Oxygen Species
TNFα	Tumor Newcrosis Factor alfa
NO	nitric oxide
MDA	malondialdehyde
IL-23	Interleukin-23
IL-17	Interleukin-17
IL-4	Interleukin-4
IL-5	Interleukin-5
TCA	trichloroacetic acid
CVI	chronic venous insufficiency
NaCl	sodium chloride
I	iodine
Br	bromide
Ca	calcium
S	sulfur
COPD	chronic obstructive pulmonary disease
WHO	World Health Organization

lead to different types of mineral water. Actually, the water chemistry is characterized by availability of mineralizing agents, temperature, CO_2 concentration and many other factors.[1]

Spa mineral waters can be classified according to different criteria, such as use, natural origin and chemical/physical properties.[1] In SMWs, sulphur, which is present as anion sulphate (SO_4^{2-}), with a concentration >200 mg/L, is the predominant element; different cations, such as calcium, magnesium, sodium are also present giving reason of SMWs multiple beneficial effects. Moreover, the high anion sulphate content lends to mineral waters a slightly bitter taste.[2]

In the SMWs the most frequent combinations are with bicarbonate, calcium and magnesium ions. The presence of bicarbonate anion is important because it increases the solubility of calcium, which is not very soluble in the form of calcium sulphate.

It is important to underline, as already mentioned, that the therapeutic effects of SMWs as well as other mineral waters strongly depend on their physical/chemical properties. In particular, the heat induction associated to administration of mineral water represents the main physical stimulus able to produce analgesic benefits through relaxing and tensor effects and by stimulating hypothalamic-pituitary-adrenal axis with consequent increase of endorphin and cortisol plasmatic levels (Fig. 1).

Sulphate mineral waters in clinical therapy are used through different administration methods such as *hydropinotherapy*, *balneotherapy*, *mud therapy*, *mud-balneotherapy*, *inhaled or irrigation crenotherapy*. Hydropinotherapy, a type of crenotherapy, consists in drinking spa mineral water for therapeutic purposes.[4] Type and quantity of spa mineral water to drink, varies depending on the pathology and age of the patient. The hydropinic cycle lasts 12 days, always suspended by a day of rest in the middle of the therapeutic cycle. For their laxative or purgative effects, for their choleretic and cholagogue effects, and for stimulation of the intestinal motility, sulphate mineral waters are used in the form of hydropinotherapy for several gastroenteric diseases.[5]

Balneotherapy consists in a complete or partial immersion of the body (head excluded) in a bath containing spa mineral waters at a temperature between 35 °C and 40 °C, depending on the mineral content, for 15–20 min. After treatment, the patient is covered with a blanket and rested for 15–30 min lying or reclined in a comfortable position. A complete cycle of balneotherapy lasts 12 days and consists of 12 consecutive baths (one per day), in the morning and preferably under fasting conditions.[1]

Mud therapy uses mud, which is a mixture of natural clay (95%) and organic substances produced from the maceration of algae, bacteria, protozoa and diatoms (6%) added in special tanks where there is a continuous flow of spa mineral water.[1] Mud is applied on specific skin areas in layers of 3–10 cm thick, at a temperature of 41–44 °C for a duration of 15–20 min. During this time, the patient is covered with sheets, cellophane and blankets to reduce heat dispersion. After 15–20 min, mud is removed using a shower (at about 37°–38 °C) with tap water or spa mineral water.[1]

Balneotherapy and mud therapy are generally used in combination (mud-balneotherapy) because there is a therapeutic synergism.

Balneotherapy, mud therapy or mud-balneotherapy with sulphate mineral water are indicated in the treatment of rheumatic and dermatological chronic diseases.[1,6,7]

The inhalation or irrigation crenotherapy cycle consists of 12 applications of 10–15 min each of spa mineral waters in form of direct jet, humide fog, dry inhalers, endotympanic insufflations, politzer. Sulphate mineral waters can be useful in the treatment of chronic inflammation and/or irritation of upper and lower respiratory tracts.[1,8]

In the following paragraphs, the correlation between specific properties of SMWs and their pharmacological and therapeutic effects in different pathologies will be discussed.

3. Methods

To summarize the current scientific knowledge concerning the therapeutic effects of SMWs in the treatment of gastroenteric, musculoskeletal, skin and respiratory disorders, we consulted Pubmed, Scopus, Web of Science, and Cochrane Library databases searching for articles published from 1983 to November 2018 and using the following key words: “spa therapy,” “sulphate mineral waters”, “sulphate anion” and “spa medicine”.

