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REVIEW PAPER

Clinical efficacy of medical hydrology: an umbrella review

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Abstract
The aim of this research was to summarize available scientific evidence on the efficacy of medical hydrology for the management of any health condition. The search was conducted on 26th March 2021, in the following databases: Medline (via PubMed), EMBASE, Web of Science, Cochrane Library, and Google Scholar. All relevant literature reviews investigating the clinical efficacy of interventions characterized by the use of natural mineral waters and muds were included. The quality of studies was assessed with the "AMSTAR 2" tool. After article screening, 49 reviews were included in this work. Overall, retrieved scientific evidence suggests that spa therapy is beneficial for patients affected by some specific musculoskeletal conditions, with improvements potentially lasting up to 9 months. Moreover, balneotherapy can be an integrative support for the management of chronic venous insufficiency and some inflammatory skin diseases like psoriasis. The role of spa therapy in rehabilitation appears relevant as well. More limited, although interesting evidence exists for inhalation and hydropinic therapies. Globally, retrieved evidence suggests that, besides individual wellbeing, medical hydrology can be useful for public health. In particular, higher-quality studies seem to support the integrative use of spa-related interventions for conditions like osteoarthritis, fibromyalgia, low back pain of rheumatic origin, and chronic venous insufficiency. However, the body of evidence has some limitations and further clinical trials should be designed for each relevant application to consolidate and expand acquired knowledge.

Keywords Medical hydrology · Clinical efficacy · Public health · Integrative medicine · Umbrella review

Introduction

Background and definitions

Medical hydrology (or balneology) is a biomedical discipline with a long-standing tradition, which investigates clinical uses and health-related applications of natural mineral waters and muds for preventive, therapeutic, and rehabilitative purposes (Nappi 2001; Gutenbrunner et al. 2010; Maraver and Karagülle 2012). These treatments are usually administered in health facilities labeled as "spa centers," where "spa" stands for *salus per aquam* or *sanitas per aquam*, an ancient Latin expression which literally refers to the pursuit of "health through water" (van Tubergen and van der Linden 2002).

According to the European Union (EU) law, as stated in the Council Directive 80/777/EEC, a natural mineral water is defined as a microbiologically wholesome water (originating in an underground water table or deposit and emerging from a spring), which can be distinguishable from ordinary drinking water by its nature and original purity (The European Parliament and the Council of the European Union 2009). In particular, natural mineral waters are characterized by a

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specific mineral content and biochemical composition and by certain effects, including their potential pharmacological, physiological, and clinical action (The European Parliament and the Council of the European Union 2009). In several European countries, this regulatory definition is also accepted by the scientific community (Gutenbrunner et al. 2010). Therefore, in this article, we referred to "natural mineral waters" or, simply, "mineral waters" following the above-mentioned description and indicating spring waters used for preventive, therapeutic, or rehabilitative purposes in spa centers.

With the aim of unequivocally classifying all spa-based interventions and considering a common set of definitions used in the scientific literature (Pittler et al. 2006; Gutenbrunner et al. 2010; Gomes et al. 2013; Fioravanti et al. 2017; Antonelli and Donelli 2018a), the following terms were used in this research work:

- "Balneotherapy": any treatment which only involves the partial or total-body immersion in natural mineral waters (Antonelli and Donelli 2018a; Antonelli et al. 2018). When sea water was used, the term "Talassotherapy" was adopted (Maraver et al. 2011).
- "Mud therapy": any treatment which only involves the application over skin of muds or other peloids, which were defined as natural products used as therapeutic agents and consisting of a mixture of minero-medicinal water with organic and inorganic material, like clay minerals (Carretero 2002). Although usually classified among balneotherapeutic interventions (Fioravanti et al. 2017), mud therapy was distinguished from standard balneotherapy for its specific characteristics.
- "Spa therapy": any spa-based multicomponent treatment which includes at least a treatment involving the therapeutic use of natural mineral waters (Pittler et al. 2006; Karagülle and Karagülle 2015; Antonelli and Donelli 2018a). Due to its complexity and integrated therapeutic action, fango-balneotherapy, namely mud baths followed or preceded by standard balneotherapy with mineral waters, was classified under this category.
- "Inhalation therapy": any treatment characterized by the inhalation of natural mineral waters and their gases in the form of vapors, nebulizations, aerosols, politzers, and humages (Costantino et al. 2006; Keller et al. 2014). Oral and nasal irrigations were also included in this category.
- "Hydropinic therapy": any treatment which implies the oral ingestion of natural mineral waters with medicinal properties (Albertini et al. 2007).

Sometimes, especially in Italy or France, the old-style term "chreno-therapy" (from the Greek "krḗnē": spring, well, fountain) is adopted to indicate all interventions based on the external and/or internal administration of mineral waters and muds (Nappi 2001; Gutenbrunner et al. 2010; Maraver and Karagülle 2012). However, this term was not used in this article to avoid potential misunderstandings. Whenever hydrologic treatments involved the sole use of tap non-mineral water, for example in the control group, the generic term "hydrotherapy" was adopted.

Rationale

In Italy, costs of treatments based on natural mineral waters and therapeutic muds can be partially or fully covered by the National Healthcare System, and the same happens in other countries, both within and outside Europe (Gutenbrunner et al. 2010). In accordance with a regulatory document approved by the Italian Ministry of Health, conditions which can benefit from medical hydrology include osteoarthritis, extra-articular rheumatisms, chronic sinusitis and rhinosinusitis, vasomotor rhinopathy, chronic laryngopharyngitis, chronic catarrhal otitis, tubaric stenosis of flogistic origin, chronic bronchitis, psoriasis, eczema and atopic dermatitis, seborrheic dermatitis, chronic venous insufficiency, constipation due to irritable bowel syndrome, dyspepsia caused by gastroenteric or biliary dysfunction, recurrent kidney stones, and some forms of chronic vaginitis (Ministero della Sanità 1995).

Globally, these conditions are mostly caused by chronic diseases with an epidemiologically considerable impact on health-related quality of life (QoL). For example, osteoarthritis is a frequent degenerative disorder of the musculoskeletal system, especially among elderly subjects, with around 14 million patients only in the USA, and it is expected to become one of the leading causes of disability worldwide (Vina and Kwoh 2018). A relevant impact on public health is also shared by other health conditions which can benefit from spa-based interventions, such as fibromyalgia (Queiroz 2013), chronic venous insufficiency (Al Shammeri et al. 2014), chronic inflammatory respiratory diseases (Ferrante et al. 2017), and phlogistic skin disorders like psoriasis (Rachakonda et al. 2014).

However, the above-mentioned clinical indications were last updated and revised years ago (Ministero della Sanità 1995), and the most recent attempt to collect all available evidence on the topic with a cross-cutting approach dates back to March 2014, when the "Hydroglobe" project was published by a panel of experts with the technical support of the World Health Organization (WHO) (Vv.Aa. 2014). In the light of what stated above, considering that medical hydrology has a long-standing tradition (a), that mineral waters and therapeutic muds are easily available as natural resources (b), that spa-based interventions are usually prescribed for epidemiologically relevant health conditions (c), and that scientific evidence rapidly evolves (d), it can be useful to synthesize and critically appraise available findings on the topic with a systematic approach, thus following the basic principles of Evidence-Based Medicine (EBM). This would help to outline an updated list of evidence-based indications for treatments with mineral waters and therapeutic muds, and to guide further research in this field, which is important for both individual wellbeing and public health.

Study objective

The aim of this research work was to summarize available scientific evidence on the efficacy of medical hydrology for the management of any health condition with a critical assessment of all relevant literature reviews.

Methods

Study design and protocol registration

A systematic review of literature reviews and meta-analyses (umbrella review) was conducted following the internationally accepted *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (Moher et al. 2009). Additional methodological recommendations for umbrella reviews were taken into account to improve the overall quality of this work (Fusar-Poli and Radua 2018). The review protocol was registered in *Open Science Framework* (OSF) under the following DOI: 10.17605/OSF.IO/2NJ5X (https://osf.io/2nj5x).

Eligibility criteria

The following PICOS criteria were applied for the inclusion and exclusion of studies in this review:

- Population: healthy subjects and/or individuals affected by any disease diagnosed in accordance with validated clinical criteria.
- Intervention: all spa interventions based on the use of natural mineral waters and therapeutic muds (balneotherapy, mud therapy, spa therapy, inhalation/irrigation therapy, hydropinic therapy). Reviews were excluded when they focused on studies with non-mineral tap water.
- Control: any type, including no control.
- Outcomes: any relevant clinical outcome (symptomatic and functional improvements, variations in laboratory parameters, reduction of drug consumption, effects on health-related quality of life).
- Study design: systematic reviews and meta-analyses of clinical studies. Reviews were excluded when they had no description of research methods and when they included only pre-clinical laboratory studies. Relevant high-quality narrative reviews (reporting a full description of their research methods and based on a quite extensive literature search) were also included along with systematic reviews, but they were synthesized in a separated section of the manuscript. Following the Cochrane recommendations, systematic reviews were defined as any "review [that] attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question" (The Cochrane Group about Cochrane Reviews 2020). Reviews had to be published in a refereed journal to be eligible for inclusion.

Information sources

Following shared recommendations for optimal database combinations (Bramer et al. 2017), the literature search was conducted in Medline (via PubMed), EMBASE, Web of Science, Cochrane Library, and Google Scholar from inception to March 2021.

Search

The search was conducted on 26th March 2021. A first tentative pilot search was performed by one author only (M.A.) on 7th January 2020, then, after refinements, the entire search was updated and all articles were screened again by two authors independently (M.A., D.D.).

The following keywords were used: "balneotherapy," "hydrotherapy," "thalassotherapy," "spa therapy," "water therapy," "aquatic therapy," "mud therapy," "peloid therapy," "psammotherapy," "inhalation therapy," "endotympanic insufflation," "politzer," "cave therapy," "hydropinotherapy," "mineral water*," "thermal water*," "hot spring water*." Specific search strategies adopted for all screened databases were disclosed in the Electronic supplementary materials.

In order to narrow down the search and increase its precision, keywords used in Google Scholar were markedly simplified. References of important regulatory papers and overviews of reviews were screened with a "snowballing technique" for an additional check. An author (M.V.), with his long-standing experience in medical hydrology research, performed a supplementary search to make sure not to have missed any highly relevant articles in this field of study.

Study selection

The article screening process was conducted with the help of EndNote® software (version X4) by two authors independently (M.A., D.D.). In cases of discrepancies, another author (C.P.) was consulted and disagreements were discussed until consensus was reached. Only systematic reviews and meta-analyses (along with the most relevant and extensive narrative reviews) matching the above-mentioned PICOS criteria were included in this umbrella review. All studies written in English, French, Italian, Spanish, and Portuguese were considered eligible for inclusion. Studies matching inclusion criteria but written in other languages (German, Japanese) were consulted with the support of a translator. In order to maximize retrievable evidence on the topic and to reduce the risk of publication bias, even articles with only an English abstract available for consultation were included in this umbrella review. This detail was reported in the table describing the main characteristics of included systematic reviews, although it was not possible to assess the quality of these research works due to the lack of detailed methodological information.

