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Reviews · Systematic REVIEW

Mud therapy and rehabilitation - scientific relevance in the last six years (2015 – 2020) Systematic literature review and meta-analysis based on the PRISMA paradigm

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Abstract

Background. Balneotherapy is a stimulation - adaptation treatment method applied in the forms of bathing, drinking, and inhalation cures performed with natural therapeutic factors, a method which is acting in three main ways: thermally, mechanically, and chemically. Mud or peloids are natural therapeutic factors formed by natural processes under the influence of biological and geological phenomena, which in a finely dissolved state and mixed with water (mud) are used in medical practice in the form of baths or local procedures.

Objective. This systematic review aims to rigorously select related articles and identify within their content, the main possible uses of therapeutic mud and physiological mechanisms, to see the main region of scientific interest for pelotherapy, and to discuss the value of mud therapy in rehabilitation medicine.

Methods. The working method is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched for open-access articles published in English, between January 2015 and December 2020, from the following databases: Cochrane, Elsevier, NCBI/PubMed, NCBI/PMC, PEDro, and ISI Web of Knowledge/Science (the latter was also used to identify ISI indexed articles). The contextually searched syntax used was "Pelotherapy/Peloidotherapy/Mud-therapy/ /Fango-therapy AND Rehabilitation". The selected articles were analyzed in detail regarding pathologies addressed by mud therapy and country scientific relevance for this therapeutic method. The meta-analysis proceeded was designated to estimate the prevalence of various pathologies in the use of mud therapy.

Results. Our search identified, first, **394** articles. Based on the successive filtering stages and, respectively, on the classification criteria of the Physiotherapy Evidence Database (PEDro), we finally identified/retained and analyzed **68** articles. Although, in principle, a rigorous method – and we have followed the PRISMA type paradigm – there still might be some missing works of our related article selection. On the other hand, to augment/ consolidate our documentation base, we have used also **40** papers freely found in the literature, and even – aiming, too, at an as exhaustive knowledge underpinning as possible – derogatively, we have also considered some articles which, probably being very new, couldn't yet have reached the PEDro threshold score we have settled.

Conclusions. This paper overviews the current state-of-the-art knowledge in the approach of peloidotherapy in rehabilitation, with a focal point on the therapeutic properties of peloids.

Keywords: mud-therapy, pelotherapy, peloidotherapy, fango therapy, rehabilitation, balneotherapy, natural therapeutic factors,

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1. INTRODUCTION

Collectively, the spa economy is estimated at $94 billion, with a consistent growth perspective in the coming decades. The general context of spa environments can support a holistic approach to health promotion (1).

Basic components of health resort interventions - spa therapies (2) - are balneotherapy (3) and climatotherapy. In many countries, treatments involving natural mineral waters, gases, or peloids (4) are referred to as balneotherapy. Routes of application include bathing, inhalations, drinking (Crenotherapy), etc. (5), often encompassing rehabilitation objectives/procedures (6)(7).

According to the definition given by the "International Society of Medical Hydrology", muds (peloids) and clays (8) are "substances formed in natural conditions under the influence of geological processes and which, mixed with water (9), are used in medical practice in the form of baths or local procedures (10).

Muds are earths or rocks of a pasty consistency, used as therapeutic remedies or cosmetics (11) from remote times. Some beneficial effects of mud are known empirically from antiquity, others have been described and studied quite recently, some have remained today in the stage of summary explanation. Mud treatment is also called pelotherapy (9), peloidotherapy, or sometimes – a largely – fango therapy. Pelotherapy should be used only as directed and under medical supervision (8).

From ancient times people used mud, when they had it at their disposal, for healing or beautification (12). Archaeological artifacts support such a hypothesis and there are no problems in understanding these data since the instinct to seek healing remedies also exists for the animal world, argued by new data also (13). Even if images in which the pig rolls in the mud for comfort seem legendary, or from a fairy-tale, we can only admit that such behavior is explainable in the equation of an adaptive benefit. The use of mud has its origins in antiquity. In ancient Egypt, the sick were anointed with the mud brought by the Nile during the floods.