4. Current results

4.1. Sulphate mineral waters in gastroenteric disorders

Sulphate mineral waters, mainly magnesium sulphate-rich and sodium sulphate-rich, have a purgative-laxative function, as a consequence of a hypertonia. They rapidly transit through the stomach and arrive in the gut where they recall the presence of water. In this way, faecal excretion is facilitated with an increase in volume and a marked decrease in consistency and improvement on both the number of evacuations and colon motility as reported by Dupont et al.[9] in a randomized double-blind clinical trial involving

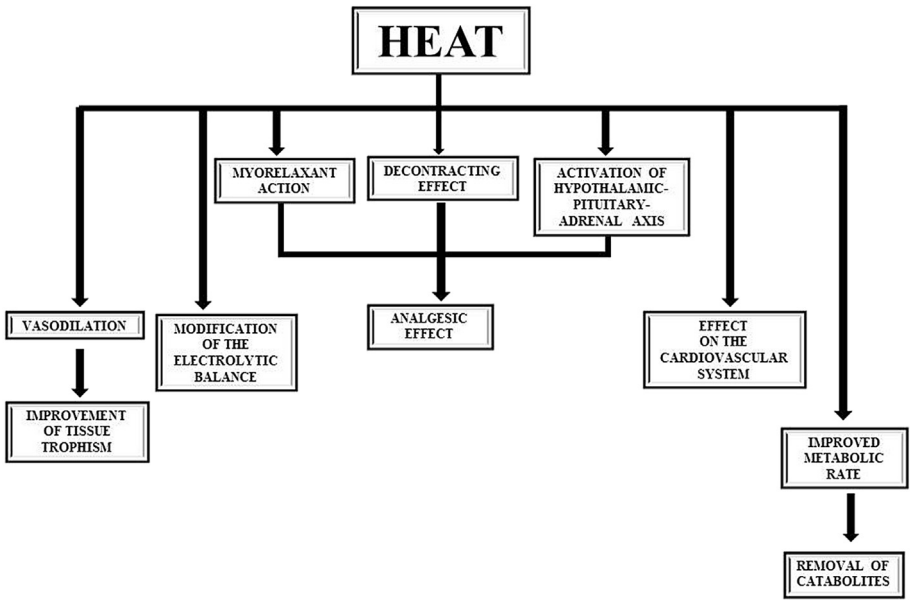

Fig. 1. Main therapeutic effects derived by the heat during spa therapy.

women with functional constipation. In particular, these authors have demonstrated that daily consumption of magnesium sulphate-rich natural mineral water was more effective than low-mineral water in reducing constipation.

Ikarashi et al.[10] demonstrated through an *in vitro* study that magnesium sulphate might increase the aquaporin 3 (AQP3) expression levels and change the osmotic pressure in the colon. Bothe et al. have recently shown that daily consumption of mineral waters, rich in magnesium sulphate and in sodium sulphate, is useful for healthy digestion improving constipation symptoms, overall bowel movements and stool consistency.[11]

A meta-analysis demonstrated that in European populations, in particular in Scandinavians, higher levels of magnesium in drinking water might reduce the risk of mortality due to coronary heart diseases.[12]

Chloride sulphate waters stimulate intestinal motility and are administered against chronic constipation and other digestive and hepatic biliary disorders.[5]

Sulphate bicarbonate-calcium-magnesiac mineral waters, administered as hydropinotherapy, are useful against disorders of the biliary tract; these waters are particularly efficacious thanks to anions that exert choleresis and cholagogue actions, thus helping in removing gallbladder hypomotility and correcting the tendency to gallstones.[2,13]

Corradini et al.[14] have shown a beneficial effect of the hydropinic treatment with sulphate-bicarbonate-calcium mineral waters in reducing the risk of biliary calculi and favoring weight control. Moreover, the same spa treatment with sulphate-calcium mineral waters may effectively normalize the echoscopy picture and the motor function of stomach and gallbladder.[15]

Fraioli et al.[16] underscore efficacy of waters rich in sulphate and bicarbonate in lithogenic bile, because of their diluting and washing activity. In addition, they show a positive effect in the treatment of biliary dyskinesia due to the release of cholecystokinin (CCK) and a consequent gallbladder contraction and Oddi sphincter relaxation. Pharmacological studies[1,17,18] have shown that magnesium participates in the synthesis of digestive enzymes and hormones such as CCK.

Magnesium, thanks to its inhibitory action on the gastric acid secretion, competes with calcium. This confirms the clinical evidence that calcium-sulphate waters (poor in magnesium) have hyper-secretive action and are not well tolerated in patients suffering from gastro-duodenal ulcer and hyper-secretive gastropathies, whereas they are indicated in digestive insufficiencies characterized by gastric hypo-secretion and hypo-motility with or without a spastic component.