Data collection process

Data extraction was conducted manually with a predefined Excel® table designed in accordance with the PICOS criteria. Data extraction was performed by one author (M.A.) with a second check by another author (C.P.). In any case of missing data, authors were contacted via e-mail or through ResearchGate®. The full-text version of a review article was retrieved in this way (Raza et al. 2020).

Data items

Data items extracted from included studies were the following ones: the number and main characteristics of study populations, the type of intervention and control, all relevant clinical outcomes, and the study design (namely whether each review was systematic or narrative, and if it was coupled or not with a meta-analysis).

To properly account for the reliability and consistency of clinical evidence on the topic, it was decided to also report the overall quality of primary studies analyzed in all systematic reviews eligible for inclusion. In this regard, the set of trials included in each review was globally judged as characterized by a good (1), fair (2), or poor (3) quality, depending on the risk-of-bias assessment performed by the review authors. This system is based on the three-tier quality rating of scientific studies recommended by the American National Institutes of Health (National Institutes of Health Study Quality Assessment Tools 2021).

Risk of bias and quality of studies

The quality of included systematic reviews was independently evaluated by two authors (M.A., D.D.) with a dedicated appraisal tool called "AMSTAR 2," specifically developed and validated by a team of expert methodologists for this purpose (Shea et al. 2017). In cases of disagreement, items were discussed with another author (C.P.) until consensus was reached. The AMSTAR 2 tool provides a 16-item checklist aimed to explore different methodological domains, including the appropriateness of inclusion/exclusion criteria, search strategies, article selection, data extraction, risk-of-bias assessment, heterogeneity evaluation, quantitative synthesis, and critical discussion. Each item corresponds to a question, which can be answered with "yes" or "no" (sometimes "yes, but partially" is available as a middle response). Included reviews were evaluated one by one and their overall quality was rated as:

- High quality (A) if zero or one non-critical weaknesses were found.
- Moderate quality (B) if two or more non-critical weaknesses were found.
- Low quality (C) if one critical flaw (with or without non-critical weaknesses) was found.
- Very low quality (D) if two or more critical flaws (with or without non-critical weaknesses) were found.

As reported in our study protocol, it was originally planned to use the appraisal tool developed by the American NIH (National Institutes of Health Study Quality Assessment Tools 2021) to assess the quality of included systematic reviews. However, in consideration of the need for a deeper methodological analysis of retrieved reviews, it was eventually decided to resort to the more specific and widely used AMSTAR 2 tool.

The methodological quality of narrative reviews was assessed with the SANRA scale (Baethge et al. 2019) during the article selection process and only higher-quality narrative reviews were included in this work. The SANRA is a 6-item scale which evaluates the relevance/importance of a narrative review (1), whether its aim is sufficiently focused (2), if the literature search is broad enough (3), whether referencing (4), scientific reasoning (5), and presentation of data (6) are appropriate. Each item score can vary from 0 to 2, and the overall review quality score can range from 0 to 12 (high-quality narrative reviews usually score 9 or more SANRA points).

Publication bias and potential biases across studies were only qualitatively assessed because no quantitative synthesis was feasible due to the detection of a high level of heterogeneity across included studies.

Synthesis of results

The main characteristics of included reviews were reported in two tables, then retrieved evidence was qualitatively synthesized and critically discussed. Results of the study quality assessment were used for a critical discussion. Included reviews were also grouped on the basis of intervention type, health condition of interest, study design (systematic/narrative) and methodological quality. Systematic reviews specifically providing regional data, namely reviews appraising evidence from clinical studies only conducted in a given country of the world, were summarized in another table and mentioned in the "Discussion" section for better comprehensiveness.

Results

Study selection

Overall, the literature search yielded 803 results and, after screening and selection of potentially eligible articles, 49 reviews (41 systematic and 8 narrative reviews) were eventually included in this research work. Details of the article selection process, along with the main reasons for exclusion of non-eligible studies, were summarized in a dedicated flowchart (Fig. 1). The list of all articles eligible for a full-text assessment and then excluded after a thorough evaluation was provided in the Electronic supplementary materials. The quality of a review available as a conference abstract in a refereed journal (Cao et al. 2020) was assessed on the basis of information retrieved from the corresponding preprint (https://www.researchsquare.com/article/rs-16293/v1). An article was kindly provided by the authors after our direct inquiry

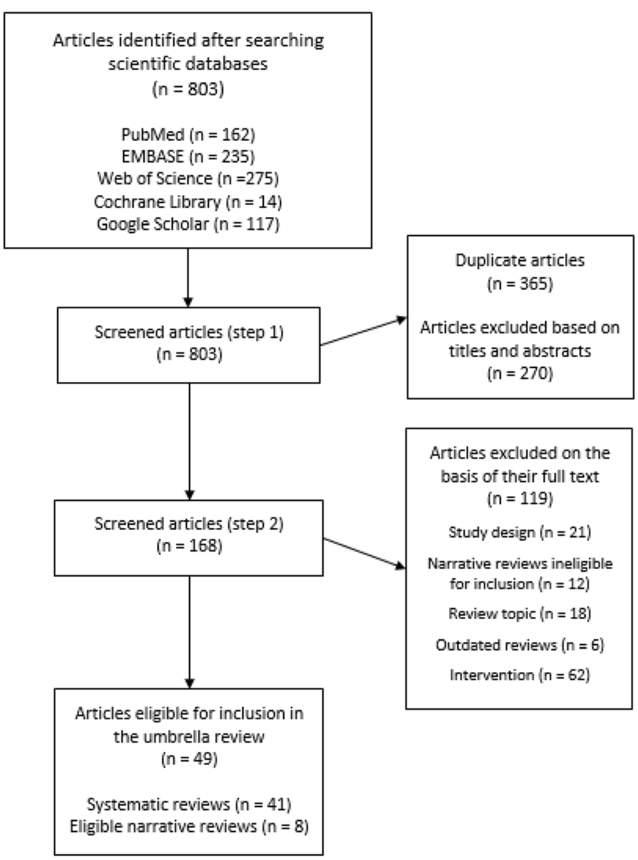


Fig. 1 Flow-chart describing the study selection process. The flow-chart was adapted from the model recommended by the PRISMA guidelines (Moher et al. 2009)

(Raza et al. 2020). It was not possible to consult the full-text version of a review, but this study was included all the same for better comprehensiveness (essential data were extracted from the abstract) (Zhen-han et al. 2014). A meta-analysis found through snowballing and published as a Ph.D. thesis was excluded from the main search but mentioned in the Discussion section to better analyze the mechanisms of action of mud therapy for osteoarthritis (Crespin 2017).

Characteristics of included studies

The main characteristics of all included studies, collected and described in accordance with the PICOS criteria, are reported in Table 1 (systematic reviews) and Table 2 (narrative reviews), along with a brief summary of the authors' conclusions and, for systematic reviews, with their overall methodological quality evaluated in accordance with the AMSTAR-2 recommendations (Bohmer et al. 2000; Brosseau et al. 2002; Kamioka et al. 2006; Pittler et al. 2006; Verhagen et al. 2007, 2015; Forestier and Françon 2008; Schuh 2009; Harzy et al. 2009; Falagas et al. 2009; Langhorst et al. 2009; Guidelli et al. 2012; Fraioli et al. 2013, 2018; Espejo-Antúnez et al. 2013; Liu et al. 2013; Zhen-han et al. 2014; Roques 2014; Keller et al. 2014; Naumann and Sadaghiani 2014; Karagülle and Karagülle 2015; Françon et al. 2015; Tenti et al. 2015; Stier-Jarmer et al. 2015; Fortunati et al. 2016; Xiang et al. 2016; Forestier et al. 2016, 2017; Bender 2016; Santos et al. 2016; Matsumoto et al. 2017; Naumann et al. 2017; Passali et al. 2017; Morer et al. 2017; Casale et al. 2018; Antonelli and Donelli 2018a; Antonelli et al. 2018; Beer et al. 2018; An et al. 2019; Corvillo et al. 2019; de Moraes Silva et al. 2019; Bai et al. 2019; Yuan et al. 2019; Raza et al. 2020; Sulaiman et al. 2020; Hou et al. 2020; Cao et al. 2020; Cacciapuoti et al. 2020; Gravelier et al. 2020).

Population

The number of study participants whose data were analyzed within included systematic reviews varied from a minimum of 54 (Bohmer et al. 2000) to a maximum of 13,782 (Stier-Jarmer et al. 2015), with a median value of 731. In the majority of included reviews, regardless of their design (systematic or narrative), study participants were patients with chronic conditions, such as rheumatic (osteoarthritis, fibromyalgia, back pain of rheumatic origin, rheumatoid arthritis), cardiovascular (chronic venous insufficiency, hypertension), dermatologic, respiratory, otorhinolaryngological, neurologic, digestive, and urologic diseases (Fig. 2). In a review, the effects of hydropinic therapy on healthy subjects were studied (Bohmer et al. 2000), whereas studies with both healthy and diseased individuals were analyzed in three research works (Antonelli and Donelli 2018a; An et al. 2019; Sulaiman et al. 2020).

Table 1 Main characteristics (PICOS, methodological quality, and study authors' conclusions) of included systematic reviews

