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Clinical efficacy of medical hydrology: an umbrella review

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Abstract:	<p>Introduction. The aim of this research was to summarize available scientific evidence on the efficacy of Medical Hydrology for the management of any health condition. Methods. The search was conducted on March 26th, 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. Results. 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 hydroponic therapies. Discussion. 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.</p>

First of all, we would like to sincerely thank the editors and referees for providing very important feedback on our research work. We tried to address all raised issues point by point in a thorough way, as reported below. Our ultimate goal was to significantly improve the quality of an article that may help Medical Hydrology upgrade its framework of scientific evidence. All text changes were highlighted in the full-text version of our revised manuscript.

Reviewer #1: Dear authors this is a very well written review, but I have some points to criticize.

REPLY: Thanks for the appreciation of our article.

You judge the quality of the reviews, which have quite often a high quality, but on this way it gets lost, that in good reviews there can be quite a lot of trials with low quality, and this is very hard to see in your umbrella review as for example the review of Stier and Jarmer Stier-Jarmer M, Kus S, Frisch D, et al (2015) Health resort medicine in non-musculoskeletal 1019 disorders: is there evidence of its effectiveness? *Int J Biometeorol* 59:1523-1544. 1020 <https://doi.org/10.1007/s00484-015-0953-6>

So the evidence appears higher reading your review than it actually is.

REPLY: We have thoroughly re-assessed the methodological quality of included systematic reviews with another appraisal tool, the so called "AMSTAR 2", an internationally validated 16-item system that can assist in grading the review quality in much more detail (it is based on a 4-tier hierarchy: good, moderate, low and very low quality). Additional domains were taken into account to better evaluate the quality and risk of bias of any relevant systematic review. For transparency, full details of the review quality assessment were reported in the Electronic Supplementary Materials. Then, to specifically account for the actual risk of bias of clinical trials, we reported in Table 1 the overall quality of any set of primary studies included in each literature review, as per the review authors' global judgement. Thus, the reader can now see at a glance both the quality of included reviews and the quality of primary studies analyzed in each review. The Discussion section has been modified accordingly.

Then you cite sometimes only abstracts and I know well the reviews of Beer 2018 and Schuh 2009 and therefore know, that it is possible to get the whole article.

Beer A, Kleinschmidt J, Jagenburg L (2018) Zur Wirksamkeit der kurörtlichen Heilorttherapie: eine

860 Literaturübersicht aus neueren Veröffentlichungen. *Phys Med Rehab Kuror* 28:365-371. 861 <https://doi.org/10.1055/a-0713-0694>

Schuh A (2009) Die Evidenz der Klima- und Thalassotherapie. Ein Review. *Schweizerische 1015 Zeitschrift für Ganzheitsmedizin / Swiss Journal of Integrative Medicine* 21:96-104

REPLY: These studies were only assessed on the basis of information provided in their abstract because their full-text version was written in German and we were unable to directly translate it (languages that we could read on our own were listed in the Methods section and included English, French, Italian, Spanish and Portuguese). We have now sought help from a translator to extract relevant data from these studies too.

In many different reviews appear the same trials which can cause a bias, as it appears that there is more evidence, when more reviews with the same trials are published.

You should address this topic better.

REPLY: We decided to tackle this issue in a practical way, by providing the reader with an example. We selected a representative sub-topic (balneotherapy for fibromyalgia) and extracted the list of all clinical studies included in any relevant review analyzed in our research. Then, we put them in a double-entry “matching table” to highlight redundancy of clinical evidence across different literature reviews and overlaps in reporting trial results (see the Electronic Supplementary Materials for further details).

For knee osteoarthritis, another example can be found here: D’Angelo, D., Coclite, D., Napoletano, A., Fauci, A. J., Latina, R., Gianola, S., ... & Iannone, P. (2021). The efficacy of balneotherapy, mud therapy and spa therapy in patients with osteoarthritis: an overview of reviews. International Journal of Biometeorology, 1-17. <https://doi.org/10.1007/s00484-021-02102-3>

The results of this analysis were briefly discussed in the Limitations section of the manuscript.

I your search in pubmed you use [Title/abstract]. Given the problems with the precise terminology (especially in English) in the field of Medical Hydrology as you correctly describe in limimtatipns,this may be a big bias missing relevant reviews.

you also use this for systematic review and meta-nalysis,but should better use the filters instead.

your search strategy in Google scholar is quite different from the other databeses and this point can only be seen in the appendix.

You should use a similar strategy as in the other databases or at least describe how and why the search in Scholar was performed in this way.

This may alsoexplain,why you haveonly 20%duplicates ba usind 5 different databases with the "same" search strategy. This is nearly impossible and you should adapt the search strategies or adress this fact at least in the discussion or limitaions

REPLY: The search strategy has now been homogenized across different scientific databases. We chose not to change the search strategy used for Google Scholar to narrow down our search and improve its precision (this detail was reported in the Methods section). Following the referee’s recommendation, we have run the search again applying proper filters and performed the selection of eligible articles another time from the beginning. The flowchart summarizing the article selection process was updated accordingly. For transparency, a complete list of articles excluded after their full-text assessment (with reasons) was provided in the Electronic Supplementary Materials. A few experts were contacted for some general feedback, and regulatory papers/literature overviews were searched as well through snowballing to avoid missing any relevant article. Finally, four new systematic reviews were included in our umbrella overview.

Many thanks again for your insightful and kind help.

1 **Title**

2 Clinical efficacy of Medical Hydrology: an umbrella review

3

4 **Abstract**

5 **Introduction.** The aim of this research was to summarize available scientific evidence on the efficacy
6 of Medical Hydrology for the management of any health condition.

7 **Methods.** The search was conducted on March 26th, 2021, in the following databases: Medline (via
8 PubMed), EMBASE, Web of Science, Cochrane Library, and Google Scholar. All relevant literature
9 reviews investigating the clinical efficacy of interventions characterized by the use of natural mineral
10 waters and muds were included. The quality of studies was assessed with the “AMSTAR 2” tool.

11 **Results.** After article screening, 49 reviews were included in this work. Overall, retrieved scientific
12 evidence suggests that spa therapy is beneficial for patients affected by some specific musculoskeletal
13 conditions, with improvements potentially lasting up to 9 months. Moreover, balneotherapy can be an
14 integrative support for the management of chronic venous insufficiency and some inflammatory skin
15 diseases like psoriasis. The role of spa therapy in rehabilitation appears relevant as well. More limited,
16 although interesting evidence exists for inhalation and hydropinic therapies.

17 **Discussion.** Globally, retrieved evidence suggests that, besides individual wellbeing, Medical
18 Hydrology can be useful for public health. In particular, higher-quality studies seem to support the
19 integrative use of spa-related interventions for conditions like osteoarthritis, fibromyalgia, low back
20 pain of rheumatic origin, and chronic venous insufficiency. However, the body of evidence has some
21 limitations and further clinical trials should be designed for each relevant application to consolidate
22 and expand acquired knowledge.

23

24 **Keywords:** Medical hydrology; Clinical efficacy; Public health; Integrative medicine; Umbrella review.

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49

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52 declared by the authors.

53 **Ethics approval:** not applicable.

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73 **Introduction**

74

75 **Background and definitions**

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

83 According to the European Union (EU) law, as stated in the Council Directive 80/777/EEC, a natural
84 mineral water is defined as a microbiologically wholesome water (originating in an underground
85 water table or deposit and emerging from a spring), which can be distinguishable from ordinary
86 drinking water by its nature and original purity (The European Parliament and the Council of the
87 European Union 2009). In particular, natural mineral waters are characterized by a specific mineral
88 content and biochemical composition, and by certain effects, including their potential
89 pharmacological, physiological, and clinical action (The European Parliament and the Council of the
90 European Union 2009). In several European countries, this regulatory definition is also accepted by
91 the scientific community (Gutenbrunner et al. 2010). Therefore, in this article, we referred to “natural
92 mineral waters” or, simply, “mineral waters” following the above mentioned description and
93 indicating spring waters used for preventive, therapeutic or rehabilitative purposes in spa centers.
94 With the aim of unequivocally classifying all spa-based interventions and considering a common set
95 of definitions used in the scientific literature (Pittler et al. 2006; Gutenbrunner et al. 2010; Gomes et
96 al. 2013; Fioravanti et al. 2017; Antonelli and Donelli 2018a), the following terms were used in this
97 research work:

- 98 ● “Balneotherapy”: any treatment which only involves the partial or total-body immersion in
99 natural mineral waters (Antonelli and Donelli 2018a; Antonelli et al. 2018). When sea water
100 was used, the term “Talassotherapy” was adopted (Maraver et al. 2011).
- 101 ● “Mud therapy”: any treatment which only involves the application over skin of muds or other
102 peloids, which were defined as natural products used as therapeutic agents and consisting of a
103 mixture of minero-medicinal water with organic and inorganic material, like clay minerals
104 (Carretero 2002). Although usually classified among balneo-therapeutic interventions
105 (Fioravanti et al. 2017), mud therapy was distinguished from standard balneotherapy for its
106 specific characteristics.
- 107 ● “Spa therapy”: any spa-based multicomponent treatment which includes at least a treatment
108 involving the therapeutic use of natural mineral waters (Pittler et al. 2006; Karagülle and

109 Karagülle 2015; Antonelli and Donelli 2018a). Due to its complexity and integrated
110 therapeutic action, fango-balneotherapy, namely mud baths followed or preceded by standard
111 balneotherapy with mineral waters, was classified under this category.

112 ● “Inhalation therapy”: any treatment characterized by the inhalation of natural mineral waters
113 and their gases in the form of vapors, nebulizations, aerosols, politzers, and humages
114 (Costantino et al. 2006; Keller et al. 2014). Oral and nasal irrigations were also included in
115 this category.

116 ● “Hydropinic therapy”: any treatment which implies the oral ingestion of natural mineral
117 waters with medicinal properties (Albertini et al. 2007).

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

124

125 **Rationale**

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

136 Globally, these conditions are mostly caused by chronic diseases with an epidemiologically
137 considerable impact on health-related quality of life (QoL). For example, osteoarthritis is a frequent
138 degenerative disorder of the musculoskeletal system, especially among elderly subjects, with around
139 14 million patients only in the USA, and it is expected to become one of the leading causes of
140 disability worldwide (Vina and Kwoh 2018). A relevant impact on public health is also shared by
141 other health conditions which can benefit from spa-based interventions, such as fibromyalgia (Queiroz
142 2013), chronic venous insufficiency (Al Shammeri et al. 2014), chronic inflammatory respiratory
143 diseases (Ferrante et al. 2017), and phlogistic skin disorders like psoriasis (Rachakonda et al. 2014).
144 However, the above mentioned clinical indications were last updated and revised years ago (Ministero
145 della Sanità 1995), and the most recent attempt to collect all available evidence on the topic with a

146 cross-cutting approach dates back to March 2014, when the “Hydroglobe” project was published by a
147 panel of experts with the technical support of the World Health Organization (WHO) (Vv.Aa. 2014).
148 In the light of what stated above, considering that Medical Hydrology has a long-standing tradition
149 (a), that mineral waters and therapeutic muds are easily available as natural resources (b), that spa-
150 based interventions are usually prescribed for epidemiologically relevant health conditions (c), and
151 that scientific evidence rapidly evolves (d), it can be useful to synthesize and critically appraise
152 available findings on the topic with a systematic approach, thus following the basic principles of
153 Evidence-Based Medicine (EBM). This would help to outline an updated list of evidence-based
154 indications for treatments with mineral waters and therapeutic muds, and to guide further research in
155 this field, which is important for both individual wellbeing and public health.

156

157 **Study objective**

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

161

162

163 **Methods**

164

165 **Study design and protocol registration**

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

172

173 **Eligibility criteria**

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

175 → Population: healthy subjects and/or individuals affected by any disease diagnosed in
176 accordance with validated clinical criteria.