Several mineral waters have a trophic, antitoxic and metabolic action on the liver. For example, it was observed that a reduction in steatosis, experimentally induced by carbon tetrachloride (CCl4), occurred as a consequence of the assumption of bicarbonate-sulphate-alkaline-earth waters.[1] As a matter of the fact, Montecatini (Italy) spa mineral water, classified as sodium-chloride sulphate alkaline and administered through hydropinotherapy, has been used for centuries to treat pathologies affecting liver, stomach and guts. Similarly, the sodium chloride-sulphate mineral waters improve the biliary function by choleretic and cholagogue actions.[1] Studies performed by using radiological and ecographic screening have highlighted significative volume variations of gallbladder after assumption of sulphate waters.[1]

The intake of sulphate sodium-chloride mineral waters activates carbohydrate metabolism. Indeed, it has been demonstrated in animal models that such kind of mineral water enhances resistance to stressful factors and may promote trophic effects of insulin and gastrin with significant reduction in peptic ulcer size.[19,20]

Magnesic-sulphate-sulphurous mineral waters have been shown to have a very good hypocholesterolaemic activity and protective effect against oxidative lipid damage.[4,21]

Studies investigating the effects of Montecatini spa mineral waters on bile acid extraction and lipid and apolipoprotein serum levels suggested that a treatment with salt-rich spring waters reduces serum LDL levels in subjects with mild hypercholesterolaemia, through a mechanism of increased excretion of the faecal bile acid sterols.[4]

Sulphate is also an important nutrient in foetal growth and development, particularly in late gestation when foetal demand for sulphate is high. For this reason sulphate mineral waters may be a useful alternative for diet of pregnant women.[2,22]

4.2. Sulphate mineral waters in musculoskeletal disorders

Sulphate mineral waters administered by using balneotherapy, mud therapy and mud-balneotherapy have shown efficacy in the treatment of various chronic diseases of the locomotor system.[23,24]

Epidemiological data show that patients suffering from osteoarthritis are among the most frequent users of spa treatments, followed by patients with respiratory disorders.[25]

It has been demonstrated that mud maturated with sodium-chloride sulphate mineral water exerts anti-inflammatory activity. Schettino and coworkers[26] showed that the anti-inflammatory activity of this mud is characterized by a 30% reduction of the edema induced by carragenin. Moreover, other authors[27,28] have underlined the benefits of a cycle of mud-balneotherapy with sodium-chloride sulphate mineral water in patients affected by gonarthrosis, one of the main causes of movement impairment in elderly. These benefits encompass a significative reduction of severity and frequency of pain symptomathology and Lequesne index, with a concomitant reduction of disability.[28] Importantly, a therapeutic synergism is observed when a pharmacological treatment is associated to mud-balneotherapy. This aspect prompts the need for a multidisciplinary approach to treat chronic diseases such as gonarthrosis.[27] Fioravanti et al. have performed a randomized, single-blind controlled trial in which the effects of mud-bath therapy were compared to usual treatment in patients with bilateral knee osteoarthritis, showing improvement of pain, WOMAC index and quality of life in subjects who have undergone spa treatment.[29]

Notably, the cost effectiveness of the mud-bath therapy used in association with usual treatment in such a clinical setting was demonstrated by medical assessment and the measurement of quality-adjusted life years (QALYs). Indeed, a favorable economic profile of a single mud-bath cycle with sulphate mineral waters provided a significant reduction of hospitalization and average costs per patient for pharmacologic therapies.[30]

A prospective randomized, single blind-controlled, trial showed that sulphate mud-balneotherapy modifies adiponectin and resistin serum levels but not the circulating levels of visfatin. In view of the recent evidences concerning the involvement of adiponectin and resistin in the pathogenesis of osteoarthritis, the decrease of these adipokines after mud-balneotherapy may contribute to delay the progression of such diseases.[31] In the osteoarthritis, an important role is also played also by release of free radical species produced by sinovial inflammatory cells and by the chondrocytes.[32] In this context mud-balneotherapy seems to have an antioxidant role as shown by several studies.[33,34] For instance, mud-balneotherapy with carbonate-sulphate alkaline mineral waters reduces the levels of oxygen free radicals in patients with rheumatological chronic diseases.[35]

Fortunati et al.,[25] have shown that balneotherapy and mud therapy induce pain relief and improve the muscular function as well as quality of life (QoL) in patients with osteoarthritis and, importantly, clinical efficacy has been proven also to persist after treatment. Scalabrino et al. have demonstrated increase of peptides and opioid hormones after a single mud-bath treatment with alkaline-saline-sulphate waters.[36]

The efficacy of balneotherapy with mineral water rich in sodium, carbonates and sulphates was also demonstrated in patients affected by fibromyalgia, where a decrease of pain intensity and depression level together with a marked improvement of the functional capacity were described.[37–39]

4.3. Sulphate mineral waters in skin disorders

Comé, one of the main representatives of the thermalism in dermatology, introduced the term of “mineral eudermic water” to identify waters able to provide the organism with all factors necessary for nutritional, eutrophic and rehydrating action. When we consider the effect of mineral waters, including sulphate mineral waters, in stimulating skin turnover and toxins removal, it is quite easy to understand the role of spa therapy for treatment of dermatological diseases such as psoriasis, atopic dermatitis and acne. From the biochemical point of view, several aspects have been underlined. Magnesium, for example, has a central role in the growth and differentiation of keratinocytes and it is responsible for helping skin in preserving the lack of water, thus acting as a natural moisturizing agent. These effects are very useful to treat and manage pathologies such as psoriasis and atopic dermatitis.[40,41]

Hercogova et al.[42] have shown anti-inflammatory effects of sodium-chloride sulphate mineral waters on human skin during inflammatory reactions caused by the direct application of irritant chemicals.