Reference	Population (*n*)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
An et al. (2019)	Both healthy and diseased subjects (212)	BT	Any type	Various (physiological and clinical)	SR (13 clinical studies of any type)	D	?	Demonstration of various cardiovascular and neuromuscular effects, but uncertain conclusions.
Brosseau et al. (2002)	Patients with knee OA (172)	BT	Any type	Pain and functionality	SR (3 RCTs)	C	2	Only short-term effects were demonstrated, with significant benefits in terms of pain relief exclusively shown for baths in Dead Sea or hot sulfur water.
Cao et al. (2020)	Patients with fibromyalgia (611)	BT	Any type	Pain, QoL and mood	SR + MA (10 RCTs) - CP	C	3	Pooled evidence from analyzed RCTs (follow-up: from 12 to 48 weeks) indicates that BT may reduce pain and improve QoL of patients with fibromyalgia.
Corvillo et al. (2019)	Patients with neck pain of different origins (658)	BT	No treatment or standard rehabilitation	Pain, functionality, QoL and mood	SR (13 clinical studies of any type)	D	2	Beneficial effects for all studied algofunctional outcomes, and for psychophysical wellbeing.
Falagas et al. (2009)	Patients with any disease (1720 subjects with rheumatic conditions)	BT	Any type	Any relevant clinical outcome	SR (29 RCTs)	C	2	Clinical improvement of several rheumatic diseases (OA, fibromyalgia, ankylosing spondylitis, rheumatoid arthritis). Preliminary evidence of benefits for psoriasis and Parkinson's disease.
Harzy et al. (2009)	Patients with knee OA (493)	BT	Any type	Pain, functionality, drugs	SR (9 RCTs)	B	2	Beneficial effects on pain and joint functionality lasting up to 24 weeks from intervention.
de Moraes Silva et al. (2019)	Patients with chronic venous insufficiency in leg veins (891)	BT	Any type	Any relevant clinical and QoL outcome	SR+MA (7 RCTs)	A	3	Low-to-moderate evidence indicates beneficial effects in terms of pain, QoL, and skin pigmentation due to chronic venous insufficiency.
Schuh (2009)	Patients with any disease (?)	BT (TT)	Any type	Any relevant clinical outcome	SR (12 studies related to marine climatotherapy and TT)	D	?	A combination of thalassotherapy with marine climatotherapy can exert positive effects on psoriasis, atopic dermatitis, and bronchial asthma.
Yuan et al. (2019)	Patients with arterial hypertension (1122)	BT	Any type	Variations of blood pressure	SR (12 RCTs)	C	3	No worsening of blood pressure parameters.
Beer et al. (2018)	Patients with any disease (728)	MT	Any type	Any relevant clinical outcome	SR (35 clinical studies)	D	2	High-quality evidence indicates a beneficial effect for the symptomatic treatment of OA and fibromyalgia.
Espejo-Antunez et al. (2013)	Patients with knee OA (2102)	MT	Any type	Symptoms and QoL	SR (20 studies of any type)	D	2	Significant improvement of pain, general symptoms, and QoL.
Hou et al. (2020)	Patients with knee OA (1106)	MT	Any type	Pain and functionality	SR+MA (11 RCTs)	B	3	Significant amelioration of knee pain and function.
Liu et al. (2013)	Patients with knee OA (410)	MT	Any type	Pain and functionality	SR+MA (7 RCTs)	D	2	Significant improvement of OA-related pain.
Xiang et al. (2016)	Patients with knee OA (1010)	MT	Any type	Functionality	SR+MA (10 RCTs)	C	2	No significant improvement in joint functionality.
Zhen-han et al. (2014)	Patients with knee OA (410)	MT	Any type	Pain	SR+MA (7 RCTs) - abstract only	?	?	Mud therapy can significantly attenuate knee osteoarthritis pain.
Antonelli and Donelli (2018)	Both healthy and diseased subjects (684)	SPA-T	Any type	Variations of salivary or serum cortisol levels	SR (15 clinical studies of any type)	C	2	The effect on cortisol levels suggests that intervention can have an anti-stress action and improve stress resilience.
Antonelli et al. (2018)	Patients with knee OA (1599)	SPA-T	Any type	QoL, algofunctional indices, drugs	SR+MA (17 RCTs)	C	3	Significant improvement of QoL. Beneficial effects on algofunctional indices and painkiller intake.
Bai et al. (2019)	Patients with chronic LBP (1038)	SPA-T	Any type	Back pain and mobility	SR+MA (12 RCTs)	C	2	Significant improvement for back pain and functionality.
Forestier and Francon (2008)	Patients with OA of the limbs (1658)	SPA-T	Any type	Pain, functionality, QoL	SR+MA (19 RCTs)	D	2	Suggestive evidence of a possible beneficial effect, but analyzed studies have some limitations.
Forestier et al. (2016)	Patients with knee OA (2917)	SPA-T	Any type	Any relevant clinical outcome	SR (30 RCTs)	C	2	Evidence of relevant clinical improvements lasting, on average, from 3 to 6 months (and up to 9 months) after intervention.
	Patients with chronic LBP (2146)	SPA-T	Any type		SR (18 RCTs)	C	2	

Table 1 (continued)

Reference	Population (*n*)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Forestier et al. (2017)				Pain, functionality, QoL, drugs				Evidence of improvements in pain, disability, and QoL, lasting 3–6 months after intervention. Possible reduction of painkiller intake.
Fraioli et al. (2013)	Patients with fibromyalgia (271)	SPA-T	Any type	Pain, symptoms and mood	SR (7 studies)	D	?	Evidence of symptomatic improvement, including pain and mood (depression).
Fraioli et al. (2018)	Patients with knee OA (1649)	SPA-T	Any type	Pain, functionality, QoL, drugs	SR (12 clinical studies)	D	?	Improvement of pain, joint mobility, NSAID intake, and QoL.
Gravelier et al. (2020)	Patients with burn scars (115)	SPA-T	Any type	Pain, skin elasticity, QoL	SR (2 RCTs)	C	3	Potential beneficial effects for burn scar recovery, but further scientific evidence is needed.
Kamioka et al. (2006)	Patients with any disease (1425)	SPA-T	Any type	Pain, QoL, drugs, occupational functionality and healthcare costs	SR (18 RCTs)	D	2	Amelioration of all analyzed outcomes with high-quality studies mostly supporting the efficacy of intervention for rheumatic disorders.
Karagulle and Karagulle (2015)	Patients with chronic LBP (769)	SPA-T	Any type	Any relevant clinical outcome	SR (8 RCTs)	D	?	Evidence of an improvement in symptomatic management, but further studies are needed to confirm these results.
Langhorst et al. (2009)	Patients with fibromyalgia (446)	SPA-T	Any type	Any clinical and QoL-related outcome	SR+MA (10 RCTs)	A	2	Moderate evidence of beneficial effects on health-related QoL.
Matsumoto et al. (2017)	Patients with knee OA (734)	SPA-T	Any type	Pain and functionality	SR+MA (8 RCTs)	B	3	Possible beneficial effects, but high heterogeneity is found across studies and evidence is not of sufficiently high quality.
Morer et al. (2017)	Patients with any rheumatic condition (1118)	SPA-T	HT	Pain, functionality, drugs, QoL, laboratory parameters	SR (27 RCTs)	D	3	Possible beneficial effects, but high heterogeneity and potential risk of bias is reported within and across available studies.
Naumann and Sadaghiani (2014)	Patients with fibromyalgia (553)	SPA-T	Any type	Pain, functionality, QoL, mood	SR+MA (12 RCTs about SPA-T and 12, excluded, about HT)	B	2	Significant improvements of symptoms and QoL with potentially long-lasting effects on pain. No significant effect was observed on depressive symptoms
Pittler et al. (2006)	Patients with chronic LBP (674)	SPA-T	Any type	Pain, functionality, QoL, drugs	SR+MA (5 RCTs)	B	2	Scant but promising evidence which suggests a possible clinical benefit.
Raza et al. (2020)	Patients with knee OA (831)	SPA-T	Any type	Pain and functionality	SR+MA (10 RCTs)	C	2	Significant improvement in pain and functionality, as measured with the WOMAC scale.
Santos et al. (2016)	Patients with rheumatoid arthritis (496)	SPA-T	Any type	Pain, functionality, QoL, drugs, laboratory parameters	SR (8 RCTs)	B	2	Evidence of a beneficial effect on studied outcomes even up to 3 months after intervention.
Verhagen et al. (2007)	Patients with OA (498)	SPA-T	Any type	Pain, functionality, QoL	SR+ MA (7 RCTs)	A	3	A positive effect is found when intervention is compared to no treatment, but the quality of evidence is low.
Verhagen et al. (2015)	Patients with rheumatoid arthritis (579)	SPA-T	Any type	Pain, functionality, QoL	SR+MA (9 RCTs)	A	3	Insufficient evidence to draw conclusions on the topic.
Casale et al. (2018)	Patients with rhinosinusitis (663)	IT/IR	Any type	Functionality of upper airways	SR (11 RCTs)	D	2	Nasal irrigations with mineral waters can be clinically beneficial for patients with rhinosinusitis in terms of endoscopic scores and mucociliary clearance if compared to isotonic solution.
Keller et al. (2014)	Patients with rhinosinusitis (840)	IT/IR	Any type	Functionality of upper airways	SR+MA (13 clinical studies of any type)	D	2	Mineral waters (for example, those ones rich in sulfur) can have an integrative role in the management of chronic inflammatory diseases of the upper respiratory tract.
Böhmer et al. (2000)	Healthy subjects (54)	HPT (mineral waters with high calcium content)	Dairy products	Bioavailability of calcium	SR (4 controlled studies)	D	?	Bioavailability of calcium from calcium-rich waters is comparable to that one from dairy product consumption.
Naumann et al. (2017)	Patients with cardiovascular risk factors (1089)	HPT (various mineral waters)	Other drinks	Glycemic control	SR (15 RCTs)	C	3	Bicarbonate- and magnesium-rich waters may have a positive impact on glycemic control.
Sulaiman et al. (2020)	Both healthy and diseased subjects at risk of kidney stone	HPT (mineral waters with high calcium,	Tap water	Kidney stone prevention,	SR (10 clinical interventional studies and 5	C	2	Bicarbonate- and magnesium-rich waters may be useful against kidney stone formation. Consumption of waters with a high calcium content can lead to hypercalciuria.

Table 1 (continued)

Reference	Population (*n*)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
	formation (470 involved in interventional studies)	bicarbonate or magnesium content)		especially calcium stones	observational studies)			
Stier-Jarmer et al. (2015)	Patients with any non-musculoskeletal disease (13782)	Any hydrologic therapy	Any type	Any improvement assessed clinically or with diagnostic devices	SR (41 clinical studies of any type)	B	3	Clinical benefits for various skin diseases (atopic dermatitis, psoriasis, ictiosis), respiratory and ENT illnesses (rhinosinusitis, COPD, catarrhal otitis), vascular problems (hypertension, chronic venous insufficiency), digestive complaints (dyspepsia, irritable bowel syndrome), and neuropsychiatric conditions (peripheral neuropathy, Parkinson's disease, psychophysical stress).

Included reviews are grouped on the basis of analyzed intervention and alphabetically sorted according to the first author's surname

BT, balneotherapy (only baths with mineral waters); *COPD*, chronic obstructive pulmonary disease; *CP*, conference proceedings (review presented at a conference/lecture/symposium and then published in a refereed journal as an abstract); *HPT*, hydropinic therapy (drinking mineral waters); *HT*, hydrotherapy (use of tap non-mineral water); *IT/IR*, inhalation therapy/irrigations (aerosols, vapors, nebulizations, humages, and oral/nasal irrigations); *LBP*, low back pain; *MA*, meta-analysis; *MT*, mud therapy (use of therapeutic muds); *NSAID*, nonsteroidal anti-inflammatory drug; *OA*, osteoarthritis; *QoL*, quality of life; *RCT*, randomized controlled trial; *RQ*, review quality or overall quality assessed on the basis of review methods (*A*, high quality; *B*, moderate quality; *C*, low quality; *D*, very low quality; "?" the review quality was not assessable because the full-text version was irretrievable); *SPA-T*, spa therapy (multicomponent spa-based treatments); *SR*, systematic review; *TQ*, trial quality or average quality of clinical studies included in each analyzed review (1, high quality; 2, fair quality; 3, poor quality; "?" trial quality was not assessed by the authors of included reviews); *TT*, thalassotherapy (baths with sea water)

Intervention

Most included reviews analyzed the efficacy of balneotherapy ($n = 10$) and mud therapy ($n = 6$) alone or in combination with other non-spa-related treatments ($n = 26$) (Fig. 3). In some cases, spa therapy also involved physical rehabilitation, relaxing massage, diet prescriptions for weight loss or for preventive purposes, pharmacological treatments, and psychological support. Only in a few reviews the efficacy of hydropinic therapy ($n = 3$) and inhalation therapy or nasal irrigations ($n = 3$) were investigated. In one ($n = 1$) research work, the efficacy of any type of spa-related therapy was studied (Stier-Jarmer et al. 2015).