177 → Intervention: all spa interventions based on the use of natural mineral waters and therapeutic
178 muds (balneotherapy, mud therapy, spa therapy, inhalation/irrigation therapy, hydropinic
179 therapy). Reviews were excluded when they focused on studies with non-mineral tap water.

180 → Control: any type, including no control.

181 → Outcomes: any relevant clinical outcome (symptomatic and functional improvements,
182 variations in laboratory parameters, reduction of drug consumption, effects on health-related
183 quality of life).
184 → Study design: systematic reviews and meta-analyses of clinical studies. Reviews were
185 excluded when they had no description of research methods and when they included only pre-
186 clinical laboratory studies. Relevant high-quality narrative reviews (reporting a full
187 description of their research methods and based on a quite extensive literature search) were
188 also included along with systematic reviews, but they were synthesized in a separated section
189 of the manuscript. Following the Cochrane recommendations, systematic reviews were
190 defined as any “review [that] attempts to identify, appraise and synthesize all the empirical
191 evidence that meets pre-specified eligibility criteria to answer a specific research question”
192 (The Cochrane Group). Reviews had to be published in a refereed journal to be eligible for
193 inclusion.

194

195 **Information sources**

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

199

200 **Search**

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

204 The following keywords were used: “balneotherapy”, “hydrotherapy”, “thalassotherapy”, “spa
205 therapy”, “water therapy”, “aquatic therapy”, “mud therapy”, “peloid therapy”, psammothrapy,
206 “inhalation therapy”, “endotympanic insufflation”, “poltizer”, “cave therapy”, “hydropinotherapy”,
207 “mineral water*”, “thermal water*”, “hot spring water*”. Specific search strategies adopted for all
208 screened databases were disclosed in the Electronic Supplementary Materials.

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

214

215 **Study selection**

216 The article screening process was conducted with the help of EndNote® software (version X4) by two
217 authors independently (M.A., D.D.). In cases of discrepancies, another author (C.P.) was consulted

218 and disagreements were discussed until consensus was reached. Only systematic reviews and meta-
219 analyses (along with the most relevant and extensive narrative reviews) matching the above-
220 mentioned PICOS criteria were included in this umbrella review. All studies written in English,
221 French, Italian, Spanish, and Portuguese were considered eligible for inclusion. **Studies matching**
222 **inclusion criteria but written in other languages (German, Japanese) were consulted with the support**
223 **of a translator.** In order to maximize retrievable evidence on the topic and to reduce the risk of
224 publication bias, even articles with only an English abstract available for consultation were included
225 in this umbrella review. This detail was reported in the table describing the main characteristics of
226 included systematic reviews, although it was not possible to assess the quality of these research works
227 due to the lack of detailed methodological information.

228

229 **Data collection process**

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

234

235 **Data items**

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

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

246

247 **Risk of bias and quality of studies**

248 **The quality of included systematic reviews was independently evaluated by two authors (M.A., D.D.)**
249 **with a dedicated appraisal tool called “AMSTAR 2”, specifically developed and validated by a team**
250 **of expert methodologists for this purpose (Shea et al. 2017). In cases of disagreement, items were**
251 **discussed with another author (C.P.) until consensus was reached. The “AMSTAR 2” tool provides a**
252 **16-item checklist aimed to explore different methodological domains, including the appropriateness**
253 **of inclusion/exclusion criteria, search strategies, article selection, data extraction, risk-of-bias**
254 **assessment, heterogeneity evaluation, quantitative synthesis and critical discussion. Each item**

255 corresponds to a question, which can be answered with “yes” or “no” (sometimes “yes, but partially”
256 is available as a middle response). Included reviews were evaluated one by one and their overall
257 quality was rated as:

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

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

267 The methodological quality of narrative reviews was assessed with the SANRA scale (Baethge et al.
268 2019) during the article selection process and only higher-quality narrative reviews were included in
269 this work. The SANRA is a 6-item scale which evaluates the relevance/importance of a narrative
270 review (1), whether its aim is sufficiently focused (2), if the literature search is broad enough (3),
271 whether referencing (4), scientific reasoning (5), and presentation of data (6) are appropriate. Each
272 item score can vary from 0 to 2, and the overall review quality score can range from 0 to 12 (high-
273 quality narrative reviews usually score 9 or more SANRA points).

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

277

278 **Synthesis of results**

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

286

287

288 **Results**

289

290 **Study selection**

291 Overall, the literature search yielded 803 results and, after screening and selection of potentially
292 eligible articles, 49 reviews (41 systematic and 8 narrative reviews) were eventually included in this
293 research work. Details of the article selection process, along with the main reasons for exclusion of
294 non-eligible studies, were summarized in a dedicated flowchart (Figure 1). The list of all articles
295 eligible for a full-text assessment and then excluded after a thorough evaluation was provided in the
296 Electronic Supplementary Materials. The quality of a review available as a conference abstract in a
297 refereed journal (Cao et al. 2020) was assessed on the basis of information retrieved from the
298 corresponding preprint (<https://www.researchsquare.com/article/rs-16293/v1>). An article was kindly
299 provided by the authors after our direct inquiry (Raza et al. 2020). It was not possible to consult the
300 full-text version of a review but this study was included all the same for better comprehensiveness
301 (essential data were extracted from the abstract) (Zhen-han et al. 2014). A meta-analysis found
302 through snowballing and published as a Ph.D. thesis was excluded from the main search but
303 mentioned in the Discussion section to better analyze the mechanisms of action of mud therapy for
304 osteoarthritis (Crespin 2017).

305

306 **Characteristics of included studies**

307 The main characteristics of all included studies, collected and described in accordance with the
308 PICOS criteria, were reported in Table 1 (systematic reviews) and Table 2 (narrative reviews), along
309 with a brief summary of the authors' conclusions and, for systematic reviews, with their overall
310 methodological quality evaluated in accordance with the AMSTAR-2 recommendations (Bohmer et
311 al. 2000; Brosseau et al. 2002; 洋青 et al. 2006; Pittler et al. 2006; Verhagen et al. 2007, 2015;
312 Forestier and Françon 2008; Schuh 2009; Harzy et al. 2009; Falagas et al. 2009; Langhorst et al.
313 2009; Guidelli et al. 2012; Fraioli et al. 2013, 2018; Espejo-Antúnez et al. 2013; Liu et al. 2013;
314 Zhen-han et al. 2014; Roques 2014; Keller et al. 2014; Naumann and Sadaghiani 2014; Karagülle and
315 Karagülle 2015; Françon et al. 2015; Tenti et al. 2015; Stier-Jarmer et al. 2015; Fortunati et al. 2016;
316 Xiang et al. 2016; Forestier et al. 2016, 2017; Bender 2016; Santos et al. 2016; Matsumoto et al. 2017;
317 Naumann et al. 2017; Passali et al. 2017; Morer et al. 2017; Casale et al. 2018; Antonelli and Donelli
318 2018a; Antonelli et al. 2018; Beer et al. 2018; An et al. 2019; Corvillo et al. 2019; de Moraes Silva et
319 al. 2019; Bai et al. 2019; Yuan et al. 2019; Raza et al. 2020; Sulaiman et al. 2020; Hou et al. 2020;
320 Cao et al. 2020; Cacciapuoti et al. 2020; Gravelier et al. 2020).

321

322 **Population**

323 The number of study participants whose data were analyzed within included systematic reviews
324 varied from a minimum of 54 (Bohmer et al. 2000) to a maximum of 13782 (Stier-Jarmer et al. 2015),
325 with a median value of 731. In the majority of included reviews, regardless of their design (systematic
326 or narrative), study participants were patients with chronic conditions, such as rheumatic
327 (osteoarthritis, fibromyalgia, back pain of rheumatic origin, rheumatoid arthritis), cardiovascular

328 (chronic venous insufficiency, hypertension), dermatologic, respiratory, otorhinolaryngological,
329 neurologic, digestive, and urologic diseases (Figure 2). In a review, the effects of hydropinic therapy
330 on healthy subjects were studied (Bohmer et al. 2000), whereas studies with both healthy and diseased
331 individuals were analyzed in three research works (Antonelli and Donelli 2018a; An et al. 2019;
332 Sulaiman et al. 2020).

333

334 **Intervention**

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

342

343 **Control**

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

352

353 **Outcomes**

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

360

361 **Study design**

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

365 Xiang et al. 2016; Matsumoto et al. 2017; Naumann et al. 2017; Antonelli et al. 2018; de Moraes
366 Silva et al. 2019; Bai et al. 2019; Raza et al. 2020; Hou et al. 2020; Cao et al. 2020). Eight (8)
367 included reviews had a narrative design, but they still provided an extensive, quasi-systematic and
368 valuable overview of the scientific literature (Guidelli et al. 2012; Roques 2014; Françon et al. 2015;
369 Tenti et al. 2015; Fortunati et al. 2016; Bender 2016; Passali et al. 2017; Cacciapuoti et al. 2020), thus
370 outlining a state-of-the-art description of specific subtopics, such as the efficacy of spa therapy for
371 respiratory illnesses (Passali et al. 2017), skin diseases (Cacciapuoti et al. 2020), or hand osteoarthritis
372 (Fortunati et al. 2016). The number of clinical studies included in the systematic reviews varied from
373 a minimum of 3 (Brosseau et al. 2002; Fortunati et al. 2016) to a maximum of 41 (Stier-Jarmer et al.
374 2015), with a median of 12. Such primary studies were mostly Randomized Controlled Trials,
375 although some of them were characterized by a different design, like nonrandomized trials,
376 uncontrolled studies, and observational investigations. The quality of clinical studies tended to range
377 from fair to poor, with a potential risk of bias mostly arising from small sample size, lack of adequate
378 control, no randomization of trial participants, and poor information about blinding of intervention.

379

380 **Quality of included studies**

381 After the methodological assessment of included systematic reviews with the “AMSTAR 2” tool, the
382 quality of analyzed research works was judged as good (A) to moderate (B) in 11 cases (Pittler et al.
383 2006; Verhagen et al. 2007, 2015; Harzy et al. 2009; Langhorst et al. 2009; Naumann and Sadaghiani
384 2014; Stier-Jarmer et al. 2015; Santos et al. 2016; Matsumoto et al. 2017; de Moraes Silva et al. 2019;
385 Hou et al. 2020) and low (C) to very low (D) in the remaining cases, as reported in Table 1 (see the
386 Supplementary Materials for further details). It was not possible to assess the quality of a systematic
387 review because its full-text version was unavailable (Zhen-han et al. 2014). In general, the most
388 frequent methodological weaknesses found within included reviews were excessively narrow search
389 strategies, a poor description of study selection and evaluation processes, and limited consideration of
390 the trial risk-of-bias assessment for informing a critical discussion. Major strengths were usually a
391 clear definition of the research question and, where applicable, a good methodological level of meta-
392 analyses.

393

394

395 **Discussion**

396

397 **Efficacy of interventions**

398 Scientific evidence from included reviews indicates that balneotherapy, mud therapy, and spa therapy
399 can significantly improve clinical parameters like pain, joint functionality, mobility, and quality of life
400 of patients with chronic musculoskeletal conditions, mostly osteoarthritis, fibromyalgia, and other

401 pain-related rheumatic diseases. For these subjects, beneficial effects may last up to 9 months after
402 intervention (on average, 3 to 6 months) (Forestier et al. 2016, 2017), and clinical improvements are
403 associated with a reduced intake of analgesic drugs (Françon et al. 2015; Tenti et al. 2015; Forestier et
404 al. 2017; Fraioli et al. 2018; Antonelli et al. 2018). Furthermore, in two included research works, it
405 was demonstrated that balneotherapy is superior to the same treatment administered in pools with tap
406 water (“sham balneotherapy”) in terms of clinical benefits and improved quality of life among
407 patients with osteoarthritis and fibromyalgia, thus underscoring the contribution of the specific
408 biochemical composition of natural mineral waters to the overall therapeutic effect (Morer et al. 2017;
409 Antonelli et al. 2018).