The most common therapeutic muds are deposits in saline basins - black sulfurous muds, which form on the bottom of marine estuaries, bays, and continental salt lakes. The activity of quality evaluation for the resources of natural therapeutic substances begins by taking samples at source and ends with their complex interdisciplinary characterization, being developed indications and contraindications for prophylaxis, therapy and/or rehabilitation by conducting a complete pharmacodynamic study.

In one of his works, Pliny (23-79 AD) recommends the use of mud, a recommendation made by Dioskorides (50 AD) in his works and later also by Galen (131-2020 AD).

In antiquity, Cleopatra's behavior is historically emphasized, considered a beauty of her time, in terms of bodily maintenance, an aspect directly correlated with skin health. The beneficial effects of the mud and salt from the Dead Sea (11) led her to ask Marc Antonius to conquer this region to benefit from this remedy. Therefore, the use of Dead Sea (14) mud for therapeutic purposes dates back thousands of years, from the time of the Roman Empire.

We have more accurate data on the use of mud from the 14th century, in a paper that talks about the use of therapeutic mud from Albano and Battaglia, and Fallopius describes in 1564 the technique of using mud. Later, mud therapy (pelotherapy/peloidotherapy) is used in France (seventeenth century) and Germany (eighteenth century). In Russia, the cradle of pelotherapy is the Crimean peninsula.

Last but not least, Romania is a country famous for its balneary resorts. For renowned mud deposits, Techirghiol, Sovata, Ocna Sibiului, Mangalia, Amara are the main resorts promoted for mud therapy.

The complex interdisciplinary characterization of the natural therapeutic factors necessarily includes interpretation of physicochemical analyzes and microbiological (15)(16) examinations.

Classification of muds (17)

Clay (18) has been used by humans since before recorded history to accomplish basic but fundamental healthcare purposes. The clay plates of Nippur, Mesopotamia, which date back to about 2500 BC, contain a reference to the use of clays for therapeutic purposes, including the treatment of wounds and the inhibition of hemorrhages. Also, the famous Papyrus Ebers dated about 1600 BC describes the treatment of some diseases using clay-based medicines. Since then, from Ancient Greece, Roman times, medieval times, renaissance times to contemporary times, there exist reports on the therapeutic, nutritional and cosmetic uses of clay and clay-based products (8). There are several types of clay and within them, the so-called healing clay (19) and edible clay had been used and are still being used, by man for therapeutic, nutritional, and cosmetic purposes. Edible clay is a particular type of healing clay which use is limited to internal application through ingestion, for instance, of cookies made of clay/ /potable water dispersion/suspension. Conceptually healing clay besides the oral use for internal health benefits of the digestive tract (20) can also be used in external or topical applications as clay and mineral water paste called mud or peloid for the treatment of muscle-skeletal and dermatological disorders (8)(21).

Peloid is a maturated mud or muddy dispersion with healing and/or cosmetic properties, composed of a complex mixture of fine-grained natural materials of geologic and/or biologic origins, mineral water or seawater, and common organic compounds from biological metabolic activity.

NATURAL peloids are formed by depositing more or less decayed, rotten, overripe, organic, and inorganic substances in bayous, sea lagoons, saltwater and freshwater lakes, rivers, marshes, mineral water spring mires, and volcanic areas (22).

ARTIFICIAL peloids are natural clays that are refined and significantly changed before their use (23).

According to their origin:

ORGANIC PELOIDS comprise those peloids consisting of over 10% of organic substances:

- ✓ peat (peat soil, elevated and leveled peat) (24)(25)
- ✓ organic mud (bitumen mud, sapropel and Gyttja)(8)

INORGANIC PELOIDS (8) *comprise:*

- ✓ mineral peloids (clay, loam, tufa)
- ✓ volcanic peloids (8)

Depending on the formation conditions and the chemical composition, the therapeutic muds are classified into:

a) **Sapropelic muds -** are represented by black deposits, rich in colloidal iron hydrosulfide, have a plastic and greasy appearance, are found on the bottom of salt waters originating from the action of microorganisms on the flora and fauna of the aquatic basin to which minerals or inorganic substances that come from the soil of the lake basin are associated. Their content in organic substances is greater than 10% to the weight of the dry matter - continental lake, lagoon;

The flora consists of microphyte and macrophyte algae in which *Cladophora vagabunda*, *Cladophora cristalina*, predominates, algae that grow only in saltwater.