An antioxidant effect of sulphate-rich waters has also been reported by Bajgai et al.[43] who showed a significant improvement of the redox balance in SKH1 hairless mice with atopic dermatitis induced by the application of 2,4-dinitrochlorobenzene (DNCB).[43]

Tsoureli-Nikita et al.[44] have demonstrated a potential anti-inflammatory effect of balneotherapy with sodium-chloride sulphate mineral water in patients with plaque psoriasis obtained by a significant decrease in Psoriasis Area and Severity Index (PASI index). Moreover, balneotherapy with carbonate-sulphate-calcium mineral waters allows softening injuries and removing the scales, alongside with an improvement of the plaque aspect itself.

An antioxidant activity of carbonate-sulphate alkaline waters used either in mud-balneotherapy or speleotherapy (exposure to mineral waters in thermal caves) has been also demonstrated.[35,45] This is very important when we consider the role played by free radical species in skin aging and in the pathogenesis of several dermatological diseases such as psoriasis, a condition in which a correlation between oxidative stress and inflammation has been provided.[46]

The evidence of an oxidant environment in psoriasis, both at the systemic and local levels, has been extensively reported in literature. This condition is produced by a massive release of Reactive Oxygen Species (ROS) from immune system cells, particularly neutrophils; it is typical of inflammatory processes and mediated by cytokines (TNFα, in particular).[47] For instance, Joly et al.[48] demonstrated the positive effects of sulphate carbonate-calcium-magnesium rich-waters in preventing ROS induced damage. Moreover, the plasmatic levels of nitric oxide (NO) and malondialdehyde (MDA), whose production in strictly linked to ROS increase, are also significantly higher in patients suffering from psoriasis than in healthy volunteers.[49]

Altogether, these evidences suggested a key role played by modifications of the normal redox balance in psoriasis pathogenesis.[46] Therefore, spa therapies, which have been reported to exert anti-oxidant activities,[35,50] could be expected to have beneficial effects in the treatment of plaque psoriasis.

An *in vivo* study performed on a psoriasis murine model[51] showed that, compared to administration of distilled water, balneotherapy with sulphate-hydrogen carbonate-thiols rich mineral waters is effective in producing immunomodulatory effects, and lead to a marked reduction of cytokines involved in psoriasis and skin erythema pathogenesis, including IL-23, IL-17, IL4 and IL5. Based on this evidence, the authors suggested that spa balneotherapy is considered an effective and safe treatment for mild-moderate plaque psoriasis. Therefore, spa balneotherapy in dermatological care might be used alone, allowing patients to stop the drugs assumption at least for a short period of time, or as complementary therapy of conventional medical approach.[52,53]

It has been observed by Ricci et al.[54] that balneotherapy with bicarbonate-sulphate-rich mineral waters ameliorate the wounds of patients with atopic dermatitis thanks to their moisturizing and soothing effect induced by the buffering-alkalizing action of bicarbonate anion.

Spa mineral waters could also have positive effects after chemical peeling procedures. Indeed, the main undesired effect of chemical peeling is local inflammation, which is generally prevented or attenuated by using of antibiotics or topical steroids. Unfortunately, since chemical peeling reduces skin corneal layers and increases skin permeability these drugs might have toxic effects. The ability of bicarbonate-sulphate-rich mineral waters to mitigate inflammatory processes produced by a 24-h treatment with an aggressive chemical exfoliating agent (trichloroacetic acid-TCA) has been demonstrated in an *in vivo* study.[55]

Also Faga et al.[56] using an animal model showed that bicarbonate-calcium-magnesium-rich mineral waters improve skin regeneration. Moreover, Casas and colleagues[57] described the positive effects of such spa mineral waters on the skin of patients affected by chronic dermatosis. Concomitantly, a sensible decrease of inflammation and a reduced colonization by *Staphylococcus aureus*, whose toxins can induce atopic dermatitis and psoriasis, were described.[56]

4.4. Sulphate mineral waters in respiratory disorders

SMWs administered through inhaled or irrigation crenotherapy thanks to specific effect of their various active components can be considered a valid therapeutic option in several chronic respiratory diseases.

Antiseptic action of sodium chloride (NaCl), increase of the metabolic and cellular activity of iodine (I), analgesic and sedative effects on mucosa induced by bromide (Br) and calcium (Ca), increase of secretory IgA activity produced by sulfur (S) have been largely recognized.

Administration methods are also important. For example, direct vapor-jet inhalation is indicated for chronic diseases of the upper respiratory tract such as rhinosinusitis, pharyngitis and laryngitis. In this method inhaled particles of about 100 μm in size exert a mechanical detergent action on the respiratory mucosa. Aerosol method (particles under 2 μm in diameter) delivers the active components of the waters to the lower respiratory tract, as far as the alveoli. Aerosol therapy is therefore indicated in chronic bronchitis (e.g., smokers' cough) and chronic obstructive pulmonary disease (COPD). Nebulization (particles of 10 μm) is utilized in cases of absent or insufficient mucosal secretion (bronchial and lung disease). In cases of rhinogenic deafness caused by the presence of catarrh in the middle ear, tubo-tympanic insufflation is used to push up the water vapor to the affected areas. Moreover, as inhalation treatments stimulate the body's overall immune defense mechanisms, they are also particularly indicated in the treatment of childhood diseases.