410 With regard to vascular health, balneotherapy can be useful for the amelioration of pain, quality of
411 life, and skin pigmentation due to chronic venous insufficiency in lower limbs (Stier-Jarmer et al.
412 2015; de Moraes Silva et al. 2019), and it appears not to have negative effects on blood pressure
413 levels (Yuan et al. 2019). More limited evidence suggests that balneotherapy, including talassotherapy
414 (sea water baths), can be beneficial for patients with skin diseases like psoriasis and atopic dermatitis
415 (Schuh 2009; Falagas et al. 2009; Stier-Jarmer et al. 2015; Cacciapuoti et al. 2020), and possibly for
416 the integrative treatment of burn scars (Gravelier et al. 2020).

417 Balneotherapy, mud therapy, and spa therapy can also improve mental wellbeing and psychophysical
418 stress, and this is demonstrated by studies in which stress hormone levels were measured (Roques
419 2014; Stier-Jarmer et al. 2015; Antonelli and Donelli 2018a). An interesting role for orthopedic or
420 neurological patients of aquatic rehabilitation in pools with natural mineral waters has been
421 underscored by several authors, with beneficial effects on the most important clinical outcomes
422 (Falagas et al. 2009; Stier-Jarmer et al. 2015).

423 With regard to inhalation therapy, clinical improvements were observed in patients with diseases of
424 the upper and lower respiratory tract, mostly chronic rhinosinusitis and bronchitis (Schuh 2009; Keller
425 et al. 2014; Stier-Jarmer et al. 2015; Casale et al. 2018), but even in subjects with chatarral otitis
426 (Stier-Jarmer et al. 2015). Scientific evidence suggests an interesting role of highly mineralized or
427 sulphur waters for these illnesses (Schuh 2009; Keller et al. 2014; Casale et al. 2018).

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

434 Systematic reviews including only clinical studies conducted in a specific country or region of the
435 world were collected in Table 3 (Karagülle and Karagülle 2004; Roques et al. 2012; Katz et al. 2012;
436 Bender et al. 2014; Stanhope et al. 2018; Khalilzadeh et al. 2019; Drobnik and Stebel 2020). These
437 research works were mostly carried out in regions where Medical Hydrology is widely spread and

438 well known, such as Europe or the Middle East, and they outlined an efficacy profile of
439 balneotherapy, mud therapy, and spa therapy which is similar to that one already described in
440 literature reviews collected in Table 1 and Table 2. Additionally, some interesting findings suggested
441 that balneotherapy with specific waters characterized by a high mineral content, like Dead Sea water,
442 can be useful for the treatment of psoriasis (Katz et al. 2012; Khalilzadeh et al. 2019). Some authors
443 also underscored the lack of relevant studies in continents like Oceania, thus urging the need for
444 clinical investigations in Australia or New Zealand, where mineral water springs exist, but they are
445 currently underused for medicinal purposes (Stanhope et al. 2018).

446 Globally, systematic reviews characterized by a higher overall quality of their methodological design
447 tended to support the efficacy of balneotherapy, mud therapy, and spa therapy for the integrative
448 management of osteoarthritis (especially knee osteoarthritis), fibromyalgia, low back pain of
449 rheumatic origin, and chronic venous insufficiency (Pittler et al. 2006; Verhagen et al. 2007, 2015;
450 Harzy et al. 2009; Langhorst et al. 2009; Naumann and Sadaghiani 2014; Stier-Jarmer et al. 2015;
451 Santos et al. 2016; Matsumoto et al. 2017; de Moraes Silva et al. 2019; Hou et al. 2020). However, the
452 authors underscored that clinical evidence needs to grow before firm conclusions can be drawn, and
453 this is even more relevant for non-rheumatic conditions (for example, respiratory or skin illnesses).
454 All the same, in general, considering both trial results and empirical observations, spa-based
455 treatments appear useful for rehabilitation and chronic disease management, because they seem
456 capable of exerting a beneficial action on symptom control and psychophysical wellbeing.

457

458 **Safety and tolerability of interventions**

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

462 The most important contraindications to treatments based on mineral waters and therapeutic muds are
463 mainly derived from tradition and they can be grouped into three categories (Nappi 2001; Vv.Aa.
464 2014):

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

474 Possible side effects of spa-based interventions are usually mild and often resolve spontaneously after
475 treatment discontinuation: they are mostly due to an individual response, thus being highly “patient-
476 specific”, and their occurrence is worsened by an improper or unsupervised administration of
477 intervention (Nappi 2001; Vv.Aa. 2014). Side effects generally include symptoms like headache,
478 dizziness and nausea, mild relapses of local chronic pain, sleep disturbances, heart palpitations, or a
479 general sensation of irritability and fatigue (rarely coupled with a short-lasting low-grade fever)
480 (Vv.Aa. 2014). Additionally, intervention-specific side effects can occur, such as diarrhea and
481 hydroelectrolytic imbalances due to an overconsumption of highly mineralized waters, a temporary
482 increase of fluid secretions in the airways (with runny nose and cough) after some inhalation
483 therapies, or cutaneous irritation caused by hot mud application on irritable skin.
484 Extreme caution is also advised in more fragile individuals like pediatric patients, pregnant women,
485 and very elderly subjects, whose clinical response to spa-based interventions can be less predictable
486 with a potential higher incidence of more severe side effects.
487 For all these reasons, a medical check and supervision are strongly advised for an appropriate
488 prescription of spa-based interventions, not only to make the most of them on the basis of the patient’s
489 characteristics and disease, but even to avoid the onset of adverse events, thus optimizing the safety
490 and tolerability of such treatments.

491

492 **Mechanisms of action: hypotheses and evidence-based explanations**

493 In light of scientific evidence described by expert authors of the “*HydroGlobe*” project, effects on
494 health of Medical Hydrology-related treatments have been reported to be the following ones (Vv.Aa.
495 2014):

- 496 ● Antalgic effect,
- 497 ● Myorelaxant action,
- 498 ● Activation of microcirculation,
- 499 ● Immunomodulation,
- 500 ● Neuro-hormonal stimulation,
- 501 ● Improvement of fat and carbohydrate metabolism.

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

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

- 509 1. Balneo-therapeutic treatments, such as baths with natural mineral waters and mud therapy.

510 2. Inhalation-based treatments, such as vapours or aerosols derived from natural mineral waters
511 inhaled for medicinal purposes.

512 3. Hydropinic treatments, when natural mineral waters are taken orally as therapeutic drinks.

513 Balneo-therapeutic treatments are believed to exert their global therapeutic effect on the body thanks
514 to a synergistic combination of mechanical (hydrostatic pressure), thermal (high temperature), and
515 biochemical actions, the latter due to both the mineral (osmotic pressure and direct activity) and the
516 organic (with anti-inflammatory and immunomodulatory properties) components of waters and muds
517 (Vv.Aa. 2014; Fioravanti et al. 2017; Antonelli and Donelli 2018b). From a physiological point of
518 view, balneo-therapeutic treatments can increase serum β -endorphins and can modulate cortisol levels
519 in such a way as to improve individual stress resilience without disrupting circadian rhythms of this
520 hormone (Fioravanti et al. 2011; Antonelli and Donelli 2018a). The long-term increase of cortisol
521 awakening response due to a cycle of balneo-therapeutic treatments may be the reason why, in some
522 clinical studies, the effects on health of balneotherapy, mud therapy, and spa therapy were observed to
523 last for a few months after intervention (Forestier et al. 2016; Antonelli and Donelli 2018a). If we
524 consider inflammatory mediators, mud applications followed by baths with natural mineral waters can
525 reduce the production of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1 β (IL-1 β),
526 and tumor necrosis factor alpha (TNF- α) (Fioravanti et al. 2011). Quantitative data from the “gray”
527 literature also show that, at least for osteoarthritis, therapeutic mud applications are superior to simple
528 hot packs to improve joint functionality and pain, thus underscoring the therapeutic importance of the
529 organic component (Crespin 2017). It is possible that the effect of balneo-therapeutic treatments on
530 the inflammatory response and interleukin production is due to modifications of microRNA
531 expressions induced by thermal and mechanical stimuli, as observed in a cohort of patients with
532 osteoarthritis (Giannitti et al. 2017). At a joint level, balneo-therapeutic treatments may stimulate
533 cartilage metabolism through mediators like the insulin-like growth factor-1 (IGF1), they may exert
534 an antioxidant effect by reducing the release of Reactive Oxygen and Nitrogen Species (Fioravanti et
535 al. 2011; Masselli et al. 2020) and also modulate intracellular mediators like protein kinases involved
536 in cartilage growth and cell proliferation (Queirolo et al. 2016; Martini et al. 2018). Mud baths are
537 also associated with a decrease in serum levels of adiponectin and resistin, hormonal substances
538 probably implied in the progression of chronic degenerative diseases like osteoarthritis (Fioravanti et
539 al. 2015). Furthermore, transcutaneous absorption of antiphlogistic substances released by water and
540 mud microflora may contribute to the overall pharmacological effect of balneo-therapeutic treatments
541 (Vv.Aa. 2014; Antonelli and Donelli 2018b). More details about possible mechanism of action of
542 balneotherapy, as hypothesized on the basis of in-vitro laboratory studies, have recently been
543 collected in a comprehensive literature review, demonstrating the anti-inflammatory, antioxidant,
544 chondroprotective, and immunosuppressive role of this type of intervention at a cellular level
545 (Cheschi et al. 2020). Regarding balneotherapy and peripheral venous circulation, it is believed that
546 the main therapeutic action of baths is determined by the hydrostatic and osmotic pressure of natural

547 mineral waters, which seems capable of reducing pain and oedema (de Moraes Silva et al. 2019). The
548 combination of baths with hydrojet massage, Kneipp therapy (in which hot and cold baths are
549 alternated), and physical exercise can determine a useful compression of peripheral veins, thanks to an
550 external (water pressure) and internal (muscle contraction) synergistic action (de Moraes Silva et al.
551 2019). In particular, beneficial effects for the cardiovascular system seem to be more frequently
552 associated with balneo-therapeutic sessions in carbon dioxide-rich water, which may be responsible
553 for lowering peripheral vascular resistance and increasing blood flow in a more pronounced way if
554 compared with other water types (Pagourelas et al. 2011). Additionally, balneo-therapeutic
555 treatments, especially those ones based on sulphur-rich waters, seem to have anti-inflammatory,
556 keratolytic, and regenerative effects on skin due to a direct pharmacological action of the mineral
557 component and to interactions between thermal and cutaneous microflora with a potential modulation
558 of local immune functions (Gobbi et al. 2009; Mirandola et al. 2011; Katz et al. 2012; Antonelli and
559 Donelli 2018b; Eliasse et al. 2020).

560 Inhalation treatments with vaporized natural mineral waters can have anti-inflammatory, mucolytic,
561 and antimicrobial properties, whereas irrigations with liquid-phase waters also have an action of
562 mechanical washing on the upper respiratory tract (Vv.Aa. 2014; Keller et al. 2014; Casale et al.
563 2018). Among others, waters with sulphur seem to promote mucociliary clearance, regulate local
564 immunity, inflammation, and have antiallergic effects (Rinaldi et al. 2006; Mirandola et al. 2007,
565 2013; Keller et al. 2014; Viegas et al. 2019; Carubbi et al. 2019). For all these reasons, sulphur-rich
566 water inhalations have been proposed as an integrative treatment for patients with chronic obstructive
567 pulmonary disease (Khaltaev et al. 2020).