The aquatic fauna is represented by the species Artemia salina 10 - 12 mm, red arthropods. The carcasses of Artemia salina, by bacterial decomposition, together with the alga *Cladophora cristalina*, form the sapropelic mud.

Sapropelic muds are black deposits underwater sediments rich in colloidal iron hydrosulfide, plastic and greasy.

b) **Mineral and vegeto-mineral muds** appear by sedimentation of the salts of some springs with sulfidic, ferruginous, carbogazeos character. Mineral muds - arise by the sedimentation of salts of carbonaceous, calcium, ferruginous or sulfurous springs;

c) **Peat** (*humus vegetabilis lutosa)* - organic, brown mud. Peat muds result from the microbiological decomposition of the remains vegetables accumulated on the bottom of some swamps. Their content in organic substances is also greater than 10% of the weight of the dry matter (24). Peat is formed in the following ways:

- ➢ natural formation through physicochemical and microbiological processes at the contact of the mineral water with the clay bed, around the natural emergents, resulting in the content of organic substances in dry mud below 10%;
- ➢ directed formation through microbiological and physicochemical processes at the contact of the mineral water with the clay bed - artificial basins - resulting in the content of organic substances in dry mud below 10%;
- ➢ incomplete transformation of the vegetal material in conditions of advanced humidity - swamps, resulting in the content of organic substances in dry mud of over 10%;
- ➢ salty clays and marls, sedimented in arid land conditions - lagoons from the biological past;
- ➢ calcareous tuffs, formed by chemical precipitation - around natural carbon dioxide emergencies.

Fangotherapy - is a particular type of pelotherapy that involves the use of fango name of Italian origin attributed to muddy natural peloids deposited from thermal springs as happens in the case of the Euganean volcanic region, in Italy, where important Thermal Resorts exist (8).

Chemical composition of peloids (26)(27)

From a physicochemical point of view, the mud is a heterogeneous system (28) consisting of a liquid phase containing water and water-soluble mineral salts, a solid phase containing mineral and organic substances, and a gaseous phase containing hydrogen sulfide (29).

The ionic balance of mud is also reflected in its pH. In general, the mud is alkaline pH = 9 – 10 (30).

The therapeutic effect of mud is given by the combination of its physical and chemical properties (31).

LIQUID PHASE

It is the solution of imbibition - the aqueous solution of organic and inorganic substances

Depending on its proportion muds are divided into:

- ➢ poorly hydrated with moisture content <37%
- ➢ medium hydrated by weight humidity = 37-40%
- ➢ strongly hydrated with a moisture content> 40%

The liquid phase results from the water of the lakes in the basin of which the mud is produced rainfall, and impact of mineral waters. Depending on the predominant ions (32), it may have a different character: sulfated, carbonated, or mixed, and with the following content:

- Water, anions, cations (33),
- Oligoelements (ug/kg) (28)

1. with pharmacological effect (Fe, Co, J, Br, and B)
2. involved in the enzymatic processes (J, Fe, Cu, Mo, Zn, Co, Mn, Ni, Ba, Sr, Cd)
3. non-essential/toxic elements (As, Pb, Hg, V, and F)
4. not yet elucidated biological role (Ti, Zr, Ir, Cs).

- Biologically active substances - protein hydrolysates, amino acids, enzymes (34).

GASEOUS PHASE - results from the physicochemical and biochemical processes involved in the mud formation (peloidogenesis): H_2S, CO_2, NH_4, CH_4, O_2, Rn (8)

Hydrogen sulfide (H_2S) is also an endogenous gas with important physiological functions (35). Endogenous hydrogen sulfide has been reported to function as a neuromodulator in the brain and within the vasculature; the main functions of H_2S are vasodilation and promoting new vessel growth (36).