Control

Most analyzed reviews did not have specific restrictions in terms of control type for primary study inclusion. In a systematic review, subjects with cervical pain undergoing balneotherapy were compared to individuals sharing the same health condition who did not receive any treatment or who were administered a cycle of standard rehabilitation (Corvillo et al. 2019). In two research works, the therapeutic efficacy of spa therapy was compared to hydrotherapy with tap non-mineral water (Morer et al. 2017; Sulaiman et al. 2020). Finally, in other systematic reviews, the health effect of orally taking two different mineral waters was compared with modifications induced by consuming other foods and nutritional products (Bohmer et al. 2000; Naumann et al. 2017).

Outcomes

Main clinical outcomes of analyzed reviews included the following ones: symptoms (mostly pain, evaluated with a Visual Analog Scale), functionality and disability (sometimes assessed in combination with pain using algo-functional scales), drug consumption (especially with regard to the long-term intake of painkillers), quality of life (measured with specific questionnaires), results of various diagnostic investigations and laboratory parameter assessment (including biomarkers of inflammation, metabolic indices, circulating levels of hormones, and other biochemical substances).

Study design

Forty-one (41) included research works were systematic literature reviews, and seventeen (17) of them were also coupled with a meta-analysis (Pittler et al. 2006; Verhagen et al. 2007, 2015; Forestier and Françon 2008; Langhorst et al. 2009; Liu et al. 2013; Zhen-han et al. 2014; Keller et al. 2014; Xiang et al. 2016; Matsumoto et al. 2017;

Table 2 Main characteristics (PICOS and study authors' conclusions) of included high-quality narrative reviews

Reference	Population (*n*)	Intervention	Control	Outcomes	Study design	Conclusions
Cacciapuoti et al. (2020)	Patients with chronic inflammatory skin diseases (?)	BT	Any type	Various health-related outcomes	NR (?)	Benefits for psoriasis and atopic dermatitis, but also for pruritus, prurigo, lichen ruber planus, acne vulgaris, and seborrheic dermatitis.
Bender (2016)	Patients with OA (?)	SPA-T	Any type	Pain and QoL	NR (50+ RCTs) - CP	Positive effect on pain and QoL of patients with OA of various joints.
Fortunati et al. (2016)	Patients with hand OA (168)	SPA-T	Any type	Pain, functionality, QoL	NR (3 RCTs)	Suggestive evidence of a potential benefit, but further investigation is advised to draw conclusions.
Francon et al. (2015)	Patients with chronic pain of rheumatic origin (2905)	SPA-T	Any type	Pain, functionality, QoL, drugs	NR (28 RCTs)	Improvement of pain, joint mobility, painkiller intake, and QoL.
Guidelli et al. (2012)	Patients with fibromyalgia (314)	SPA-T	Any type	Pain, functionality, QoL, mood	NR (8 RCTs)	Evidence of benefits in terms of pain, functionality, QoL, and mood, lasting 3 to 9 months after intervention.
Roques (2014)	Patients with any disease (?)	SPA-T	Any type	Any relevant clinical outcome	NR (90 RCTs) - CP	Beneficial effects mostly for arthrorheumatic diseases, but even for psoriasis, atopic dermatitis, vessel disorders of lower limbs, gynecological conditions, and psychosomatic diseases.
Tenti et al. (2015)	Patients with knee OA (1198)	SPA-T	Any type	Pain, functionality, QoL, drugs	NR (14 RCTs)	Evidence of a positive effect on pain, disability, and QoL, which may last up to 6–9 months.
Passali et al. (2017)	Patients with chronic rhinosinusitis, allergic rhinitis or asthmatic bronchitis (110)	IT	Any type	Functionality of upper and lower airways	NR (4 clinical studies of any type)	A 2-week inhalation therapy with radon-enriched water may improve nasal function and respiratory obstruction in patients with allergic respiratory diseases.

Included reviews are grouped on the basis of analyzed intervention and alphabetically sorted according to the first author's surname

BT, balneotherapy (only baths with mineral waters); *COPD*, chronic obstructive pulmonary disease; *CP*, conference proceedings (review presented at a conference/lecture/symposium and then published in a refereed journal as an abstract); *HT*, hydrotherapy (use of tap non-mineral water); *IT/IR*, inhalation therapy/irrigations (aerosols, vapors, nebulizations, humages, and oral/nasal irrigations); LBP, low back pain; *MT*, mud therapy (use of therapeutic muds); *NR*, narrative review; *NSAID*, nonsteroidal anti-inflammatory drug; *OA*, osteoarthritis; *QoL*, quality of life; *RCT*, randomized controlled trial; *SPA-T*, spa therapy (multicomponent spa-based treatments)

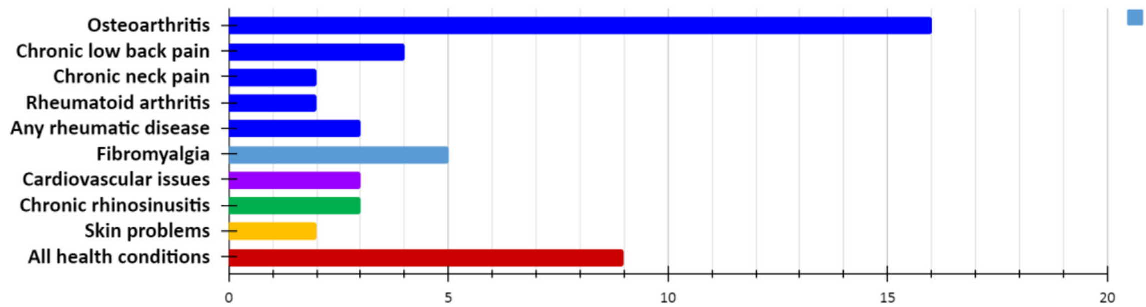


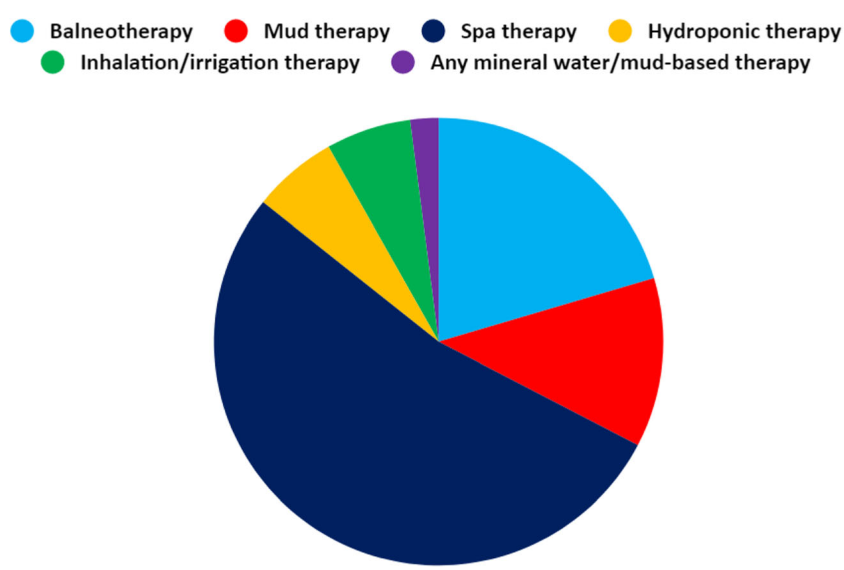
Fig. 2 Number of included reviews for each health condition

Naumann et al. 2017; Antonelli et al. 2018; de Moraes Silva et al. 2019; Bai et al. 2019; Raza et al. 2020; Hou et al. 2020; Cao et al. 2020). Eight (8) included reviews had a narrative design, but they still provided an extensive, quasi-systematic, and valuable overview of the scientific literature (Guidelli et al. 2012; Roques 2014; Françon et al. 2015; Tenti et al. 2015; Fortunati et al. 2016; Bender 2016; Passali et al. 2017; Cacciapuoti et al. 2020), thus outlining a state-of-the-art description of specific subtopics, such as the efficacy of spa therapy for respiratory illnesses (Passali et al. 2017), skin diseases (Cacciapuoti et al. 2020), or hand osteoarthritis (Fortunati et al. 2016). The number of clinical studies included in the systematic reviews varied from a minimum of 3 (Brosseau et al. 2002; Fortunati et al. 2016) to a maximum of 41 (Stier-Jarmer et al. 2015), with a median of 12. Such primary studies were mostly Randomized Controlled Trials, although some of them were characterized by a different design, like nonrandomized trials, uncontrolled studies, and observational investigations. The quality of clinical studies tended to range from fair to poor, with a potential risk of bias mostly arising from small sample size, lack of adequate control, no randomization of trial participants, and poor information about blinding of intervention.

Quality of included studies

After the methodological assessment of included systematic reviews with the AMSTAR 2 tool, the quality of analyzed research works was judged as good (A) to moderate (B) in 11 cases (Pittler et al. 2006; Verhagen et al. 2007, 2015; Harzy et al. 2009; Langhorst et al. 2009; Naumann and Sadaghiani 2014; Stier-Jarmer et al. 2015; Santos et al. 2016; Matsumoto et al. 2017; de Moraes Silva et al. 2019; Hou et al. 2020) and low (C) to very low (D) in the remaining cases, as reported in Table 1 (see the Supplementary Materials for further details). It was not possible to assess the quality of a systematic review because its full-text version was unavailable (Zhen-han et al. 2014). In general, the most frequent methodological weaknesses found within included reviews were excessively narrow search strategies, a poor description of study selection and evaluation processes, and limited consideration of the trial risk-of-bias assessment for informing a critical discussion. Major strengths were usually a clear definition of the research question and, where applicable, a good methodological level of meta-analyses.

Fig. 3 Number of included reviews for each type of therapy



Discussion

Efficacy of interventions

Scientific evidence from included reviews indicates that balneotherapy, mud therapy, and spa therapy can significantly improve clinical parameters like pain, joint functionality, mobility, and quality of life of patients with chronic musculoskeletal conditions, mostly osteoarthritis, fibromyalgia, and other pain-related rheumatic diseases. For these subjects, beneficial effects may last up to 9 months after intervention (on average, 3 to 6 months) (Forestier et al. 2016, 2017), and clinical improvements are associated with a reduced intake of analgesic drugs (Françon et al. 2015; Tenti et al. 2015; Forestier et al. 2017; Fraioli et al. 2018; Antonelli et al. 2018). Furthermore, in two included research works, it was demonstrated that balneotherapy is superior to the same treatment administered in pools with tap water ("sham balneotherapy") in terms of clinical benefits and improved quality of life among patients with osteoarthritis and fibromyalgia, thus underscoring the contribution of the specific biochemical composition of natural mineral waters to the overall therapeutic effect (Morer et al. 2017; Antonelli et al. 2018).

With regard to vascular health, balneotherapy can be useful for the amelioration of pain, quality of life, and skin pigmentation due to chronic venous insufficiency in lower limbs (Stier-Jarmer et al. 2015; de Moraes Silva et al. 2019), and it appears not to have negative effects on blood pressure levels (Yuan et al. 2019). More limited evidence suggests that balneotherapy, including talassotherapy (sea water baths), can be beneficial for patients with skin diseases like psoriasis and atopic dermatitis (Schuh 2009; Falagas et al. 2009; Stier-Jarmer et al. 2015; Cacciapuoti et al. 2020), and possibly for the integrative treatment of burn scars (Gravelier et al. 2020).