568 Health effects of hydropinic treatments are mainly mediated by the intake of water minerals (osmotic
569 and prokinetic action on the intestine when the mineral content is high, diuretic effect when the
570 mineral content is low) and by the interaction between water and gut microflora (Vv.Aa. 2014).

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

574

575 **Limitations of this study and new perspectives for future research**

576 First, a major limitation of both primary (clinical) and secondary (review) studies on the topic, which
577 is responsible for hindering optimal retrieval and dissemination of scientific information, is the lack of
578 a widely accepted consensus on a precise English terminology in the field of Medical Hydrology. In
579 other words, terms like balneotherapy, hydrotherapy, and spa therapy are given diverse (and
580 sometimes misleading or confusing) meanings when used by different authors, and this aspect has
581 already been underscored even by several experts (Gutenbrunner et al. 2010; Fioravanti et al. 2017).

582 For this reason, a list of specific definitions was provided in the Introduction section to avoid possible
583 misunderstandings and to address this issue as best as possible.

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

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

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

612 Moreover, authors of some included reviews underscored the difficulty to find a specifically tailored
613 assessment tool to evaluate the quality of primary studies on the topic, which regard atypical, non-
614 pharmacological and hard-to-blind interventions like balneotherapy. Different solutions were adopted
615 by review authors to find an adequate solutions, ranging from the use of a modified version of the
616 standard Cochrane tool (Higgins et al. 2011) to other tools often employed for the evaluation of public
617 health interventions like the Canadian "Quality Assessment Tool for Quantitative Studies" (Armijo-
618 Olivo et al. 2012). To properly address this issue, world experts should agree on a set of essential
619 domains that any assessment tool should include to be adequately usable for evaluating the quality
620 and risk of bias of Medical Hydrology-related trials. In fact, some efforts have already been made

621 towards this direction, for example by developing the “SPAC” checklist (Kamioka et al. 2013) or by
622 evaluating the biasing impact of unblinded balneotherapy (Verhagen et al. 1998).
623 Finally, in order to optimize the collection of available evidence on the topic, any effort was made to
624 retrieve all relevant data reported both in the scientific and in the so called “gray” literature (Petticrew
625 et al. 2008), including findings only displayed in conference proceedings and lectures published in
626 peer-reviewed journals (Roques 2014; Bender 2016; Cao et al. 2020). However, the risk of
627 publication bias, although minimized, could not be fully excluded, and it was not possible to
628 statistically assess it because no quantitative synthesis was feasible.

629
630

631 **Conclusions**

632 Globally, retrieved evidence suggests that Medical Hydrology can be useful for individual wellbeing
633 and public health. In particular, higher-quality studies support the use of spa-related interventions for
634 conditions like osteoarthritis, fibromyalgia, and chronic back pain, but also for chronic venous
635 insufficiency. However, as discussed above, the existing body of evidence has some relevant
636 limitations, especially with regard to non-rheumatic diseases. For this reason, further high-quality
637 clinical trials and observational studies should be designed to confirm the beneficial effects of
638 Medical Hydrology and to thoroughly estimate its effectiveness outside experimental settings in real-
639 life clinical practice.

640

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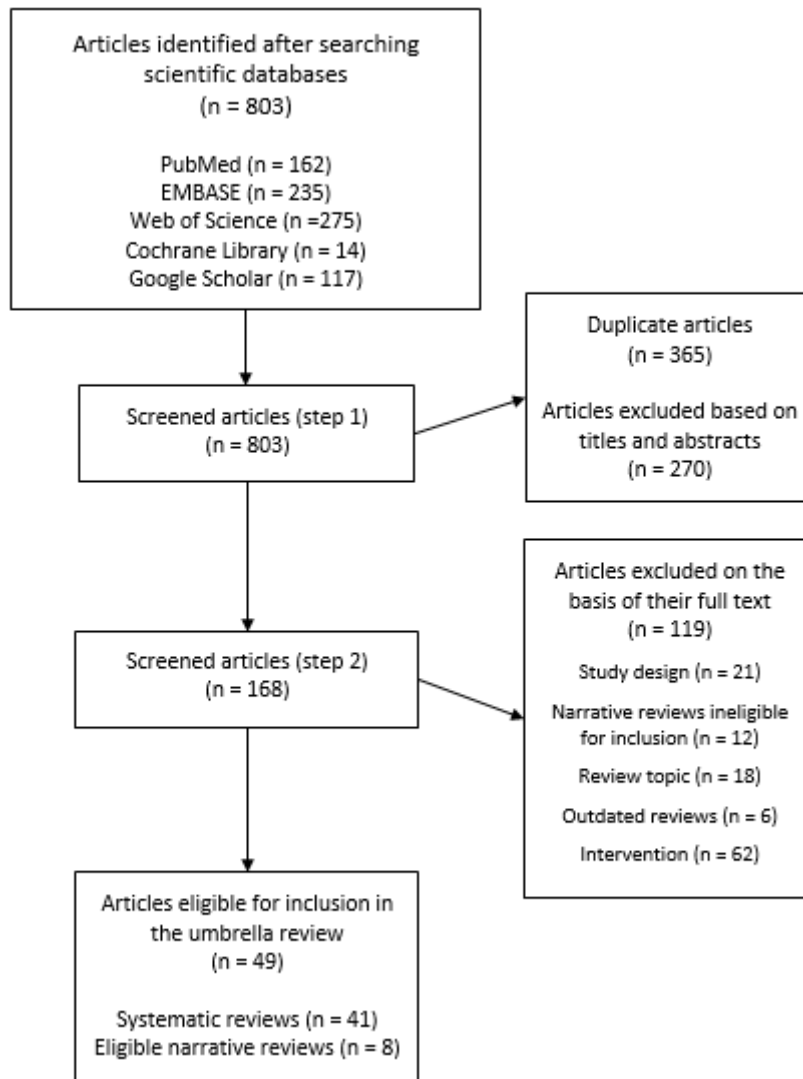


Figure 1. Flow-chart describing the study selection process.

The flow-chart was adapted from the model recommended by the PRISMA guidelines (Moher et al. 2009).

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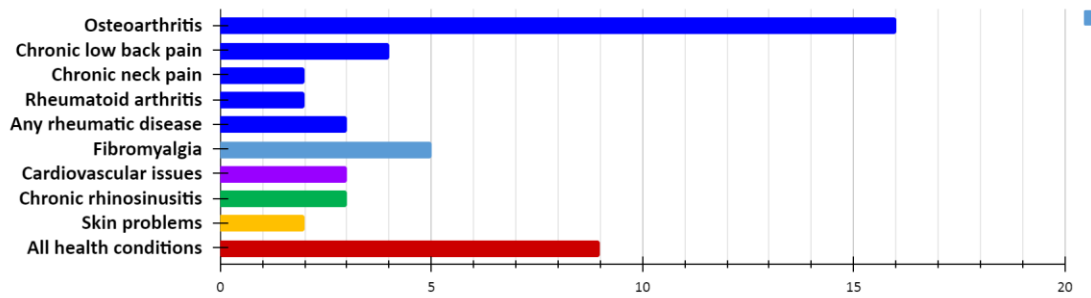


Figure 2. Number of included reviews for each health condition.

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● Balneotherapy ● Mud therapy ● Spa therapy ● Hydroponic therapy
● Inhalation/irrigation therapy ● Any mineral water/mud-based therapy

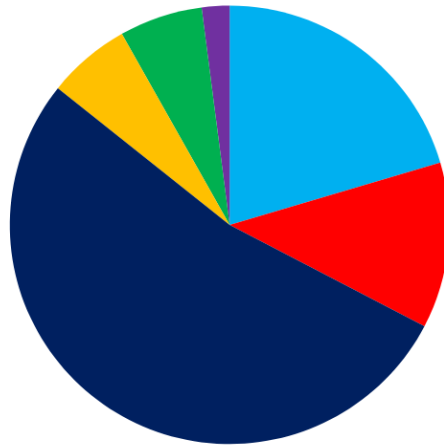


Figure 3. Number of included reviews for each type of therapy.

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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 (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. 2013 (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 sulphur water.
Cao et al. 2020 (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 (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 (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 (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.
Moraes Silva et al. 2019 (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 (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 (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.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Beer et al. 2018 (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 (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 (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 (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 (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	?	?	Mud therapy can significantly attenuate knee osteoarthritis pain.

Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Antonelli & Donelli 2018 (Antonelli and Donelli 2018a)	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 (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 (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 & Francon 2008 (Forestier and Françon 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 (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.
Forestier et al. 2017 (Forestier et al. 2017)	Patients with chronic LBP (2146)	SPA-T	Any type	Pain, functionality, QoL, drugs	SR (18 RCTs)	C	2	Evidence of improvements in pain, disability, and QoL, lasting 3-6 months after intervention. Possible reduction of painkiller intake.
Fraioli et al. 2013 (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 (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 (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 (祥晴 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 M. & Karagulle M.Z. 2015 (Karagülle and Karagülle 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 (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 (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 (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 &	Patients with	SPA-T	Any type	Pain, functionality,	SR+MA (12	B	2	Significant improvements of symptoms and

Sadaghiani 2014 (Naumann and Sadaghiani 2014)	fibromyalgia (553)			QoL, mood	RCTs about SPA-T and 12, excluded, about HT)			QoL with potentially long-lasting effects on pain. No significant effect was observed on depressive symptoms
Pittler et al. 2006 (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 (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 (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 (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 (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.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Casale et al. 2018 (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 (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 sulphur) can have an integrative role in the management of chronic inflammatory diseases of the upper respiratory tract.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Böhmer et al. 2000 (Bohmer 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 (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 (Sulaiman et al. 2020)	Both healthy and diseased subjects at risk of kidney stone formation (470 involved in interventional studies)	HPT (mineral waters with high calcium, bicarbonate or magnesium content)	Tap water	Kidney stone prevention, especially calcium stones	SR (10 clinical interventional studies and 5 observational studies)	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.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Stier-Jarmer et al. 2015 (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).
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- 1034 **Legends:**
1035 BT=Balneotherapy (only baths with mineral waters)
1036 COPD=Chronic Obstructive Pulmonary Disease
1037 CP=Conference Proceedings (review presented at a conference/lecture/symposium and then published in a refereed journal as an abstract)
1038 HPT=Hydropinic therapy (drinking mineral waters)
1039 HT=Hydrotherapy (use of tap non-mineral water)
1040 IT/IR=Inhalation therapy/irrigations (aerosols, vapors, nebulizations, humages, and oral/nasal irrigations)
1041 LBP=Low Back Pain
1042 MA=Meta-analysis
1043 MT=Mud therapy (use of therapeutic muds)
1044 NSAID=NonSteroidal Anti-Inflammatory Drug
1045 OA=Osteoarthritis
1046 QoL=Quality of Life
1047 RCT=Randomized Controlled Trial
1048 RQ=Review Quality or overall quality assessed on the basis of review methods (A=high quality, B=moderate quality, C=low quality,
1049 D=very low quality, ?=the review quality was not assessable because the full-text version was irretrievable)
1050 SPA-T=Spa therapy (multicomponent spa-based treatments)
1051 SR=Systematic Review
1052 TQ=Trials Quality or average quality of clinical studies included in each analyzed review (1=high quality, 2=fair quality, 3=poor quality,
1053 ?=trial quality was not assessed by the authors of included reviews)
1054 TT=Thalassotherapy (baths with sea water)

1055 **Caption:**
1056 Included reviews are grouped on the basis of analyzed intervention and alphabetically sorted according to the first author's surname.