Passali et al.[58] showed that inhalation treatment with bicarbonate-sulphate-alkaline-earth carbonated waters is beneficial against catarrhal conditions of the upper respiratory tract.

Ricevuti et al.[59] showed particular benefits on the homeostasis of the alveolar surfactant compromised by tobacco smoke in rats exposed to inhalation crenotherapy with sulphate mineral waters. It has also been documented an anti-reactive action of magnesium, generally present in sulphate mineral waters, which is responsible for reduction of bronchial hyperactivity at different stimuli.[60]

Cantone et al.[61] have shown that spa treatment with sodium-chloride sulphate waters results in a statistically significant improvement of ciliary motility in elderly subjects suffering from chronic rhinosinusitis.

Passariello et al.[62] demonstrated that spa therapy consisting of sulphate-sodium chloride mineral water inhalations by aerosol (15min/day) induced in pediatric patients suffering from chronic rhinosinusitis a significant improvement of symptoms such as nasal obstruction, nasal discharge, sense of smell and a reduction in TNF-α, calprotectin and human β-defensin 2 concentrations.

5. Summary

Spa treatment with SMWs may be foreseen as a therapeutic approach for treatment of gastroenteric, musculoskeletal, cutaneous and respiratory disorders thanks to several actions and effects (Fig. 1).

Among gastroenteric disorders, hydropinotherapy with SMWs is useful to treat dyspepsia (by increasing gastric secretion; prompt emptying of the stomach and increase in interdigestive motility); irritable bowel syndrome and simple chronic constipation (by promoting of smooth muscle motility and releasing substances that stimulate motility and osmotic exchange); disorders of the hepato-biliary system such as biliary dyskinesia, chronic and sub-chronic biliary inflammation, cholecystopathy, biliary dyspepsia, active slow-evolution chronic hepatitis (by exerting effects on both the production of bile and its excretion into the duodenum).

In musculoskeletal disorders, the administration of mud- and/or balneotherapy has been correlated to sensitive improvements in terms of pain reduction, stiffness and functional limitations in the execution of daily activities. Mud applications determine an increase in skin temperature, both at local and systemic level. Such increase is sufficient to exert muscle-relaxing and analgesic effects alongside with activation of neuro-endocrine mechanisms. Therapeutic effects produced by application of bath whit SMWs is mainly based on hydrostatic effect (a body immersed in water is subjected to an upward thrust that allows it to remain afloat, this thrust is directly proportional to salt concentration), and hydrothermal effect (the water temperature induces muscle relaxation, which in turn produces analgesic and sedative effects, thereby facilitating motor activity).

In the dermatological diseases, including plaque psoriasis, atopic dermatitis and acne, spa treatment with SMWs, it might represents a useful therapeutic strategy thanks to anti-inflammatory, lenitive and antioxidant effects.

Beneficial effects of SMWs in the treatment and prevention of respiratory diseases are widely documented. Among its main effects, it is worth noting the mucolytic action induced at tracheo-bronchial level; the relaxing action of radical sulfates on the tracheobronchial smooth muscle; the induction of hyperemia that leads to an improvement in the trophism of mucosa, increasing cell turnover and restoring effective ciliary motility.

6. Conclusions and future perspectives

The benefits produced by spa medicine, thanks to a combination of physical (such as heat, mechanical action of the water, osmotic phenomena) and chemical (such as presence of active ions) properties, and psychological effects (sense of well-being, hydration, relaxation from daily stress), are well recognized.

Therefore, treatments with SMWs in several chronic diseases may be a valuable adjuvant or complementary therapy, able to provide support in clinical and psychological management of several patients. Noteworthy, spa therapy could guide to the reduction of duration and dosage of therapies with symptomatic drugs (e.g. acetaminophen and non-steroidal anti-inflammatory drugs) potentially toxic, particularly in aged patients.

All spa treatments could allow to reduce the number and/or dosage of the drugs administered in many chronic pathological

conditions with a positive impact on the quality of life of the treated subjects. As matter of the fact, the World Health Organization (WHO) has included spa medicine in the strategies and objectives of traditional medicine 2014–2023.

Actually, another aspect very important is that besides its beneficial effects spa therapy with sulphate mineral waters is well tolerated with a lower percentage of side effects compared to the drugs commonly used in gastroenteric, musculoskeletal, cutaneous and respiratory disorders.