Balneotherapy, mud therapy, and spa therapy can also improve mental wellbeing and psychophysical stress, and this is demonstrated by studies in which stress hormone levels were measured (Roques 2014; Stier-Jarmer et al. 2015; Antonelli and Donelli 2018a). An interesting role for orthopedic or neurological patients of aquatic rehabilitation in pools with natural mineral waters was underscored by several authors, with beneficial effects on the most important clinical outcomes (Falagas et al. 2009; Stier-Jarmer et al. 2015).

With regard to inhalation therapy, clinical improvements were observed not only in patients with diseases of the upper and lower respiratory tract, mostly chronic rhinosinusitis and bronchitis (Schuh 2009; Keller et al. 2014; Stier-Jarmer et al. 2015; Casale et al. 2018), but even in subjects with chatarral otitis (Stier-Jarmer et al. 2015). Scientific evidence suggests an interesting role of highly mineralized or sulphur waters for these illnesses (Schuh 2009; Keller et al. 2014; Casale et al. 2018).

Considering hydropinic therapy, study results indicate that the bioavailability of calcium from calcium-rich waters is comparable to that one derived from dairy products (Bohmer et al. 2000), and that the consumption of bicarbonate- and magnesium-rich waters may be beneficial for kidney stone prevention and for an improvement of glycemic control (Naumann et al. 2017; Sulaiman et al. 2020). Moreover, hydropinic therapy with highly mineralized waters can be useful for constipation due to irritable bowel syndrome (Stier-Jarmer et al. 2015).

Systematic reviews including only clinical studies conducted in a specific country or region of the world were collected in Table 3 (Karagülle and Karagülle 2004; Roques et al. 2012; Katz et al. 2012; Bender et al. 2014; Stanhope et al. 2018; Khalilzadeh et al. 2019; Drobnik and Stebel 2020). These research works were mostly carried out in regions where medical hydrology is widely spread and well known, such as Europe or the Middle East, and they outlined an efficacy profile of balneotherapy, mud therapy, and spa therapy which is similar to that one already described in literature reviews collected in Table 1 and Table 2. Additionally, some interesting findings suggested that balneotherapy with specific waters characterized by a high mineral content, like Dead Sea water, can be useful for the treatment of psoriasis (Katz et al. 2012; Khalilzadeh et al. 2019). Some authors also underscored the lack of relevant studies in continents like Oceania, thus urging the need for clinical investigations in Australia or New Zealand, where mineral water springs exist, but they are currently underused for medicinal purposes (Stanhope et al. 2018).

Globally, systematic reviews characterized by a higher overall quality of their methodological design tended to support the efficacy of balneotherapy, mud therapy, and spa therapy for the integrative management of osteoarthritis (especially knee osteoarthritis), fibromyalgia, low back pain of rheumatic origin, and chronic venous insufficiency (Pittler et al. 2006; Verhagen et al. 2007, 2015; Harzy et al. 2009; Langhorst et al. 2009; Naumann and Sadaghiani 2014; Stier-Jarmer et al. 2015; Santos et al. 2016; Matsumoto et al. 2017; de Moraes Silva et al. 2019; Hou et al. 2020). However, the authors underscored that clinical evidence needs to grow before firm conclusions can be drawn, and this is even more relevant for non-rheumatic conditions (for example, respiratory or skin illnesses).

All the same, in general, considering both trial results and empirical observations, spa-based treatments appear useful for rehabilitation and chronic disease management, because they seem capable of exerting a beneficial action on symptom control and psychophysical wellbeing.

Safety and tolerability of interventions

Globally, evidence from included studies suggests that balneotherapy, mud therapy, spa therapy, inhalation therapy, and hydropinic therapy are quite safe and well tolerated by patients, provided that all necessary medical and hygienic precautions are taken in advance.

The most important contraindications to treatments based on mineral waters and therapeutic muds are mainly derived from tradition and they can be grouped into three categories (Nappi 2001; Vv.Aa. 2014):

- Contraindications related to the disease stage: spa-based interventions are not to be administered when a patient is affected by an acute disease or during symptomatic relapses of chronic conditions.
- Contraindications related to the patient's illnesses and comorbidities: they include infectious conditions, cancer, and unstable or poorly controlled diseases (severe heart failure, advanced kidney insufficiency, uncontrolled hypertension, cirrosis, medically unresponsive epilepsy…).
- Contraindications related to the type of intervention: they depend on specific characteristics of single mineral waters and therapeutic muds.

Possible side effects of spa-based interventions are usually mild and often resolve spontaneously after treatment discontinuation: they are mostly due to an individual response, thus being highly "patient-specific", and their occurrence is worsened by an improper or unsupervised administration of intervention (Nappi 2001; Vv.Aa. 2014). Side effects generally include symptoms like headache, dizziness and nausea, mild relapses of local chronic pain, sleep disturbances, heart palpitations, or a general sensation of irritability and fatigue (rarely coupled with a short-lasting low-grade fever) (Vv.Aa. 2014). Additionally, intervention-specific side effects can occur, such as diarrhea and hydroelectrolytic imbalances due to an overconsumption of highly mineralized waters, a temporary increase of fluid secretions in the airways (with runny nose and cough) after some inhalation therapies, or cutaneous irritation caused by hot mud application on irritable skin.

Extreme caution is also advised in more fragile individuals like pediatric patients, pregnant women, and very elderly subjects, whose clinical response to spa-based interventions can be less predictable with a potential higher incidence of more severe side effects.

For all these reasons, a medical check and supervision are strongly advised for an appropriate prescription of spa-based interventions, not only to make the most of them on the basis of the patient's characteristics and disease, but even to avoid the onset of adverse events, thus optimizing the safety and tolerability of such treatments.

Mechanisms of action: hypotheses and evidence-based explanations

In light of scientific evidence described by expert authors of the "HydroGlobe" project, effects on health of medical hydrology-related treatments have been reported to be the following ones (Vv.Aa. 2014):

- Antalgic effect,
- Myorelaxant action,
- Activation of microcirculation,
- Immunomodulation,
- Neuro-hormonal stimulation,
- Improvement of fat and carbohydrate metabolism.

In the same project, traditional uses of different types of natural mineral waters (each of them characterized by specific biochemical component/s) were collected, with general clinical indications formulated for various health conditions, as reported in Table 4 (Nappi 2001; Vv.Aa. 2014; Quattrini et al. 2016).

In general, treatments used in medical hydrology can be classified into three main categories on the basis of their route of administration (external or internal) and the state of matter of the therapeutic medium (liquid or gaseous):

1. Balneotherapeutic treatments, such as baths with natural mineral waters and mud therapy.
2. Inhalation-based treatments, such as vapors or aerosols derived from natural mineral waters inhaled for medicinal purposes.
3. Hydropinic treatments, when natural mineral waters are taken orally as therapeutic drinks.

Balneotherapeutic treatments are believed to exert their global therapeutic effect on the body thanks to a synergistic combination of mechanical (hydrostatic pressure), thermal (high temperature), and biochemical actions, the latter due to both the mineral (osmotic pressure and direct activity) and the organic (with anti-inflammatory and immunomodulatory properties) components of waters and muds (Vv.Aa. 2014; Fioravanti et al. 2017; Antonelli and Donelli 2018b). From a physiological point of view, balneotherapeutic treatments can increase serum β-endorphins and can modulate cortisol levels in such a way as to improve individual stress resilience without disrupting circadian rhythms of this hormone (Fioravanti et al. 2011; Antonelli and Donelli 2018a). The long-term increase of cortisol awakening response due to a cycle of balneotherapeutic treatments may be the reason why, in some clinical studies, the effects on health of balneotherapy, mud therapy, and spa therapy were observed to last for a few months after intervention (Forestier et al. 2016; Antonelli and Donelli 2018a). If we consider inflammatory mediators, mud applications followed by baths with natural mineral waters can reduce the production of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1β (IL-1β), and tumor necrosis factor alpha (TNF-α) (Fioravanti et al. 2011). Quantitative data from the "gray" literature also show that,

Table 3 Systematic reviews including only clinical studies conducted in a specific country or region of the world

Reference	Country	Conclusions
Bender et al. (2014)	Hungary	Some evidence of efficacy of Hungarian mud baths for several rheumatic conditions, mostly osteoarthritis.
Drobnik and Stebel (2020)	Poland and Austria	Scientific evidence on the "Tolpa" peloid is not strong enough to formulate specific clinical indications.
Karagulle and Karagulle (2004)	Turkey	Efficacy of spa therapy with Turkish mineral waters and muds for various rheumatic conditions, including osteoarthritis, fibromyalgia, and rheumatoid arthritis.
Katz et al. (2012)	Israel	Baths in Dead Sea water and mud can be useful for the treatment of rheumatic diseases and psoriasis.
Khalilzadeh et al. (2019)	Iran	Possible efficacy of balneotherapy with Persian mineral waters for the management of psoriasis.
Roques et al. (2012)	France	Spa therapy with French mineral waters and muds can be effective for the complementary treatment of osteoarthritis, tendinopathies, benign chronic low back pain, and leg chronic venous insufficiency. Beneficial effects were found for anxiety. Preliminary studies also reported some improvements in patients with neurologic and metabolic conditions.
Stanhope et al. (2018)	Australia and New Zealand	No evidence of efficacy due to complete lack of clinical studies on the topic.

at least for osteoarthritis, therapeutic mud applications are superior to simple hot packs to improve joint functionality and pain, thus underscoring the therapeutic importance of the organic component (Crespin 2017). It is possible that the effect of balneotherapeutic treatments on the inflammatory response and interleukin production is due to modifications of microRNA expressions induced by thermal and mechanical stimuli, as observed in a cohort of patients with osteoarthritis (Giannitti et al. 2017). At a joint level, balneotherapeutic treatments may stimulate cartilage metabolism through mediators like the insulin-like growth factor-1 (IGF1), they may exert an antioxidant effect by reducing the release of reactive oxygen and nitrogen species (Fioravanti et al. 2011; Masselli et al. 2020) and also modulate intracellular mediators like protein kinases involved in cartilage growth and cell proliferation (Queirolo et al. 2016; Martini et al. 2018). Mud baths are also associated with a decrease in serum levels of adiponectin and resistin, hormonal substances probably implied in the progression of chronic degenerative diseases like osteoarthritis (Fioravanti et al. 2015). Furthermore, transcutaneous absorption of antiphlogistic substances released by water and mud microflora may contribute to the overall pharmacological effect of balneotherapeutic treatments (Vv.Aa. 2014; Antonelli and Donelli 2018b). More details about possible mechanism of action of balneotherapy, as hypothesized on the basis of in vitro laboratory studies, have recently been collected in a comprehensive literature review, demonstrating the anti-inflammatory, antioxidant, chondroprotective, and immunosuppressive role of this type of intervention at a cellular level (Cheleschi et al. 2020). Regarding balneotherapy and peripheral venous circulation, it is believed that the main therapeutic action of baths is determined by the hydrostatic and osmotic pressure of natural mineral waters, which seems capable of reducing pain and edema (de Moraes Silva et al. 2019). The combination of baths with hydrojet massage, Kneipp therapy (in which hot and cold baths are alternated), and physical exercise can determine a useful compression of peripheral veins, thanks to an external (water pressure) and internal (muscle contraction) synergistic action (de Moraes Silva et al. 2019). In particular, beneficial effects for the cardiovascular system seem to be more frequently associated with balneotherapeutic sessions in carbon dioxide-rich water, which may be responsible for lowering peripheral vascular resistance and increasing blood flow in a more pronounced way if compared with other water types (Pagourelias et al. 2011). Additionally, balneotherapeutic treatments, especially those ones based on sulfur-rich waters, seem to have anti-inflammatory, keratolytic, and regenerative effects on skin due to a direct pharmacological action of the mineral component and to interactions between thermal and cutaneous microflora with a potential modulation of local immune functions (Gobbi et al. 2009; Mirandola et al. 2011; Katz et al. 2012; Antonelli and Donelli 2018b; Eliasse et al. 2020).