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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 (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 (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 (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 (Françon 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 (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 (Roques 2014)	Patients with any disease (?)	SPA-T	Any type	Any relevant clinical outcome	NR (90 RCTs) - CP	Beneficial effects mostly for arthro-rheumatic diseases, but even for psoriasis, atopic dermatitis, vessel disorders of lower limbs, gynecological conditions, and psychosomatic diseases.
Tenti et al. 2015 (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 (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.

Legends:

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)

Caption:

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

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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 (Bender et al. 2014)	Hungary	Some evidence of efficacy of Hungarian mud baths for several rheumatic conditions, mostly osteoarthritis.
Drobnik and Stebel 2020 (Drobnik and Stebel 2020)	Poland and Austria	Scientific evidence on the “Tolpa” peloid is not strong enough to formulate specific clinical indications.
Karagülle and Karagülle 2004 (Karagülle and Karagülle 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 (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 (Khalilzadeh et al. 2019)	Iran	Possible efficacy of balneotherapy with Persian mineral waters for the management of psoriasis.
Roques et al. 2012 (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 (Stanhope et al. 2018)	Australia and New Zealand	No evidence of efficacy due to complete lack of clinical studies on the topic.

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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	Sulphurous; Salt, bromine; Bicarbonate; Sulphate.
Urinary tract	Recurrent kidney stones	Oral intake	Oligomineral (low mineral content); Bicarbonate.
Gastrointestinal system	Irritable bowel disease with constipation	Oral intake	Bicarbonate; Sulphate; Salt.
Skin	Psoriasis, atopic dermatitis	Baths	Salt, bromine and iodine; Radioactive; Bicarbonate; Sulphurous.
Musculoskeletal system	Osteoarthritis, fibromyalgia	Baths	Sulphurous; Salt, bromine and iodine; Radioactive.

Legends:

According to relevant directives of the European Union and to traditional definitions, mineral waters are labelled as follows (Nappi 2001; Vv.Aa. 2014; Quattrini et al. 2016):

- “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.
- “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.
- “Carbonic” waters: they spring up naturally with a detectable content of free carbon dioxide. When CO₂ content is > 250 mg/L, they are defined as “acid waters” due to their low pH.
- “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”.
- “Radioactive” waters: they have a radioactivity of at least 1 nCi/L, mostly due to their content of Radon.
- “Sulphate-rich” waters: when sulphate 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.
- “Sulphurous” waters: they have a high content of bivalent sulphur.
- “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 labelled as “sodium-rich” waters. They can also contain elements like bromine and iodine.

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1 **Title**

2 Clinical efficacy of Medical Hydrology: an umbrella review

3

4 **Abstract**

5 **Introduction.** The aim of this research was to summarize available scientific evidence on the efficacy
6 of Medical Hydrology for the management of any health condition.

7 **Methods.** The search was conducted on March 26th, 2021, in the following databases: Medline (via
8 PubMed), EMBASE, Web of Science, Cochrane Library, and Google Scholar. All relevant literature
9 reviews investigating the clinical efficacy of interventions characterized by the use of natural mineral
10 waters and muds were included. The quality of studies was assessed with the “AMSTAR 2” tool.

11 **Results.** After article screening, 49 reviews were included in this work. Overall, retrieved scientific
12 evidence suggests that spa therapy is beneficial for patients affected by some specific musculoskeletal
13 conditions, with improvements potentially lasting up to 9 months. Moreover, balneotherapy can be an
14 integrative support for the management of chronic venous insufficiency and some inflammatory skin
15 diseases like psoriasis. The role of spa therapy in rehabilitation appears relevant as well. More limited,
16 although interesting evidence exists for inhalation and hydropinic therapies.

17 **Discussion.** Globally, retrieved evidence suggests that, besides individual wellbeing, Medical
18 Hydrology can be useful for public health. In particular, higher-quality studies seem to support the
19 integrative use of spa-related interventions for conditions like osteoarthritis, fibromyalgia, low back
20 pain of rheumatic origin, and chronic venous insufficiency. However, the body of evidence has some
21 limitations and further clinical trials should be designed for each relevant application to consolidate
22 and expand acquired knowledge.

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24 **Keywords:** Medical hydrology; Clinical efficacy; Public health; Integrative medicine; Umbrella review.

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73 **Introduction**

74

75 **Background and definitions**

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

83 According to the European Union (EU) law, as stated in the Council Directive 80/777/EEC, a natural
84 mineral water is defined as a microbiologically wholesome water (originating in an underground
85 water table or deposit and emerging from a spring), which can be distinguishable from ordinary
86 drinking water by its nature and original purity (The European Parliament and the Council of the
87 European Union 2009). In particular, natural mineral waters are characterized by a specific mineral
88 content and biochemical composition, and by certain effects, including their potential
89 pharmacological, physiological, and clinical action (The European Parliament and the Council of the
90 European Union 2009). In several European countries, this regulatory definition is also accepted by
91 the scientific community (Gutenbrunner et al. 2010). Therefore, in this article, we referred to “natural
92 mineral waters” or, simply, “mineral waters” following the above mentioned description and
93 indicating spring waters used for preventive, therapeutic or rehabilitative purposes in spa centers.
94 With the aim of unequivocally classifying all spa-based interventions and considering a common set
95 of definitions used in the scientific literature (Pittler et al. 2006; Gutenbrunner et al. 2010; Gomes et
96 al. 2013; Fioravanti et al. 2017; Antonelli and Donelli 2018a), the following terms were used in this
97 research work:

- 98 ● “Balneotherapy”: any treatment which only involves the partial or total-body immersion in
99 natural mineral waters (Antonelli and Donelli 2018a; Antonelli et al. 2018). When sea water
100 was used, the term “Talassotherapy” was adopted (Maraver et al. 2011).
- 101 ● “Mud therapy”: any treatment which only involves the application over skin of muds or other
102 peloids, which were defined as natural products used as therapeutic agents and consisting of a
103 mixture of minero-medicinal water with organic and inorganic material, like clay minerals
104 (Carretero 2002). Although usually classified among balneo-therapeutic interventions
105 (Fioravanti et al. 2017), mud therapy was distinguished from standard balneotherapy for its
106 specific characteristics.
- 107 ● “Spa therapy”: any spa-based multicomponent treatment which includes at least a treatment
108 involving the therapeutic use of natural mineral waters (Pittler et al. 2006; Karagülle and

109 Karagülle 2015; Antonelli and Donelli 2018a). Due to its complexity and integrated
110 therapeutic action, fango-balneotherapy, namely mud baths followed or preceded by standard
111 balneotherapy with mineral waters, was classified under this category.

112 ● “Inhalation therapy”: any treatment characterized by the inhalation of natural mineral waters
113 and their gases in the form of vapors, nebulizations, aerosols, politzers, and humages
114 (Costantino et al. 2006; Keller et al. 2014). Oral and nasal irrigations were also included in
115 this category.

116 ● “Hydropinic therapy”: any treatment which implies the oral ingestion of natural mineral
117 waters with medicinal properties (Albertini et al. 2007).

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

124

125 **Rationale**

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

136 Globally, these conditions are mostly caused by chronic diseases with an epidemiologically
137 considerable impact on health-related quality of life (QoL). For example, osteoarthritis is a frequent
138 degenerative disorder of the musculoskeletal system, especially among elderly subjects, with around
139 14 million patients only in the USA, and it is expected to become one of the leading causes of
140 disability worldwide (Vina and Kwok 2018). A relevant impact on public health is also shared by
141 other health conditions which can benefit from spa-based interventions, such as fibromyalgia (Queiroz
142 2013), chronic venous insufficiency (Al Shammeri et al. 2014), chronic inflammatory respiratory
143 diseases (Ferrante et al. 2017), and phlogistic skin disorders like psoriasis (Rachakonda et al. 2014).
144 However, the above mentioned clinical indications were last updated and revised years ago (Ministero
145 della Sanità 1995), and the most recent attempt to collect all available evidence on the topic with a

146 cross-cutting approach dates back to March 2014, when the “Hydroglobe” project was published by a
147 panel of experts with the technical support of the World Health Organization (WHO) (Vv.Aa. 2014).
148 In the light of what stated above, considering that Medical Hydrology has a long-standing tradition
149 (a), that mineral waters and therapeutic muds are easily available as natural resources (b), that spa-
150 based interventions are usually prescribed for epidemiologically relevant health conditions (c), and
151 that scientific evidence rapidly evolves (d), it can be useful to synthesize and critically appraise
152 available findings on the topic with a systematic approach, thus following the basic principles of
153 Evidence-Based Medicine (EBM). This would help to outline an updated list of evidence-based
154 indications for treatments with mineral waters and therapeutic muds, and to guide further research in
155 this field, which is important for both individual wellbeing and public health.

156

157 **Study objective**

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

161

162

163 **Methods**

164

165 **Study design and protocol registration**

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

172

173 **Eligibility criteria**

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

175 → Population: healthy subjects and/or individuals affected by any disease diagnosed in
176 accordance with validated clinical criteria.

177 → Intervention: all spa interventions based on the use of natural mineral waters and therapeutic
178 muds (balneotherapy, mud therapy, spa therapy, inhalation/irrigation therapy, hydropinic
179 therapy). Reviews were excluded when they focused on studies with non-mineral tap water.

180 → Control: any type, including no control.

181 → Outcomes: any relevant clinical outcome (symptomatic and functional improvements,
182 variations in laboratory parameters, reduction of drug consumption, effects on health-related
183 quality of life).
184 → Study design: systematic reviews and meta-analyses of clinical studies. Reviews were
185 excluded when they had no description of research methods and when they included only pre-
186 clinical laboratory studies. Relevant high-quality narrative reviews (reporting a full
187 description of their research methods and based on a quite extensive literature search) were
188 also included along with systematic reviews, but they were synthesized in a separated section
189 of the manuscript. Following the Cochrane recommendations, systematic reviews were
190 defined as any “review [that] attempts to identify, appraise and synthesize all the empirical
191 evidence that meets pre-specified eligibility criteria to answer a specific research question”
192 (The Cochrane Group). Reviews had to be published in a refereed journal to be eligible for
193 inclusion.

194

195 **Information sources**

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

199

200 **Search**

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

204 The following keywords were used: “balneotherapy”, “hydrotherapy”, “thalassotherapy”, “spa
205 therapy”, “water therapy”, “aquatic therapy”, “mud therapy”, “peloid therapy”, psammothrapy,
206 “inhalation therapy”, “endotympanic insufflation”, “poltizer”, “cave therapy”, “hydropinotherapy”,
207 “mineral water*”, “thermal water*”, “hot spring water*”. Specific search strategies adopted for all
208 screened databases were disclosed in the Electronic Supplementary Materials.

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

214

215 **Study selection**

216 The article screening process was conducted with the help of EndNote® software (version X4) by two
217 authors independently (M.A., D.D.). In cases of discrepancies, another author (C.P.) was consulted

218 and disagreements were discussed until consensus was reached. Only systematic reviews and meta-
219 analyses (along with the most relevant and extensive narrative reviews) matching the above-
220 mentioned PICOS criteria were included in this umbrella review. All studies written in English,
221 French, Italian, Spanish, and Portuguese were considered eligible for inclusion. Studies matching
222 inclusion criteria but written in other languages (German, Japanese) were consulted with the support
223 of a translator. In order to maximize retrievable evidence on the topic and to reduce the risk of
224 publication bias, even articles with only an English abstract available for consultation were included
225 in this umbrella review. This detail was reported in the table describing the main characteristics of
226 included systematic reviews, although it was not possible to assess the quality of these research works
227 due to the lack of detailed methodological information.