However, despite its very high tolerability, there are situations in which the use of spa therapy is not recommended, for example during the acute phase of the diseases, or in complex patients such as those with tumors, heart failure, severe respiratory failure, epilepsy. Well-documented scientific evidence and targeted experimental approaches are needed to definitively recognize the beneficial effects of spa treatment in the various medical areas. In particular, randomized clinical trials, with rigorous methodological criteria should be performed for further evaluation of long-term beneficial effects of sulphate mineral waters.

Finally, crenotherapy with sulphate mineral waters should be considered not cheaply as an approach to be used when conventional treatments have failed or are contraindicated but as an effective medical resource for treatment and management of chronic diseases.

There is an urgent need to reevaluate, the ancient culture of spa medicine that already live in excellent Spas located in several countries around the world.

Conflicts of interest

The authors declares no conflict of interest.

Acknowledgments

We thank Prof. Walter Filippelli, dr. Teresa Iannaccone, dr. Bruno Charlier and dr. Francesco Marongiu for the helpful collaboration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2019.04.004.

References

1. Queneau P, Boulangé M, Francon A, et al. *Médecine Thermale*. Ed. Paris-France: Masson; 2000.
2. Quattrini S, Pampaloni B, Brandi ML. Natural mineral waters: chemical characteristics and health effects. *Clin Cases Miner Bone Metab*. 2016;13(3):173–180.
3. Marotta D, Sica C. Composition and classification of Italian mineral waters Nota II. *Ann Chim Appl*. 1933;23:245–257.
4. Albertini MC, Dachà M, Teodori L, Conti ME. Drinking mineral waters: biochemical effects and health implications - the state of the art. *Int J Environ Health*. 2007;1(154):153–169.
5. Casado Á, Ramos P, Rodríguez J, Moreno N, Gil P. *Types and Characteristics of Drinking Water for Hydration in the Elderly Critical Reviews in Food Science and Nutrition*. vol 55. 2015:1633–1641 (12).
6. Costantino M, Conti V, Corbi G, Marongiu F, Marongiu MB, Filippelli A. Sulphurous Mud-Bath Therapy for Treatment of Chronic Low Back Pain Caused by Lumbar Spine Osteoarthritis Internal and Emergency Medicine. https://doi.org/10.1007/s11739-018-1967-y; 2018.
7. Cozzi F, Carrara M, Sfriso P, Todesco S, Cima L. Anti-inflammatory effect of mud-bath applications on adjuvant arthritis in rats. *Clin Exp Rheumatol*. 2004;22:763–766.
8. Costantino M. Inhalation spa therapy: current events and future perspectives. In: *IL Pavone, Chianciano Terme, Italy*. 2008.
9. Dupont C, Campagne A, Constant F. Efficacy and safety of a magnesium sulfate-rich natural mineral water for patients with functional constipation. *Clin Gastroenterol Hepatol*. 2014;12(8):1280–1287.
10. Ikarashi N, Mochiduki T, Takasaki A, et al. A mechanism by which the osmotic laxative magnesium sulphate increases the intestinal aquaporin 3 expression in HT-29 cells. *Life Sci*. 2011;88(3-4):194–200.
11. Bothe G, Coh A, Auinger A. Efficacy and safety of a natural mineral water rich in magnesium and sulphate for bowel function: a double-blind, randomized, placebo-controlled study. *Eur J Nutr*. 2017;56(6):491–499.
12. Jiang L, He P, Chen J, et al. Magnesium levels in drinking water and coronary heart disease mortality risk. *Meta-Anal Nutrients*. 2016;8(1):5.
13. Mennuni G, Petraccia L, Fontana M, et al. The Therapeutic activity of sulphate-bicarbonate-calcium-magnesiac mineral water in the functional disorders of the biliary tract. *Clin Ter*. 2014;165(5):e346–e352.
14. Corradini SG, Ferri F, Mordenti M, et al. Beneficial effect of sulphate-bicarbonate-calcium water on gallstone risk and weight control World. *J Gastroenterol*. 2012;18(9):930–937.
15. Guliaeva SF, Pomaskina TV, Guliaev PV, Martusevich AK, Aistov VI. Efficacy of sulfate calcium mineral water in disorders of motor evacuatory function of the stomach and gallbladder. *Vopr Kurortol Fizioter Lech Fiz Kult*. 2004;6:20–22.
16. Fraioli A, Mennuni G, Petraccia L, Fontana M, Nocchi S, Grassi M. Sulphate-bicarbonate mineral waters in the treatment of biliary and digestive tract diseases. *Clin Ter*. 2010;161(2):163–168.