Inhalation treatments with vaporized natural mineral waters can have anti-inflammatory, mucolytic, and antimicrobial properties, whereas irrigations with liquid-phase waters also have an action of mechanical washing on the upper respiratory tract (Vv.Aa. 2014; Keller et al. 2014; Casale et al. 2018). Among others, waters with sulphur seem to promote mucociliary clearance, regulate local immunity, inflammation, and have antiallergic effects (Rinaldi et al. 2006; Mirandola et al. 2007, 2013; Keller et al. 2014; Viegas et al. 2019; Carubbi et al. 2019). For all these reasons, sulfur-rich water inhalations have been proposed as an integrative treatment for patients with chronic obstructive pulmonary disease (Khaltaev et al. 2020).

Health effects of hydropinic treatments are mainly mediated by the intake of water minerals (osmotic and prokinetic action on the intestine when the mineral content is high,

Table 4 Water types and clinical indications according to the "HydroGlobe" study (2014)

Affected apparatus	Example	Administration	Recommended water types
Ear-nose-throat and respiratory tract	Chronic rhinosinusitis or bronchitis	Inhalations, irrigations	Sulphurous; salt, bromine and iodine; bicarbonate; arsenical-ferruginous.
Cardiovascular system	Chronic venous insufficiency	Baths	Carbonic
Gynecological apparatus	Chronic vaginitis	Irrigations	Sulfurous; salt, bromine; bicarbonate; sulfate
Urinary tract	Recurrent kidney stones	Oral intake	Oligomineral (low mineral content); Bicarbonate.
Gastrointestinal system	Irritable bowel disease with constipation	Oral intake	Bicarbonate; sulfate; salt
Skin	Psoriasis, atopic dermatitis	Baths	Salt, bromine and iodine; eadioactive; bicarbonate; sulfurous
Musculoskeletal system	Osteoarthritis, fibromyalgia	Baths	Sulfurous; salt, bromine and iodine; radioactive

Legends: According to relevant directives of the European Union and to traditional definitions, mineral waters are labeled as follows (Nappi 2001; Vv.Aa. 2014; Quattrini et al. 2016): (a) "Arsenical-ferruginous" waters: when they contain both arsenic and iron, either as a ferrous or ferric ion. Waters are considered "ferrous" or "ferruginous" when iron content is > 1 mg/L. (b) "Bicarbonate-rich" waters: when bicarbonate content is > 600 mg/L. If the calcium content of these waters is > 150 mg/L and magnesium content is > 50 mg/L, they are also defined as "calcium- and magnesium-rich" waters. (c) "Carbonic" waters: they spring up naturally with a detectable content of free carbon dioxide. When CO_2 content is > 250 mg/L, they are defined as "acid waters" due to their low pH. (d) "Oligomineral" waters: characterized by a low mineral content, with a fixed residue at 180°C inferior to 500 mg/L. On the contrary, when the fixed residue exceeds 1500 mg/L, waters are defined as "highly mineralized". (e) "Radioactive" waters: they have a radioactivity of at least 1 nCi/L, mostly due to their content of radon. (f) "Sulfate-rich" waters: when sulfate content is > 200 mg/L. If the calcium content of these waters is > 150 mg/L and magnesium content is > 50 mg/L, they are also defined as "calcium- and magnesium-rich" waters. (g) "Sulfurous" waters: they have a high content of bivalent sulfur. (h) "Waters rich in salt, bromine and iodine": they have a high mineral content and, like seawater, they are rich in sodium (in the form of NaCl) and other minerals. If sodium content is > 200 mg/L, they are labeled as sodium-rich waters. They can also contain elements like bromine and iodine

diuretic effect when the mineral content is low) and by the interaction between water and gut microflora (Vv.Aa. 2014).

Globally, the mechanisms of action of spa-related treatments, although not fully understood, seem to be determined by a synergistic action of all water and mud components, capable of eliciting beneficial effects both locally and at a systemic level.

Limitations of this study and new perspectives for future research

First, a major limitation of both primary (clinical) and secondary (review) studies on the topic, which is responsible for hindering optimal retrieval and dissemination of scientific information, is the lack of a widely accepted consensus on a precise English terminology in the field of medical hydrology. In other words, terms like balneotherapy, hydrotherapy, and spa therapy are given diverse (and sometimes misleading or confusing) meanings when used by different authors, and this aspect has already been underscored even by several experts (Gutenbrunner et al. 2010; Fioravanti et al. 2017). For this reason, a list of specific definitions was provided in the "Introduction" section to avoid possible misunderstandings and to address this issue as best as possible.

Even if the number of reviews included in this research work is considerable, the actual basis of clinical evidence in support of spa-related treatments is quite limited. In fact, there is a demonstrated substantial degree of clinical evidence overlap among analyzed reviews (see the Electronic supplementary materials for an example about balneotherapy for fibromyalgia or refer to a recently published overview of literature reviews for another example about spa therapy for knee osteoarthritis (D'Angelo et al. 2021)). For this reason, it is important to keep on studying medical hydrology with further clinical research projects to expand the existing evidence basis.

With regard to the quality of clinical trials analyzed in included reviews, the most frequent limitations were reported to be the low number of study participants, poor information about proper randomization, and the lack of adequate control. Instead, if we consider the quality of included reviews, major limitations involved methodological issues like excessively narrow search strategies (with the literature search sometimes only run in PubMed), poor description of the details about article selection and quality assessment, and an often inadequate evaluation of the risk of publication bias. The trial quality assessment was not adequately used by some review authors for informing a critical discussion, with potentially inflated results and biased conclusions. The high level of heterogeneity across primary and secondary studies on the topic makes it difficult to synthesize available data, especially from a quantitative point of view, thus urging the necessity to conduct further investigations adopting a more homogeneous design.

As a proposal, it would be useful to promote a wider and better application of the PRISMA guidelines among researchers who want to conduct systematic reviews about medical hydrology, since, if we consider included research works, only some authors actually followed these internationally accepted methodological recommendations in a thorough way (Moher et al. 2009). Poor compliance with the PRISMA guidelines can result in omitting essential information which is useful for clinicians and policymakers to translate research findings into practice (external validity), or, even worse, this lack of transparency can hide substantial flaws in the conduction of the review, thus undermining the conclusion reliability (internal validity). For this reason, our umbrella review was conducted in accordance with the PRISMA statement, and methodological quality of included systematic reviews was weighted as best as possible.

Moreover, authors of some included reviews underscored the difficulty to find a specifically tailored assessment tool to evaluate the quality of primary studies on the topic, which regard atypical, non-pharmacological and hard-to-blind interventions like balneotherapy. Different solutions were adopted by review authors to find an adequate solutions, ranging from the use of a modified version of the standard Cochrane tool (Higgins et al. 2011) to other tools often employed for the evaluation of public health interventions like the Canadian "Quality Assessment Tool for Quantitative Studies" (Armijo-Olivo et al. 2012). To properly address this issue, world experts should agree on a set of essential domains that any assessment tool should include to be adequately usable for evaluating the quality and risk of bias of medical hydrology-related trials. In fact, some efforts have already been made towards this direction, for example by developing the "SPAC" checklist (Kamioka et al. 2013) or by evaluating the biasing impact of unblinded balneotherapy (Verhagen et al. 1998).

Finally, in order to optimize the collection of available evidence on the topic, any effort was made to retrieve all relevant data reported both in the scientific and in the so-called gray literature (Petticrew et al. 2008), including findings only displayed in conference proceedings and lectures published in peer-reviewed journals (Roques 2014; Bender 2016; Cao et al. 2020). However, the risk of publication bias, although minimized, could not be fully excluded, and it was not possible to statistically assess it because no quantitative synthesis was feasible.

Conclusions

Globally, retrieved evidence suggests that medical hydrology can be useful for individual wellbeing and public health. In particular, higher-quality studies support the use of spa-related interventions for not only conditions like osteoarthritis, fibromyalgia, and chronic back pain but also for chronic venous insufficiency. However, as discussed above, the existing body of evidence has some relevant limitations, especially with regard to non-rheumatic diseases. For this reason, further high-quality clinical trials and observational studies should be designed to confirm the beneficial effects of medical hydrology and to thoroughly estimate its effectiveness outside experimental settings in real-life clinical practice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00484-021-02133-w.

Declarations

Ethics approval Not applicable.

Conflict of interest The authors declare no conflict of interest.