228

229 **Data collection process**

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

234

235 **Data items**

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

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

246

247 **Risk of bias and quality of studies**

248 The quality of included systematic reviews was independently evaluated by two authors (M.A., D.D.)
249 with a dedicated appraisal tool called “AMSTAR 2”, specifically developed and validated by a team
250 of expert methodologists for this purpose (Shea et al. 2017). In cases of disagreement, items were
251 discussed with another author (C.P.) until consensus was reached. The “AMSTAR 2” tool provides a
252 16-item checklist aimed to explore different methodological domains, including the appropriateness
253 of inclusion/exclusion criteria, search strategies, article selection, data extraction, risk-of-bias
254 assessment, heterogeneity evaluation, quantitative synthesis and critical discussion. Each item

255 corresponds to a question, which can be answered with “yes” or “no” (sometimes “yes, but partially”
256 is available as a middle response). Included reviews were evaluated one by one and their overall
257 quality was rated as:

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

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

267 The methodological quality of narrative reviews was assessed with the SANRA scale (Baethge et al.
268 2019) during the article selection process and only higher-quality narrative reviews were included in
269 this work. The SANRA is a 6-item scale which evaluates the relevance/importance of a narrative
270 review (1), whether its aim is sufficiently focused (2), if the literature search is broad enough (3),
271 whether referencing (4), scientific reasoning (5), and presentation of data (6) are appropriate. Each
272 item score can vary from 0 to 2, and the overall review quality score can range from 0 to 12 (high-
273 quality narrative reviews usually score 9 or more SANRA points).

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

277

278 **Synthesis of results**

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

286

287

288 **Results**

289

290 **Study selection**

291 Overall, the literature search yielded 803 results and, after screening and selection of potentially
292 eligible articles, 49 reviews (41 systematic and 8 narrative reviews) were eventually included in this
293 research work. Details of the article selection process, along with the main reasons for exclusion of
294 non-eligible studies, were summarized in a dedicated flowchart (Figure 1). The list of all articles
295 eligible for a full-text assessment and then excluded after a thorough evaluation was provided in the
296 Electronic Supplementary Materials. The quality of a review available as a conference abstract in a
297 refereed journal (Cao et al. 2020) was assessed on the basis of information retrieved from the
298 corresponding preprint (<https://www.researchsquare.com/article/rs-16293/v1>). An article was kindly
299 provided by the authors after our direct inquiry (Raza et al. 2020). It was not possible to consult the
300 full-text version of a review but this study was included all the same for better comprehensiveness
301 (essential data were extracted from the abstract) (Zhen-han et al. 2014). A meta-analysis found
302 through snowballing and published as a Ph.D. thesis was excluded from the main search but
303 mentioned in the Discussion section to better analyze the mechanisms of action of mud therapy for
304 osteoarthritis (Crespin 2017).

305

306 **Characteristics of included studies**

307 The main characteristics of all included studies, collected and described in accordance with the
308 PICOS criteria, were reported in Table 1 (systematic reviews) and Table 2 (narrative reviews), along
309 with a brief summary of the authors' conclusions and, for systematic reviews, with their overall
310 methodological quality evaluated in accordance with the AMSTAR-2 recommendations (Bohmer et
311 al. 2000; Brosseau et al. 2002; 洋青 et al. 2006; Pittler et al. 2006; Verhagen et al. 2007, 2015;
312 Forestier and Françon 2008; Schuh 2009; Harzy et al. 2009; Falagas et al. 2009; Langhorst et al.
313 2009; Guidelli et al. 2012; Fraioli et al. 2013, 2018; Espejo-Antúnez et al. 2013; Liu et al. 2013;
314 Zhen-han et al. 2014; Roques 2014; Keller et al. 2014; Naumann and Sadaghiani 2014; Karagülle and
315 Karagülle 2015; Françon et al. 2015; Tenti et al. 2015; Stier-Jarmer et al. 2015; Fortunati et al. 2016;
316 Xiang et al. 2016; Forestier et al. 2016, 2017; Bender 2016; Santos et al. 2016; Matsumoto et al. 2017;
317 Naumann et al. 2017; Passali et al. 2017; Morer et al. 2017; Casale et al. 2018; Antonelli and Donelli
318 2018a; Antonelli et al. 2018; Beer et al. 2018; An et al. 2019; Corvillo et al. 2019; de Moraes Silva et
319 al. 2019; Bai et al. 2019; Yuan et al. 2019; Raza et al. 2020; Sulaiman et al. 2020; Hou et al. 2020;
320 Cao et al. 2020; Cacciapuoti et al. 2020; Gravelier et al. 2020).

321

322 **Population**

323 The number of study participants whose data were analyzed within included systematic reviews
324 varied from a minimum of 54 (Bohmer et al. 2000) to a maximum of 13782 (Stier-Jarmer et al. 2015),
325 with a median value of 731. In the majority of included reviews, regardless of their design (systematic
326 or narrative), study participants were patients with chronic conditions, such as rheumatic
327 (osteoarthritis, fibromyalgia, back pain of rheumatic origin, rheumatoid arthritis), cardiovascular

328 (chronic venous insufficiency, hypertension), dermatologic, respiratory, otorhinolaryngological,
329 neurologic, digestive, and urologic diseases (Figure 2). In a review, the effects of hydropinic therapy
330 on healthy subjects were studied (Bohmer et al. 2000), whereas studies with both healthy and diseased
331 individuals were analyzed in three research works (Antonelli and Donelli 2018a; An et al. 2019;
332 Sulaiman et al. 2020).

333

334 **Intervention**

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

342

343 **Control**

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

352

353 **Outcomes**

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

360

361 **Study design**

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

365 Xiang et al. 2016; Matsumoto et al. 2017; Naumann et al. 2017; Antonelli et al. 2018; de Moraes
366 Silva et al. 2019; Bai et al. 2019; Raza et al. 2020; Hou et al. 2020; Cao et al. 2020). Eight (8)
367 included reviews had a narrative design, but they still provided an extensive, quasi-systematic and
368 valuable overview of the scientific literature (Guidelli et al. 2012; Roques 2014; Françon et al. 2015;
369 Tenti et al. 2015; Fortunati et al. 2016; Bender 2016; Passali et al. 2017; Cacciapuoti et al. 2020), thus
370 outlining a state-of-the-art description of specific subtopics, such as the efficacy of spa therapy for
371 respiratory illnesses (Passali et al. 2017), skin diseases (Cacciapuoti et al. 2020), or hand osteoarthritis
372 (Fortunati et al. 2016). The number of clinical studies included in the systematic reviews varied from
373 a minimum of 3 (Brosseau et al. 2002; Fortunati et al. 2016) to a maximum of 41 (Stier-Jarmer et al.
374 2015), with a median of 12. Such primary studies were mostly Randomized Controlled Trials,
375 although some of them were characterized by a different design, like nonrandomized trials,
376 uncontrolled studies, and observational investigations. The quality of clinical studies tended to range
377 from fair to poor, with a potential risk of bias mostly arising from small sample size, lack of adequate
378 control, no randomization of trial participants, and poor information about blinding of intervention.

379

380 **Quality of included studies**

381 After the methodological assessment of included systematic reviews with the “AMSTAR 2” tool, the
382 quality of analyzed research works was judged as good (A) to moderate (B) in 11 cases (Pittler et al.
383 2006; Verhagen et al. 2007, 2015; Harzy et al. 2009; Langhorst et al. 2009; Naumann and Sadaghiani
384 2014; Stier-Jarmer et al. 2015; Santos et al. 2016; Matsumoto et al. 2017; de Moraes Silva et al. 2019;
385 Hou et al. 2020) and low (C) to very low (D) in the remaining cases, as reported in Table 1 (see the
386 Supplementary Materials for further details). It was not possible to assess the quality of a systematic
387 review because its full-text version was unavailable (Zhen-han et al. 2014). In general, the most
388 frequent methodological weaknesses found within included reviews were excessively narrow search
389 strategies, a poor description of study selection and evaluation processes, and limited consideration of
390 the trial risk-of-bias assessment for informing a critical discussion. Major strengths were usually a
391 clear definition of the research question and, where applicable, a good methodological level of meta-
392 analyses.

393

394

395 **Discussion**

396

397 **Efficacy of interventions**

398 Scientific evidence from included reviews indicates that balneotherapy, mud therapy, and spa therapy
399 can significantly improve clinical parameters like pain, joint functionality, mobility, and quality of life
400 of patients with chronic musculoskeletal conditions, mostly osteoarthritis, fibromyalgia, and other

401 pain-related rheumatic diseases. For these subjects, beneficial effects may last up to 9 months after
402 intervention (on average, 3 to 6 months) (Forestier et al. 2016, 2017), and clinical improvements are
403 associated with a reduced intake of analgesic drugs (Françon et al. 2015; Tenti et al. 2015; Forestier et
404 al. 2017; Fraioli et al. 2018; Antonelli et al. 2018). Furthermore, in two included research works, it
405 was demonstrated that balneotherapy is superior to the same treatment administered in pools with tap
406 water (“sham balneotherapy”) in terms of clinical benefits and improved quality of life among
407 patients with osteoarthritis and fibromyalgia, thus underscoring the contribution of the specific
408 biochemical composition of natural mineral waters to the overall therapeutic effect (Morer et al. 2017;
409 Antonelli et al. 2018).

410 With regard to vascular health, balneotherapy can be useful for the amelioration of pain, quality of
411 life, and skin pigmentation due to chronic venous insufficiency in lower limbs (Stier-Jarmer et al.
412 2015; de Moraes Silva et al. 2019), and it appears not to have negative effects on blood pressure
413 levels (Yuan et al. 2019). More limited evidence suggests that balneotherapy, including talassotherapy
414 (sea water baths), can be beneficial for patients with skin diseases like psoriasis and atopic dermatitis
415 (Schuh 2009; Falagas et al. 2009; Stier-Jarmer et al. 2015; Cacciapuoti et al. 2020), and possibly for
416 the integrative treatment of burn scars (Gravelier et al. 2020).

417 Balneotherapy, mud therapy, and spa therapy can also improve mental wellbeing and psychophysical
418 stress, and this is demonstrated by studies in which stress hormone levels were measured (Roques
419 2014; Stier-Jarmer et al. 2015; Antonelli and Donelli 2018a). An interesting role for orthopedic or
420 neurological patients of aquatic rehabilitation in pools with natural mineral waters has been
421 underscored by several authors, with beneficial effects on the most important clinical outcomes
422 (Falagas et al. 2009; Stier-Jarmer et al. 2015).

423 With regard to inhalation therapy, clinical improvements were observed in patients with diseases of
424 the upper and lower respiratory tract, mostly chronic rhinosinusitis and bronchitis (Schuh 2009; Keller
425 et al. 2014; Stier-Jarmer et al. 2015; Casale et al. 2018), but even in subjects with chatarral otitis
426 (Stier-Jarmer et al. 2015). Scientific evidence suggests an interesting role of highly mineralized or
427 sulphur waters for these illnesses (Schuh 2009; Keller et al. 2014; Casale et al. 2018).