17. Inoue K, Weiner I, Fagan CJ, Watson LC, Thompson JC. Correlation between gallbladder size and release of cholecystokinin after oral magnesium sulfate in man. *Ann Surg*. 1983;197(4):412–415.
18. Gasbarrini G, De Luca S, Nappi G. Gastrointestinal and gallbladder motility effects with san pellegrino water med. *Clin Ter*. 2002;50–51:389–399.
19. Razumov AN, Surkov NV, Frolkov VK, Ziniakov NT. Therapeutic and preventive effects of sulfate-chloride-sodium mineral water in experimental peptic ulcer Vopr Kurortol Fizioter Lech. *Fiz Kult*. 2009;3:22–25.
20. Mooventhan A, Nivethitha L. Scientific evidence-based effects of hydrotherapy on various systems of the body N. *Am J Med Sci*. 2014;6(5):199–209.
21. Cantalamessa F, Nasuti C. Hypocholesterolemic activity of calcic and magnesic sulphate-sulphurous spring mineral water in the rat'. *Nutr Res*. 2003;23:775–789.
22. Dawson PA, Elliott A, Bowling FG. *Sulphate pregnancy Nutrients*. 2015;7(3):1594–1606.
23. Fioravanti A, Giannitti C, Bellissai B, Iacoponi F, Galeazzi M. Efficacy of balneotherapy on pain, function and quality of life in patients with osteoarthritis of the knee. *Int J Biometeorol*. 2012;56(4):583–590.
24. Paoloni M, Bernetti A, Brignoli O, et al. Appropriateness and efficacy of Spa therapy for musculoskeletal disorders. A Delphi method consensus initiative among experts in Italy. *Ann Ist Super Sanità*. 2017;53(1):70–76. https://doi.org/10.4415/ANN_17_01_13.
25. Fortunati NA, Fioravanti A, Seri G, Cinelli S, Tenti S. May spa therapy be a valid opportunity to treat hand osteoarthritis? A review of clinical trials and mechanisms of action. *Int J Biometeorol*. 2016;60(1):1–8.
26. Schettino O, Ferrara L, Minerva A, et al. Study of maturation process of thermal mud in Ischia island. *Clin Ter*. 2000;151(suppl.2):1–23.
27. Costantino M, Magrassi P, Granieri MA, Nappi G, De Luca S. SPA and pharmachological therapy in the treatment of osteoarthritis of knee Med. *Clin Ter*. 2006;62–63:89–95.
28. Fraioli A, Serio A, Mennuni G, et al. A study on the efficacy of treatment with mud packs and baths with Sillene mineral water (Chianciano Spa Italy) in patients suffering from knee osteoarthritis. *Rheumatol Int*. 2011;31(10):1333–1340.
29. Fioravanti A, Bacaro G, Giannitti C, et al. One-year follow-up of mud-bath therapy in patients with bilateral knee osteoarthritis: a randomized, single-blind controlled trial. *Int J Biometeorol*. 2015;59(9):1333–1343. https://doi.org/10.1007/s00484-014-0943-0.
30. Ciani O, Pascarelli NA, Giannitti C, et al. A mud-bath therapy in addition to usual care in bilateral knee osteoarthritis: an economic evaluation alongside a randomized controlled trial. *Arthritis Care Res*. 2017;69(7):966–972. https://doi.org/10.1002/acr.23116.
31. Fioravanti A, Giannitti C, Cheleschi S, Simpatico A, Pascarelli NA, Galeazzi M. Circulating levels of adiponectin, resistin, and visfatin after mud-bath therapy in patients with bilateral knee osteoarthritis Inter. *J Biometeorol*. 2015;59(11):1691–1700.
32. Mazzetti I, Gigolo B, Pulsatelli L, et al. Differential roles of nitric oxide and oxygen radicals in chondrocytes affected by osteoarthritis and rheumatoid arthritis. *Clin Sci*. 2001;101:593–599.
33. Bellometti S, Poletto M, Gregotti C, Richelmi P, Berté F. Mud bath therapy influences nitric oxide, myeloperoxidase and glutathione peroxidase serum levels in arthritic patients. *Int J Clin Pharmacol Res*. 2000;20(3-4):69–80.
34. Caraglia M, Beninati S, Giuberti G, et al. Alternative therapy of earth elements increases the chondroprotective effects of chondroitin-sulfate in mice. *Exp Mol Med*. 2005;37(5):476–481.
35. Nappi G, De Luca S, Baronio L. Free radical variation with mud-bath therapy by San pellegrino SPA (Italy). *Med Clin. Termale*. 2005;56:8–18.
36. Scalabrino A, Galassi A, Pierallini F, et al. A single mud-bath treatment induces increased levels of circulating endogeneous opioids. *Current*. 1994;2/3:5–10.
37. Evcik D, kizilay B, Gokcen E. The effects of balneotherapy on fibromyalgia patients. *Rheumatol Int*. 2002;22(2):56–59.
38. Broggini M, Galvani L. Spa treatment for fibromyalgia syndrome. *Clin Ter*. 2015;62(3-4):41–48.
39. Fioravanti A, Manica P, Bortolotti R, Cevenini G, Tenti S, Paolazzi G. Is balneotherapy effective for fibromyalgia? Results from a 6-month double-blind randomized clinical trial. *Clin Rheumatol*. 2018;37(8):2203–2212. https://doi.org/10.1007/s10067-018-4117-z.