References

Al Shammeri O, AlHamdan N, Al-Hothaly B et al (2014) Chronic venous insufficiency: prevalence and effect of compression stockings. Int J Health Sci 8:231–236. https://doi.org/10.12816/0023975

Albertini MC, Dacha M, Teodori L, Conti ME (2007) Drinking mineral waters: biochemical effects and health implications the state-of-the-art. International Journal of Environment and Health 1:153

An J, Lee I, Yi Y (2019) The thermal effects of water immersion on health outcomes: an integrative review. Int J Environ Res Public Health 16. https://doi.org/10.3390/ijerph16071280

Antonelli M, Donelli D (2018a) Effects of balneotherapy and spa therapy on levels of cortisol as a stress biomarker: a systematic review. Int J Biometeorol 62:913–924. https://doi.org/10.1007/s00484-018-1504-8

Antonelli M, Donelli D (2018b) Mud therapy and skin microbiome: a review. Int J Biometeorol 62:2037–2044. https://doi.org/10.1007/s00484-018-1599-y

Antonelli M, Donelli D, Fioravanti A (2018) Effects of balneotherapy and spa therapy on quality of life of patients with knee osteoarthritis: a systematic review and meta-analysis. Rheumatol Int 38:1807–1824. https://doi.org/10.1007/s00296-018-4081-6

Armijo-Olivo S, Stiles CR, Hagen NA et al (2012) Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. J Eval Clin Pract 18:12–18. https://doi.org/10.1111/j.1365-2753.2010.01516.x

Baethge C, Goldbeck-Wood S, Mertens S (2019) SANRA—a scale for the quality assessment of narrative review articles. Res Integr Peer Rev 4:5. https://doi.org/10.1186/s41073-019-0064-8

Bai R, Li C, Xiao Y et al (2019) Effectiveness of spa therapy for patients with chronic low back pain: An updated systematic review and meta-analysis. Medicine 98:e17092. https://doi.org/10.1097/MD.0000000000017092

Beer A, Kleinschmidt J, Jagenburg L (2018) Zur Wirksamkeit der kurörtlichen Heiltorftherapie: eine Literaturübersicht aus neueren Veröffentlichungen. Phys Med Rehab Kuror 28:365–371. https://doi.org/10.1055/a-0713-0694

Bender T (2016) SP0165 Balneotherapy: efficacy and safety in osteoarthritis. Ann Rheum Dis 75:40.4–40.4040. https://doi.org/10.1136/annrheumdis-2016-eular.6267

Bender T, Bálint G, Prohászka Z et al (2014) Evidence-based hydro- and balneotherapy in Hungary—a systematic review and meta-analysis. Int J Biometeorol 58:311–323

Bohmer H, Müller H, Resch KL (2000) Calcium supplementation with calcium-rich mineral waters: a systematic review and meta-analysis of its bioavailability. Osteoporos Int 11:938–943. https://doi.org/10.1007/s001980070032

Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH (2017) Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev 6:245. https://doi.org/10.1186/s13643-017-0644-y

Brosseau L, MacLeay L, Robinson V et al (2002) Efficacy of balneotherapy for osteoarthritis of the knee: A systematic review. Phys Ther Rev 7:209–222. https://doi.org/10.1179/108331902235001976

Cacciapuoti S, Luciano MA, Megna M et al (2020) The role of thermal water in chronic skin diseases management: a review of the literature. J Clin Med Res 9. https://doi.org/10.3390/jcm9093047

Cao C-F, Ma K-L, Li Q-L, et al (2020) Benefits of balneotherapy in the management of fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. Pain Pract 20(S1): 102. https://doi.org/10.1111/papr.12887

Carretero MI (2002) Clay minerals and their beneficial effects upon human health. A review. Appl Clay Sci 21:155–163. https://doi.org/10.1016/S0169-1317(01)00085-0

Carubbi C, Masselli E, Calabrò E et al (2019) Sulphurous thermal water inhalation impacts respiratory metabolic parameters in heavy smokers. Int J Biometeorol 63:1209–1216. https://doi.org/10.1007/s00484-019-01737-7

Casale M, Moffa A, Cassano M et al (2018) Saline nasal irrigations for chronic rhinosinusitis: From everyday practice to evidence-based medicine. An update. Int J Immunopathol Pharmacol 32: 2058738418802676. https://doi.org/10.1177/2058738418802676

Cheleschi S, Gallo I, Tenti S (2020) A comprehensive analysis to understand the mechanism of action of balneotherapy: why, how, and where they can be used? Evidence from in vitro studies performed on human and animal samples. Int J Biometeorol 64:1247–1261. https://doi.org/10.1007/s00484-020-01890-4

Corvillo I, Armijo F, Álvarez-Badillo A et al (2019) Efficacy of aquatic therapy for neck pain: a systematic review. Int J Biometeorol. https://doi.org/10.1007/s00484-019-01738-6

Costantino M, Lampa E, Nappi G (2006) Effectiveness of sulphur spa therapy with politzer in the treatment of rhinogenic deafness. Acta Otorhinolaryngol Ital 26:7–13

Crespin M (2017) The effects of mud pack therapy versus hot pack treatment to improve functionality and decrease pain in older adults suffering with knee osteoarthritis. PhD, College of Health and Human Services California State University

D'Angelo D, Coclite D, Napoletano A et al (2021) The efficacy of balneotherapy, mud therapy and spa therapy in patients with osteoarthritis: an overview of reviews. Int J Biometeorol. https://doi.org/10.1007/s00484-021-02102-3

de Moraes Silva MA, Nakano LC, Cisneros LL, Miranda F Jr (2019) Balneotherapy for chronic venous insufficiency. Cochrane Database Syst Rev 8:CD013085. https://doi.org/10.1002/14651858.CD013085.pub2

Drobnik J, Stebel A (2020) Central European ethnomedical and officinal uses of peat, with special emphasis on the Tołpa peat preparation (TPP): an historical review. J Ethnopharmacol 246:112248. https://doi.org/10.1016/j.jep.2019.112248

Eliasse Y, Redoules D, Espinosa E (2020) Impact of Avène Thermal Spring Water on immune cells. J Eur Acad Dermatol Venereol 34(Suppl 5):21–26. https://doi.org/10.1111/jdv.16335

Espejo-Antúnez L, Cardero-Durán MA, Garrido-Ardila EM et al (2013) Clinical effectiveness of mud pack therapy in knee osteoarthritis. Rheumatology 52:659–668. https://doi.org/10.1093/rheumatology/kes322

Falagas ME, Zarkadoulia E, Rafailidis PI (2009) The therapeutic effect of balneotherapy: evaluation of the evidence from randomised controlled trials. Int J Clin Pract 63:1068–1084. https://doi.org/10.1111/j.1742-1241.2009.02062.x

Ferrante G, Baldissera S, Campostrini S (2017) Epidemiology of chronic respiratory diseases and associated factors in the adult Italian population. Eur J Pub Health 27:1110–1116. https://doi.org/10.1093/eurpub/ckx109

Fioravanti A, Cantarini L, Guidelli GM, Galeazzi M (2011) Mechanisms of action of spa therapies in rheumatic diseases: what scientific evidence is there? Rheumatol Int 31:1–8

Fioravanti A, Giannitti C, Cheleschi S et al (2015) Circulating levels of adiponectin, resistin, and visfatin after mud-bath therapy in patients with bilateral knee osteoarthritis. Int J Biometeorol 59:1691–1700

Fioravanti A, Karagülle M, Bender T, Karagülle MZ (2017) Balneotherapy in osteoarthritis: facts, fiction and gaps in knowledge. Eur J Integr Med 9:148–150. https://doi.org/10.1016/j.eujim.2017.01.001

Forestier R, Françon A (2008) Crenobalneotherapy for limb osteoarthritis: systematic literature review and methodological analysis. Joint Bone Spine 75:138–148. https://doi.org/10.1016/j.jbspin.2007.06.009

Forestier R, Erol Forestier FB, Francon A (2016) Spa therapy and knee osteoarthritis: a systematic review. Ann Phys Rehabil Med 59:216–226. https://doi.org/10.1016/j.rehab.2016.01.010

Forestier RJ, Erol Forestier FB, Francon A (2017) Crénothérapie (crénobalnéothérapie) dans la lombalgie chronique: une revue critique. Revue du Rhumatisme Monographies 84:91–98. https://doi.org/10.1016/j.monrhu.2016.11.008

Fortunati NA, Fioravanti A, Seri G et al (2016) May spa therapy be a valid opportunity to treat hand osteoarthritis? A review of clinical trials and mechanisms of action. Int J Biometeorol 60:1–8. https://doi.org/10.1007/s00484-015-1030-x

Fraioli A, Grassi M, Mennuni G et al (2013) Clinical researches on the efficacy of spa therapy in fibromyalgia. A systematic review. Ann Ist Super Sanita 49:219–229. https://doi.org/10.4415/ANN_13_02_13

Fraioli A, Mennuni G, Fontana M et al (2018, 2018) Efficacy of spa therapy, mud-pack therapy, balneotherapy, and mud-bath therapy in the management of knee osteoarthritis. A systematic review. Biomed Res Int:1042576. https://doi.org/10.1155/2018/1042576

Françon A, Duplan B, Forestier FBE, Forestier R (2015) Thermalisme et douleur chronique en rhumatologie: revue des essais cliniques randomisés (ECR) et des méta-analyses. Douleur analg 28:47–53. https://doi.org/10.1007/s11724-015-0410-7

Fusar-Poli P, Radua J (2018) Ten simple rules for conducting umbrella reviews. Evid Based Ment Health 21:95–100. https://doi.org/10.1136/ebmental-2018-300014

Giannitti C, De Palma A, Pascarelli NA et al (2017) Can balneotherapy modify microRNA expression levels in osteoarthritis? A comparative study in patients with knee osteoarthritis. Int J Biometeorol 61: 2153–2158. https://doi.org/10.1007/s00484-017-1420-3

Gobbi G, Ricci F, Malinverno C et al (2009) Hydrogen sulfide impairs keratinocyte cell growth and adhesion inhibiting mitogen-activated protein kinase signaling. Lab Investig 89:994–1006. https://doi.org/10.1038/labinvest.2009.61

Gomes C, Carretero MI, Pozo M et al (2013) Peloids and pelotherapy: historical evolution, classification and glossary. Appl Clay Sci 75-76:28–38. https://doi.org/10.1016/j.clay.2013.02.008

Gravelier C, Kanny G, Adetu S, Goffinet L (2020) Spa therapy and burn scar treatment: a systematic review of the literature. Int J Biometeorol 64:2195–2203. https://doi.org/10.1007/s00484-020-01988-9

Guidelli GM, Tenti S, De Nobili E, Fioravanti A (2012) Fibromyalgia syndrome and spa therapy: myth or reality? Clin Med Insights Arthritis Musculoskelet Disord 5:19–26. https://doi.org/10.4137/CMAMD.S8797

Gutenbrunner C, Bender T, Cantista P, Karagülle Z (2010) A proposal for a worldwide definition of health resort medicine, balneology, medical hydrology and climatology. Int J Biometeorol 54:495–507. https://doi.org/10.1007/s00484-010-0321-5

Harzy T, Ghani N, Akasbi N et al (2009) Short- and long-term therapeutic effects of thermal mineral waters in knee osteoarthritis: a systematic review of randomized controlled trials. Clin Rheumatol 28:501–507. https://doi.org/10.1007/s10067-009-1114-2

Higgins JPT, Altman DG, Gøtzsche PC et al (2011) The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928. https://doi.org/10.1136/bmj.d5928

Hou C, Liang L, Chu X et al (2020) The short-term efficacy of mud therapy for knee osteoarthritis: a meta-analysis. Medicine 99:e19761. https://doi.org/10.1097/MD.0000000000019761

Kamioka H, Kuroyanagi R, Komatsu T et al (2006) A systematic review of randomized controlled trials on the therapeutic and health-promoting effects of spas. J Jpn Soc Balneol Climatol Phys Med 69:155–166. https://doi.org/10.11390/onki1962.69.155

Kamioka H, Kawamura Y, Tsutani K et al (2013) A checklist to assess the quality of reports on spa therapy and balneotherapy trials was developed using the Delphi consensus method: the SPAC checklist. Complement Ther Med 21:324–332. https://doi.org/10.1016/j.ctim.2013.05.002

Karagülle MZ, Karagülle M (2004) Balneotherapy and spa therapy of rheumatic diseases in Turkey: a systematic review. Forsch Komplementarmed Klass Naturheilkd 11:33–41. https://doi.org/10.1159/000077194

Karagülle M, Karagülle MZ (2015) Effectiveness of balneotherapy and spa therapy for the treatment of chronic low back pain: a review on latest evidence. Clin Rheumatol 34:207–214. https://doi.org/10.1007/s10067-014-2845-2