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

434 Systematic reviews including only clinical studies conducted in a specific country or region of the
435 world were collected in Table 3 (Karagülle and Karagülle 2004; Roques et al. 2012; Katz et al. 2012;
436 Bender et al. 2014; Stanhope et al. 2018; Khalilzadeh et al. 2019; Drobnik and Stebel 2020). These
437 research works were mostly carried out in regions where Medical Hydrology is widely spread and

438 well known, such as Europe or the Middle East, and they outlined an efficacy profile of
439 balneotherapy, mud therapy, and spa therapy which is similar to that one already described in
440 literature reviews collected in Table 1 and Table 2. Additionally, some interesting findings suggested
441 that balneotherapy with specific waters characterized by a high mineral content, like Dead Sea water,
442 can be useful for the treatment of psoriasis (Katz et al. 2012; Khalilzadeh et al. 2019). Some authors
443 also underscored the lack of relevant studies in continents like Oceania, thus urging the need for
444 clinical investigations in Australia or New Zealand, where mineral water springs exist, but they are
445 currently underused for medicinal purposes (Stanhope et al. 2018).
446 Globally, systematic reviews characterized by a higher overall quality of their methodological design
447 tended to support the efficacy of balneotherapy, mud therapy, and spa therapy for the integrative
448 management of osteoarthritis (especially knee osteoarthritis), fibromyalgia, low back pain of
449 rheumatic origin, and chronic venous insufficiency (Pittler et al. 2006; Verhagen et al. 2007, 2015;
450 Harzy et al. 2009; Langhorst et al. 2009; Naumann and Sadaghiani 2014; Stier-Jarmer et al. 2015;
451 Santos et al. 2016; Matsumoto et al. 2017; de Moraes Silva et al. 2019; Hou et al. 2020). However, the
452 authors underscored that clinical evidence needs to grow before firm conclusions can be drawn, and
453 this is even more relevant for non-rheumatic conditions (for example, respiratory or skin illnesses).
454 All the same, in general, considering both trial results and empirical observations, spa-based
455 treatments appear useful for rehabilitation and chronic disease management, because they seem
456 capable of exerting a beneficial action on symptom control and psychophysical wellbeing.

457

458 **Safety and tolerability of interventions**

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

462 The most important contraindications to treatments based on mineral waters and therapeutic muds are
463 mainly derived from tradition and they can be grouped into three categories (Nappi 2001; Vv.Aa.
464 2014):

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

474 Possible side effects of spa-based interventions are usually mild and often resolve spontaneously after
475 treatment discontinuation: they are mostly due to an individual response, thus being highly “patient-
476 specific”, and their occurrence is worsened by an improper or unsupervised administration of
477 intervention (Nappi 2001; Vv.Aa. 2014). Side effects generally include symptoms like headache,
478 dizziness and nausea, mild relapses of local chronic pain, sleep disturbances, heart palpitations, or a
479 general sensation of irritability and fatigue (rarely coupled with a short-lasting low-grade fever)
480 (Vv.Aa. 2014). Additionally, intervention-specific side effects can occur, such as diarrhea and
481 hydroelectrolytic imbalances due to an overconsumption of highly mineralized waters, a temporary
482 increase of fluid secretions in the airways (with runny nose and cough) after some inhalation
483 therapies, or cutaneous irritation caused by hot mud application on irritable skin.
484 Extreme caution is also advised in more fragile individuals like pediatric patients, pregnant women,
485 and very elderly subjects, whose clinical response to spa-based interventions can be less predictable
486 with a potential higher incidence of more severe side effects.
487 For all these reasons, a medical check and supervision are strongly advised for an appropriate
488 prescription of spa-based interventions, not only to make the most of them on the basis of the patient’s
489 characteristics and disease, but even to avoid the onset of adverse events, thus optimizing the safety
490 and tolerability of such treatments.

491

492 **Mechanisms of action: hypotheses and evidence-based explanations**

493 In light of scientific evidence described by expert authors of the “*HydroGlobe*” project, effects on
494 health of Medical Hydrology-related treatments have been reported to be the following ones (Vv.Aa.
495 2014):

- 496 ● Antalgic effect,
- 497 ● Myorelaxant action,
- 498 ● Activation of microcirculation,
- 499 ● Immunomodulation,
- 500 ● Neuro-hormonal stimulation,
- 501 ● Improvement of fat and carbohydrate metabolism.

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

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

- 509 1. Balneo-therapeutic treatments, such as baths with natural mineral waters and mud therapy.

510 2. Inhalation-based treatments, such as vapours or aerosols derived from natural mineral waters
511 inhaled for medicinal purposes.

512 3. Hydropinic treatments, when natural mineral waters are taken orally as therapeutic drinks.

513 Balneo-therapeutic treatments are believed to exert their global therapeutic effect on the body thanks
514 to a synergistic combination of mechanical (hydrostatic pressure), thermal (high temperature), and
515 biochemical actions, the latter due to both the mineral (osmotic pressure and direct activity) and the
516 organic (with anti-inflammatory and immunomodulatory properties) components of waters and muds
517 (Vv.Aa. 2014; Fioravanti et al. 2017; Antonelli and Donelli 2018b). From a physiological point of
518 view, balneo-therapeutic treatments can increase serum β -endorphins and can modulate cortisol levels
519 in such a way as to improve individual stress resilience without disrupting circadian rhythms of this
520 hormone (Fioravanti et al. 2011; Antonelli and Donelli 2018a). The long-term increase of cortisol
521 awakening response due to a cycle of balneo-therapeutic treatments may be the reason why, in some
522 clinical studies, the effects on health of balneotherapy, mud therapy, and spa therapy were observed to
523 last for a few months after intervention (Forestier et al. 2016; Antonelli and Donelli 2018a). If we
524 consider inflammatory mediators, mud applications followed by baths with natural mineral waters can
525 reduce the production of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1 β (IL-1 β),
526 and tumor necrosis factor alpha (TNF- α) (Fioravanti et al. 2011). Quantitative data from the “gray”
527 literature also show that, at least for osteoarthritis, therapeutic mud applications are superior to simple
528 hot packs to improve joint functionality and pain, thus underscoring the therapeutic importance of the
529 organic component (Crespin 2017). It is possible that the effect of balneo-therapeutic treatments on
530 the inflammatory response and interleukin production is due to modifications of microRNA
531 expressions induced by thermal and mechanical stimuli, as observed in a cohort of patients with
532 osteoarthritis (Giannitti et al. 2017). At a joint level, balneo-therapeutic treatments may stimulate
533 cartilage metabolism through mediators like the insulin-like growth factor-1 (IGF1), they may exert
534 an antioxidant effect by reducing the release of Reactive Oxygen and Nitrogen Species (Fioravanti et
535 al. 2011; Masselli et al. 2020) and also modulate intracellular mediators like protein kinases involved
536 in cartilage growth and cell proliferation (Queirolo et al. 2016; Martini et al. 2018). Mud baths are
537 also associated with a decrease in serum levels of adiponectin and resistin, hormonal substances
538 probably implied in the progression of chronic degenerative diseases like osteoarthritis (Fioravanti et
539 al. 2015). Furthermore, transcutaneous absorption of antiphlogistic substances released by water and
540 mud microflora may contribute to the overall pharmacological effect of balneo-therapeutic treatments
541 (Vv.Aa. 2014; Antonelli and Donelli 2018b). More details about possible mechanism of action of
542 balneotherapy, as hypothesized on the basis of in-vitro laboratory studies, have recently been
543 collected in a comprehensive literature review, demonstrating the anti-inflammatory, antioxidant,
544 chondroprotective, and immunosuppressive role of this type of intervention at a cellular level
545 (Cheschi et al. 2020). Regarding balneotherapy and peripheral venous circulation, it is believed that
546 the main therapeutic action of baths is determined by the hydrostatic and osmotic pressure of natural

547 mineral waters, which seems capable of reducing pain and oedema (de Moraes Silva et al. 2019). The
548 combination of baths with hydrojet massage, Kneipp therapy (in which hot and cold baths are
549 alternated), and physical exercise can determine a useful compression of peripheral veins, thanks to an
550 external (water pressure) and internal (muscle contraction) synergistic action (de Moraes Silva et al.
551 2019). In particular, beneficial effects for the cardiovascular system seem to be more frequently
552 associated with balneo-therapeutic sessions in carbon dioxide-rich water, which may be responsible
553 for lowering peripheral vascular resistance and increasing blood flow in a more pronounced way if
554 compared with other water types (Pagourelas et al. 2011). Additionally, balneo-therapeutic
555 treatments, especially those ones based on sulphur-rich waters, seem to have anti-inflammatory,
556 keratolytic, and regenerative effects on skin due to a direct pharmacological action of the mineral
557 component and to interactions between thermal and cutaneous microflora with a potential modulation
558 of local immune functions (Gobbi et al. 2009; Mirandola et al. 2011; Katz et al. 2012; Antonelli and
559 Donelli 2018b; Eliasse et al. 2020).

560 Inhalation treatments with vaporized natural mineral waters can have anti-inflammatory, mucolytic,
561 and antimicrobial properties, whereas irrigations with liquid-phase waters also have an action of
562 mechanical washing on the upper respiratory tract (Vv.Aa. 2014; Keller et al. 2014; Casale et al.
563 2018). Among others, waters with sulphur seem to promote mucociliary clearance, regulate local
564 immunity, inflammation, and have antiallergic effects (Rinaldi et al. 2006; Mirandola et al. 2007,
565 2013; Keller et al. 2014; Viegas et al. 2019; Carubbi et al. 2019). For all these reasons, sulphur-rich
566 water inhalations have been proposed as an integrative treatment for patients with chronic obstructive
567 pulmonary disease (Khaltaev et al. 2020).

568 Health effects of hydropinic treatments are mainly mediated by the intake of water minerals (osmotic
569 and prokinetic action on the intestine when the mineral content is high, diuretic effect when the
570 mineral content is low) and by the interaction between water and gut microflora (Vv.Aa. 2014).

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

574

575 **Limitations of this study and new perspectives for future research**

576 First, a major limitation of both primary (clinical) and secondary (review) studies on the topic, which
577 is responsible for hindering optimal retrieval and dissemination of scientific information, is the lack of
578 a widely accepted consensus on a precise English terminology in the field of Medical Hydrology. In
579 other words, terms like balneotherapy, hydrotherapy, and spa therapy are given diverse (and
580 sometimes misleading or confusing) meanings when used by different authors, and this aspect has
581 already been underscored even by several experts (Gutenbrunner et al. 2010; Fioravanti et al. 2017).

582 For this reason, a list of specific definitions was provided in the Introduction section to avoid possible
583 misunderstandings and to address this issue as best as possible.

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

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

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

612 Moreover, authors of some included reviews underscored the difficulty to find a specifically tailored
613 assessment tool to evaluate the quality of primary studies on the topic, which regard atypical, non-
614 pharmacological and hard-to-blind interventions like balneotherapy. Different solutions were adopted
615 by review authors to find an adequate solutions, ranging from the use of a modified version of the
616 standard Cochrane tool (Higgins et al. 2011) to other tools often employed for the evaluation of public
617 health interventions like the Canadian "Quality Assessment Tool for Quantitative Studies" (Armijo-
618 Olivo et al. 2012). To properly address this issue, world experts should agree on a set of essential
619 domains that any assessment tool should include to be adequately usable for evaluating the quality
620 and risk of bias of Medical Hydrology-related trials. In fact, some efforts have already been made

621 towards this direction, for example by developing the “SPAC” checklist (Kamioka et al. 2013) or by
622 evaluating the biasing impact of unblinded balneotherapy (Verhagen et al. 1998).
623 Finally, in order to optimize the collection of available evidence on the topic, any effort was made to
624 retrieve all relevant data reported both in the scientific and in the so called “gray” literature (Petticrew
625 et al. 2008), including findings only displayed in conference proceedings and lectures published in
626 peer-reviewed journals (Roques 2014; Bender 2016; Cao et al. 2020). However, the risk of
627 publication bias, although minimized, could not be fully excluded, and it was not possible to
628 statistically assess it because no quantitative synthesis was feasible.

629

630

631 **Conclusions**

632 Globally, retrieved evidence suggests that Medical Hydrology can be useful for individual wellbeing
633 and public health. In particular, higher-quality studies support the use of spa-related interventions for
634 conditions like osteoarthritis, fibromyalgia, and chronic back pain, but also for chronic venous
635 insufficiency. However, as discussed above, the existing body of evidence has some relevant
636 limitations, especially with regard to non-rheumatic diseases. For this reason, further high-quality
637 clinical trials and observational studies should be designed to confirm the beneficial effects of
638 Medical Hydrology and to thoroughly estimate its effectiveness outside experimental settings in real-
639 life clinical practice.