40. Proksch 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):151–157.
41. Shani J, Barak S, Levi D, et al. Skin penetration of minerals in psoriatics and Guinea-pigs bathing in hypertonic salt solutions. *Pharmacol Res Commun*. 1985;17(6):501–512.
42. Hercogova J, Stanghellini E, Tsoureli-Nikita E, Menchini G. Inhibitory effects of Leopoldine spa water on inflammation caused by sodium lauryl sulphate. *J Eur Acad Dermatol Venereol*. 2002;16(3):263–266.
43. Bajgai J, Fadriquela A, Ara J, et al. Balneotherapeutic effects of high mineral spring water on the atopic dermatitis-like inflammation in hairless mice via immunomodulation and redox balance. *BMC Complement Altern Med*. 2017;17:481.
44. Tsoureli-Nikita E, Menchini G, Ghersetich I, Hercogova J. Alternative treatment of psoriasis with balneotherapy using Leopoldine spa water. *J Eur Acad Dermatol Venereol*. 2002;16(3):260–262.
45. Costantino M, Giacomelli A, Nappi G. Cave thermal therapy, antioxidant effect and osteoarthritis Med. *Clin Ter*. 2008;64:25–28.
46. Kadam DP, Suryakar AN, Ankush RD, Kadam CY, Deshpande KH. Role of oxidative stress in various stages of Psoriasis. *Indian J Clin Biochem*. 2010;25(4):388–392.
47. Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell*. 2001;104(4):487–501.
48. Joly F, Branka JE, Lefeuvre L. 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. *Dermatol Sci Appl*. 2014;4:99–106.
49. Sikar Akturk A, Ozdogan HK, Bayramgurler D, Cekmen MB, Bilen N, Kıran R. Nitric oxide and malondialdehyde levels in plasma and tissue of psoriasis patients. *JEADV*. 2012;26(7):833–837.
50. Costantino M, Marongiu MB, Iannotti S. A. Filippelli Sulphurous Mud balneotherapy: an possible strategy for de plaque psoriasis. *Paripex - Indian J Res*. 2015;4(3):69–74.
51. Lee YB, Lee JY, Lee HJ, et al. Immunomodulatory effects of balneotherapy with Hae-Un-Dae thermal water on imiquimod-induced psoriasis-like murine model. *Ann Dermatol*. 2014;26(2):221–230.
52. Riyaz N, Arakkal FR. Spa therapy in dermatology Indian. *J Dermatol Venereol Leprol*. 2011;77(2):128–134.
53. Golusin Z, Jovanovic M, Magda N, Stojanovic S, Matic M, Petrovic A. Effects of Rusanda Spa balneotherapy combined with calcipotriol on plaque psoriasis. *Vojnosant Pregl*. 2015;72(11):1010–1017.
54. Ricci S, Panduri S, Cervadoro G, Dattola E. Chronic contact eczema and thermal evironment: experience of clinical dermatology University of Pisa. *Clin Ter*. 2014;61(1-2):47–50.
55. Gregotti C, Veronesi AM, Fioravanti L, Nitto A, Gioglio L. Anti-inflammatory and antiphlogistic action of bicarbonate-calcium-magnesium thermal water when applied to skin treated with TCA 25%. *Clin Ter*. 2009;56(3-4):157–162.
56. Faga A, Nicoletti G, Gregotti C, Finotti V, Nitto A, Gioglio L. Effects of thermal water on skin regeneration. *Int J Mol Med*. 2012;29:732–740.
57. Casas C, Ribet V, Alvarez-Georges S, et al. Modulation of Interleukin-8 and staphylococcal flora by Avène hydrotherapy in patients suffering from chronic inflammatory dermatoses. *J Eur Acad Dermatol Venereol*. 2011;25(Suppl 1):19–23.
58. Passali D, Salerni L, D'Aco L, Gaudini E, Passali FM. The effects of bicarbonate-sulphate-alkaline- carbonic waters ("Santissima water"of Chianciano Thermae) in catarrhal diseases of upper respiratory ways. *Riv Orl Aud Fon*. 2003;23(1):39–49.
59. Ricevuti G, De Bernardi M, Re A, Pedrinazzi GM, Zanasi A, Barni S. Effects of inhalation crenotherapy on the respiratory tract of rats exposed to cigarette smoke Acts and Memories Academy. *Hist Health Art*. 1988;68(3):48–50.
60. Skobeloff EM, Spivey WH, McNamara RM, Greenspon L. Intravenous magnesium sulfate for the treatment of acute asthma in the Emergency Department. *J Am Med Assoc*. 1989;262:1210–1213.
61. Cantone E, Marino A, Ferranti I, et al. Nasal cytological assessment after crenotherapy in the treatment of chronic rhinosinusitis in the elderly. *Int J Immunopathol Pharmacol*. 2014;27(4):683–687.
62. Passariello A, Di Costanzo M, Terrin G, et al. Crenotherapy modulates the expression of pro-inflammatory cytokines and immunoregulatory peptides in nasal secretions of children with chronic rhinosinusitis. *Am J Rhinol Allergy*. 2012;26(1):e15–e19. https://doi.org/10.2500/ajra.2012.26.3733, 13.