Katz U, Shoenfeld Y, Zakin V et al (2012) Scientific evidence of the therapeutic effects of dead sea treatments: a systematic review. Semin Arthritis Rheum 42:186–200. https://doi.org/10.1016/j.semarthrit.2012.02.006

Keller S, König V, Mösges R (2014) Thermal water applications in the treatment of upper respiratory tract diseases: a systematic review and meta-analysis. J Allergy Ther 2014:943824. https://doi.org/10.1155/2014/943824

Khalilzadeh S, Shirbeigi L, Naghizadeh A et al (2019) Use of mineral waters in the treatment of psoriasis: perspectives of Persian and conventional medicine. Dermatol Ther 32:e12969. https://doi.org/10.1111/dth.12969

Khaltaev N, Solimene U, Vitale F, Zanasi A (2020) Balneotherapy and hydrotherapy in chronic respiratory disease. J Thorac Dis 12:4459–4468. https://doi.org/10.21037/jtd-gard-2019-009

Langhorst J, Musial F, Klose P, Häuser W (2009) Efficacy of hydrotherapy in fibromyalgia syndrome–a meta-analysis of randomized controlled clinical trials. Rheumatology 48:1155–1159. https://doi.org/10.1093/rheumatology/kep182

Liu H, Zeng C, Gao S-G et al (2013) The effect of mud therapy on pain relief in patients with knee osteoarthritis: a meta-analysis of randomized controlled trials. J Int Med Res 41:1418–1425. https://doi.org/10.1177/0300060513488509

Maraver F, Karagülle MZ (2012) Medical hydrology and balneology: environmental aspects. Publicaciones Universidad Complutense de Madrid

Maraver F, Michán A, Morer C, Aguilera L (2011) Is thalassotherapy simply a type of climatotherapy? Int J Biometeorol 55:107–108

Martini S, Soliman T, Gobbi G et al (2018) PKCε controls mitotic progression by regulating centrosome migration and mitotic spindle assembly. Mol Cancer Res 16:3–15. https://doi.org/10.1158/1541-7786.MCR-17-0244

Masselli E, Pozzi G, Vaccarezza M et al (2020) ROS in platelet biology: functional aspects and methodological insights. Int J Mol Sci 21. https://doi.org/10.3390/ijms21144866

Matsumoto H, Hagino H, Hayashi K et al (2017) The effect of balneotherapy on pain relief, stiffness, and physical function in patients with osteoarthritis of the knee: a meta-analysis. Clin Rheumatol 36:1839–1847. https://doi.org/10.1007/s10067-017-3592-y

Ministero della Sanità (1995) Modificazioni all'elenco delle patologie che possono trovare reale beneficio dalle cure termali e proroga della sua validità. Gazzetta Ufficiale

Mirandola P, Gobbi G, Sponzilli I et al (2007) Exogenous hydrogen sulfide induces functional inhibition and cell death of cytotoxic lymphocytes subsets. J Cell Physiol 213:826–833. https://doi.org/10.1002/jcp.21151

Mirandola P, Gobbi G, Micheloni C et al (2011) Hydrogen sulfide inhibits IL-8 expression in human keratinocytes via MAP kinase signaling. Lab Investig 91:1188–1194. https://doi.org/10.1038/labinvest.2011.76

Mirandola P, Gobbi G, Malinverno C et al (2013) Impact of sulphurous water politzer inhalation on audiometric parameters in children with otitis media with effusion. Clin Exp Otorhinolaryngol 6:7–11. https://doi.org/10.3342/ceo.2013.6.1.7

Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097. https://doi.org/10.1371/journal.pmed.1000097

Morer C, Roques C-F, Françon A et al (2017) The role of mineral elements and other chemical compounds used in balneology: data from double-blind randomized clinical trials. Int J Biometeorol 61:2159–2173. https://doi.org/10.1007/s00484-017-1421-2

Nappi G (2001) Medicina e clinica termale

National Institutes of Health Study Quality Assessment Tools. (2021) https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed 2 Apr 2021

Naumann J, Sadaghiani C (2014) Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials. Arthritis Res Ther 16:R141. https://doi.org/10.1186/ar4603

Naumann J, Biehler D, Lüty T, Sadaghiani C (2017) Prevention and therapy of type 2 diabetes-what is the potential of daily water intake and its mineral nutrients? Nutrients 9. https://doi.org/10.3390/nu9080914

Pagourelias ED, Zorou PG, Tsaligopoulos M et al (2011) Carbon dioxide balneotherapy and cardiovascular disease. Int J Biometeorol 55:657–663. https://doi.org/10.1007/s00484-010-0380-7

Passali D, Gabelli G, Passali GC et al (2017) Radon-enriched hot spring water therapy for upper and lower respiratory tract inflammation. Otolaryngol Pol 71:8–13. https://doi.org/10.5604/01.3001.0010.2242

Petticrew M, Egan M, Thomson H et al (2008) Publication bias in qualitative research: what becomes of qualitative research presented at conferences? J Epidemiol Community Health 62:552–554. https://doi.org/10.1136/jech.2006.059394

Pittler MH, Karagülle MZ, Karagülle M, Ernst E (2006) Spa therapy and balneotherapy for treating low back pain: meta-analysis of randomized trials. Rheumatology 45:880–884. https://doi.org/10.1093/rheumatology/kel018

Quattrini S, Pampaloni B, Brandi ML (2016) Natural mineral waters: chemical characteristics and health effects. Clin Cases Miner Bone Metab 13:173–180. https://doi.org/10.11138/ccmbm/2016.13.3.173

Queirolo V, Galli D, Masselli E et al (2016) PKCε is a regulator of hypertrophic differentiation of chondrocytes in osteoarthritis.

Osteoarthr Cartil 24:1451–1460. https://doi.org/10.1016/j.joca.2016.04.003
Queiroz LP (2013) Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 17:356. https://doi.org/10.1007/s11916-013-0356-5
Rachakonda TD, Schupp CW, Armstrong AW (2014) Psoriasis prevalence among adults in the United States. J Am Acad Dermatol 70:512–516. https://doi.org/10.1016/j.jaad.2013.11.013
Raza HMA, Krutulyte G, Rimdeikiene I, Savickas R (2020) Efficacy of balneotherapy and mud therapy in patients with knee osteoarthritis: a systematic literature review. Aktuelle Rheumatol 46:187–197. https://doi.org/10.1055/a-1157-8570
Rinaldi L, Gobbi G, Pambianco M et al (2006) Hydrogen sulfide prevents apoptosis of human PMN via inhibition of p38 and caspase 3. Lab Investig 86:391–397. https://doi.org/10.1038/labinvest.3700391
Roques CF (2014) Balneotherapy actual medical benefit. Data of evidence for the last twenty years. Ann Phys Rehabil Med 57:e159. https://doi.org/10.1016/j.rehab.2014.03.576
Roques C-C, Mancret R, Tabone W (2012) Beneficial effect of balneotherapy: achievements of the French association of balneotherapy research and methodological difficulties. Annals of Physical and Rehabilitation Medicine 55:e351
Santos I, Cantista P, Vasconcelos C (2016) Balneotherapy in rheumatoid arthritis-a systematic review. Int J Biometeorol 60:1287–1301. https://doi.org/10.1007/s00484-015-1108-5
Schuh A (2009) Die Evidenz der Klima- und Thalassotherapie. Ein Review. Schweizerische Zeitschrift für Ganzheitsmedizin / Swiss Journal of Integrative Medicine 21:96–104
Shea BJ, Reeves BC, Wells G et al (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 358:j4008. https://doi.org/10.1136/bmj.j4008
Stanhope J, Weinstein P, Cook A (2018) Do natural spring waters in Australia and New Zealand affect health? A systematic review. J Water Health 16:1–13
Stier-Jarmer M, Kus S, Frisch D et al (2015) Health resort medicine in non-musculoskeletal disorders: is there evidence of its effectiveness? Int J Biometeorol 59:1523–1544. https://doi.org/10.1007/s00484-015-0953-6
Sulaiman SK, Enakshee J, Traxer O, Somani BK (2020) Which type of water is recommended for patients with stone disease (hard or soft water, tap or bottled water): evidence from a systematic review over the last 3 decades. Curr Urol Rep 21:6. https://doi.org/10.1007/s11934-020-0968-3
Tenti S, Cheleschi S, Galeazzi M, Fioravanti A (2015) Spa therapy: can be a valid option for treating knee osteoarthritis? Int J Biometeorol 59:1133–1143. https://doi.org/10.1007/s00484-014-0913-6
The Cochrane Group About Cochrane Reviews. https://www.cochranelibrary.com/about/about-cochrane-reviews (2020). Accessed 25 Dec 2020
The European Parliament and the Council of the European Union (2009) Directive 2009/54/EC of the European Parliament and of the Council of 18 June 2009 on the exploitation and marketing of natural mineral waters. European Union law
van Tubergen A, van der Linden S (2002) A brief history of spa therapy. Ann Rheum Dis 61:273–275. https://doi.org/10.1136/ard.61.3.273
Verhagen AP, de Vet HCW, de Bie RA et al (1998) Balneotherapy and quality assessment: interobserver reliability of the Maastricht criteria list and the need for blinded quality assessment. J Clin Epidemiol 51:335–341. https://doi.org/10.1016/S0895-4356(97)00297-7
Verhagen AP, Bierma-Zeinstra SMA, Boers M et al (2007) Balneotherapy for osteoarthritis. Cochrane Database Syst Rev CD006864 4:1–30. https://doi.org/10.1002/14651858.CD006864
Verhagen AP, Bierma-Zeinstra SMA, Boers M et al (2015) Balneotherapy (or spa therapy) for rheumatoid arthritis. Cochrane Database Syst Rev CD000518 4:1–48. https://doi.org/10.1002/14651858.CD000518.pub2
Viegas J, Esteves AF, Cardoso EM et al (2019) Biological effects of thermal water-associated hydrogen sulfide on human airways and associated immune cells: implications for respiratory diseases. Front Public Health 7:128. https://doi.org/10.3389/fpubh.2019.00128
Vina ER, Kwoh CK (2018) Epidemiology of osteoarthritis: literature update. Curr Opin Rheumatol 30:160–167. https://doi.org/10.1097/BOR.0000000000000479
Vv.Aa. (2014) Hydroglobe. Definizione di un quadro di riferimento complessivo mondiale per l'idroterapia. Narcissus.me
Xiang J, Wu D, J'an L (2016) Clinical efficacy of mudpack therapy in treating knee osteoarthritis: a meta-analysis of randomized controlled studies. Am J Phys Med Rehabil 95:121–131. https://doi.org/10.1097/PHM.0000000000000354
Yuan D, Yu Z-X, Wang W, Chen Y (2019) Head-out immersion in natural thermal mineral water for the management of hypertension: a review of randomized controlled trials. Int J Biometeorol 63:1707–1718. https://doi.org/10.1007/s00484-019-01780-4
Zhen-han D, Tuo Y, Hui L et al (2014) A meta-analysis of mud therapy on knee osteoarthritis pain. Journal of Clinical Rehabilitative Tissue Engineering Research:2455–2460