640

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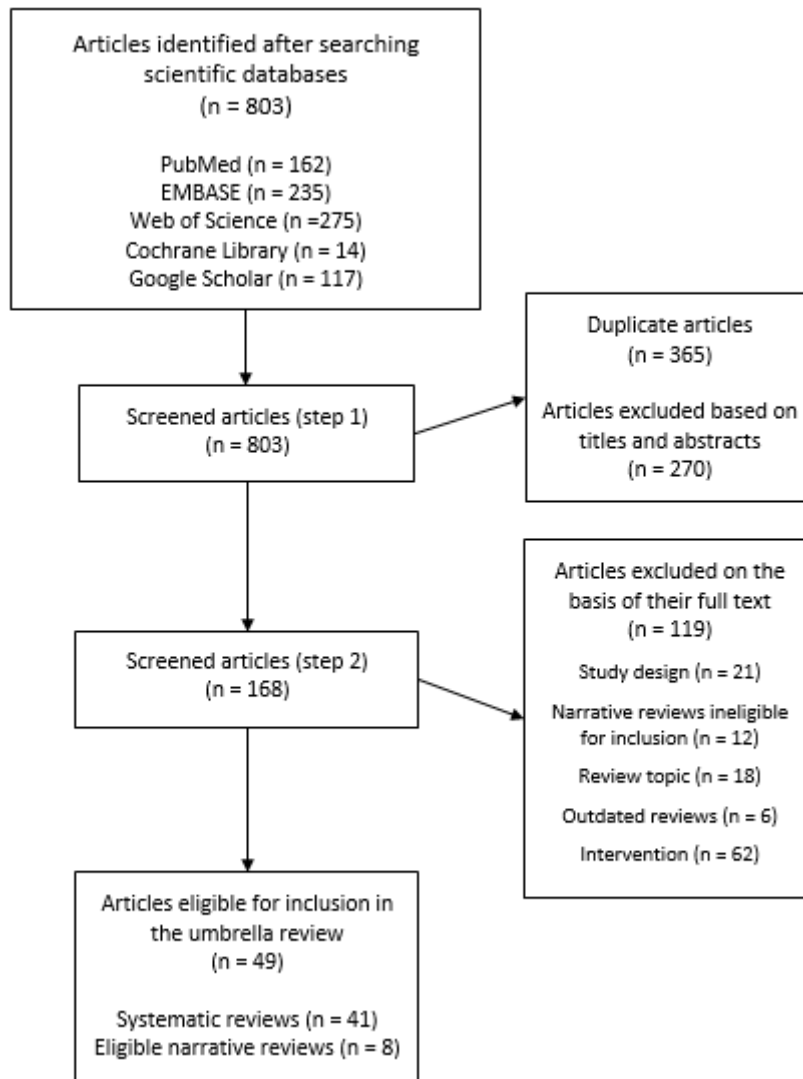


Figure 1. Flow-chart describing the study selection process.

The flow-chart was adapted from the model recommended by the PRISMA guidelines (Moher et al. 2009).

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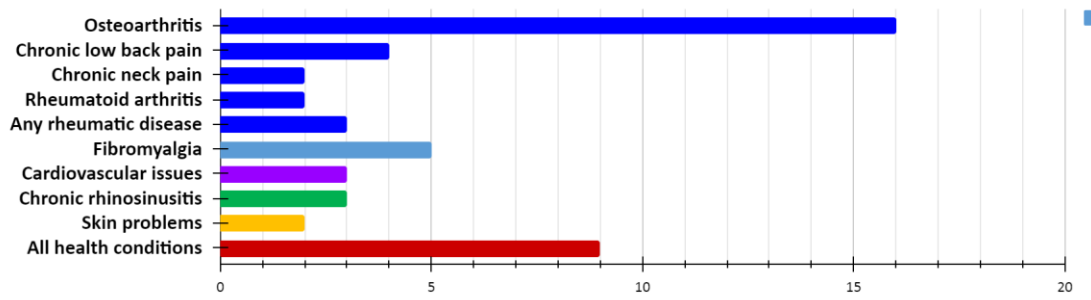


Figure 2. Number of included reviews for each health condition.

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● Balneotherapy ● Mud therapy ● Spa therapy ● Hydroponic therapy
● Inhalation/irrigation therapy ● Any mineral water/mud-based therapy

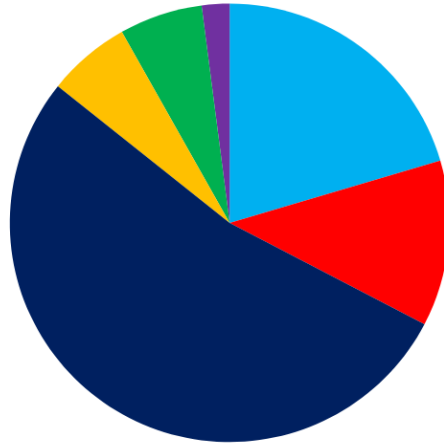


Figure 3. Number of included reviews for each type of therapy.

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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 (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. 2013 (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 sulphur water.
Cao et al. 2020 (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 (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 (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 (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.
Moraes Silva et al. 2019 (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 (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) (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.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Beer et al. 2018 (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 (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 (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 (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 (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	?	?	Mud therapy can significantly attenuate knee osteoarthritis pain.

(Zhen-han et al. 2014)					only			
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Antonelli & Donelli 2018 (Antonelli and Donelli 2018a)	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 (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 (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 & Francon 2008 (Forestier and Françon 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 (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.
Forestier et al. 2017 (Forestier et al. 2017)	Patients with chronic LBP (2146)	SPA-T	Any type	Pain, functionality, QoL, drugs	SR (18 RCTs)	C	2	Evidence of improvements in pain, disability, and QoL, lasting 3-6 months after intervention. Possible reduction of painkiller intake.
Fraioli et al. 2013 (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 (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 (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 (祥晴 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 M. & Karagulle M.Z. 2015 (Karagülle and Karagülle 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 (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 (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 (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 &	Patients with	SPA-T	Any type	Pain, functionality,	SR+MA (12	B	2	Significant improvements of symptoms and

Sadaghiani 2014 (Naumann and Sadaghiani 2014)	fibromyalgia (553)			QoL, mood	RCTs about SPA-T and 12, excluded, about HT)			QoL with potentially long-lasting effects on pain. No significant effect was observed on depressive symptoms
Pittler et al. 2006 (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 (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 (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 (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 (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.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Casale et al. 2018 (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 (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 sulphur) can have an integrative role in the management of chronic inflammatory diseases of the upper respiratory tract.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Böhmer et al. 2000 (Bohmer 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 (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 (Sulaiman et al. 2020)	Both healthy and diseased subjects at risk of kidney stone formation (470 involved in interventional studies)	HPT (mineral waters with high calcium, bicarbonate or magnesium content)	Tap water	Kidney stone prevention, especially calcium stones	SR (10 clinical interventional studies and 5 observational studies)	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.
Reference	Population (n)	Intervention	Control	Outcomes	Study design	RQ	TQ	Conclusions
Stier-Jarmer et al. 2015 (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).
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- 1034 **Legends:**
1035 BT=Balneotherapy (only baths with mineral waters)
1036 COPD=Chronic Obstructive Pulmonary Disease
1037 CP=Conference Proceedings (review presented at a conference/lecture/symposium and then published in a refereed journal as an abstract)
1038 HPT=Hydropinic therapy (drinking mineral waters)
1039 HT=Hydrotherapy (use of tap non-mineral water)
1040 IT/IR=Inhalation therapy/irrigations (aerosols, vapors, nebulizations, humages, and oral/nasal irrigations)
1041 LBP=Low Back Pain
1042 MA=Meta-analysis
1043 MT=Mud therapy (use of therapeutic muds)
1044 NSAID=NonSteroidal Anti-Inflammatory Drug
1045 OA=Osteoarthritis
1046 QoL=Quality of Life
1047 RCT=Randomized Controlled Trial
1048 RQ=Review Quality or overall quality assessed on the basis of review methods (A=high quality, B=moderate quality, C=low quality,
1049 D=very low quality, ?=the review quality was not assessable because the full-text version was irretrievable)
1050 SPA-T=Spa therapy (multicomponent spa-based treatments)
1051 SR=Systematic Review
1052 TQ=Trials Quality or average quality of clinical studies included in each analyzed review (1=high quality, 2=fair quality, 3=poor quality,
1053 ?=trial quality was not assessed by the authors of included reviews)
1054 TT=Thalassotherapy (baths with sea water)

1055 **Caption:**
1056 Included reviews are grouped on the basis of analyzed intervention and alphabetically sorted according to the first author's surname.

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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 (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 (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 (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 (Françon 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 (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 (Roques 2014)	Patients with any disease (?)	SPA-T	Any type	Any relevant clinical outcome	NR (90 RCTs) - CP	Beneficial effects mostly for arthro-rheumatic diseases, but even for psoriasis, atopic dermatitis, vessel disorders of lower limbs, gynecological conditions, and psychosomatic diseases.
Tenti et al. 2015 (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 (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.

Legends:

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)

Caption:

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

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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 (Bender et al. 2014)	Hungary	Some evidence of efficacy of Hungarian mud baths for several rheumatic conditions, mostly osteoarthritis.
Drobnik and Stebel 2020 (Drobnik and Stebel 2020)	Poland and Austria	Scientific evidence on the “Tolpa” peloid is not strong enough to formulate specific clinical indications.
Karagülle and Karagülle 2004 (Karagülle and Karagülle 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 (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 (Khalilzadeh et al. 2019)	Iran	Possible efficacy of balneotherapy with Persian mineral waters for the management of psoriasis.
Roques et al. 2012 (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 (Stanhope et al. 2018)	Australia and New Zealand	No evidence of efficacy due to complete lack of clinical studies on the topic.

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TABLE 4. Water types and clinical indications according to the “HydroGlobe” study (2014).

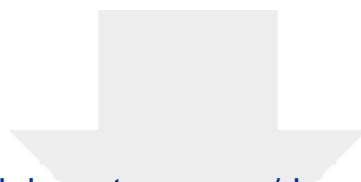
Affected apparatus	Example	Administration	Recommended water types
Ear-Nose-Throat and Respiratory tract	Chronic rhinosinusitis or bronchitis	Inhalations, irrigations	Sulphurous; Salt, bromine and iodine; Bicarbonate; Arsenical-ferruginous.
Cardiovascular system	Chronic venous insufficiency	Baths	Carbonic.
Gynecological apparatus	Chronic vaginitis	Irrigations	Sulphurous; Salt, bromine; Bicarbonate; Sulphate.
Urinary tract	Recurrent kidney stones	Oral intake	Oligomineral (low mineral content); Bicarbonate.
Gastrointestinal system	Irritable bowel disease with constipation	Oral intake	Bicarbonate; Sulphate; Salt.
Skin	Psoriasis, atopic dermatitis	Baths	Salt, bromine and iodine; Radioactive; Bicarbonate; Sulphurous.
Musculoskeletal system	Osteoarthritis, fibromyalgia	Baths	Sulphurous; Salt, bromine and iodine; Radioactive.

Legends:

According to relevant directives of the European Union and to traditional definitions, mineral waters are labelled as follows (Nappi 2001; Vv.Aa. 2014; Quattrini et al. 2016):

- “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.
- “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.
- “Carbonic” waters: they spring up naturally with a detectable content of free carbon dioxide. When CO₂ content is > 250 mg/L, they are defined as “acid waters” due to their low pH.
- “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”.
- “Radioactive” waters: they have a radioactivity of at least 1 nCi/L, mostly due to their content of Radon.
- “Sulphate-rich” waters: when sulphate 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.
- “Sulphurous” waters: they have a high content of bivalent sulphur.
- “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 labelled as “sodium-rich” waters. They can also contain elements like bromine and iodine.

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