SOLID PHASE

- Crystal framework (peloid skeleton) – *determines the mechanical structure*
- Oxides (SiO2, Al2O3, Fe2O3, CaO, MgO, Na2O, K2O, TiO2, MnO, P2O5), Na2O/CaO < 1
- Colloid complex - *plastic hydrophilic basis which absorbs moisture and defines thermal properties*
- Inorganic component Fe(HS)3, Fe(OH)3, Al(OH)3, H2SiO3
- Organic component – humic substances: humin, humic and fulvic acids (34)

Humic substances are generally considered to have occurred during the humidification process of the organic material. Their color varies from yellow to black, molecular mass from 2000 to over 300,000 Da, have a C content between 45 and 62%, O between 30 and 48%, and free acidity between 500 and 1400 mEq% (37).

The heterogeneity of the molecular weight of many individual compounds with different chemical compositions containing biogenic elements (C, N, O, P, S) in carboxyl, phenol, alcohol, peptide, amide, and other functional groups causes humic substances to be polydisperse, heterogeneous, biophilic and multifunctional (37).

The mud can be fractionated using the variation of pH and polarity of solvents and humic extracts can be characterized spectrophotometrically based on absorption in the wavelength range 340-700 nm, humic acids, and fulvic acids being differentiated based on solubility and molecular weight. Briefly, the mud is treated with a KOH solution, obtaining the alkaline extract of soluble humates and fulvates and the precipitation of insoluble humin(37).

Physical properties of mud (38)(27)

- ✓ **Specific weight** - depends on the components **mineral substances > organic substances**, is maximum for strongly mineralized muds, minimum for peat muds
- ✓ **Hydropexy:** water absorption and retention capacity, practical value - peloids with low hydropexy (mineral mud) are used only for packaging, those with medium hydropexy (sapropelic mud) and high (peat mud) can also be used for baths.
- ✓ **Plasticity**: the property of stretching and molding on the surface of the body - is given by the solids in their content; low plasticity (mineral mud), medium (peat), and high (sapropelic) (25)
- ✓ **Thermopexy:** heat absorption and storage - peloids have a high ability to retain heat (39)(40).
- ✓ **Consistency** – it depends on the viscosity conditions the frictional force that is exerted on the skin when applied (40)
- ✓ **Specific heat** - represents no. of calories to raise the heat of one gram of mud by one degree (40)(41)(42)
- ✓ **Granulometry -** the degree of mud dispersion and the size of the solid particles (41)

Methods of mud applications

- ✓ **Mud baths,** full, half body, or arm-leg - in tubs with heated lake water in which 10 - 12 kg of mud are added, progressively increasing its concentration up to 10 - 25%. The mixture can be heated to 42 ° C (43). In the case of patients with cardiovascular diseases, the temperature should not exceed 37ºC, and for those with inflammatory rheumatic diseases below 36ºC. The duration of the bath is 20 ´- 40´. The bath must be followed by a shower at 37º - 38ºC and a rest of at least one hour. A cure consists of 12-15 daily baths.
- ✓ **Mud Packages applications:** peloids are applied to specific areas of the body (44)
- ✓ **Mud anointing** - is the oldest method that involves applying cold mud on the patient's skin, after it has been heated 10-15, in a thin layer, on limited areas or the whole body. The patient should then be exposed to the sun, in an upright position, until the mud dries, approximately 30 - 60´, followed by a bath of 10´ - 15´ in sea or lake water accompanied by movement and a short shower with cold water and bed rest for at least an hour. It is a method of stressing the mechanisms of thermoregulation, neuroendocrine stimulation, and adaptation processes by alternating hot-cold contrasting factors.
- ✓ **Mud wraps** - consist of applying mud in a layer of 1 - 2 cm heated to 38º - 46ºC on a limited region or the entire body surface for 20´ - 40´.
- ✓ **Poultices** - applications with mud at different temperatures on limited regions of the body (24).
- ✓ **Gynecological applications** - in the form of vaginal swabs with mud at 39º - 40ºC for 2 hours or vaginal irrigation with mud dissolved in lake water and heated to 37ºC (43).
- ✓ **Mud massage** - stretching and mud massage

Application method:

1. After application, the body gets freed of mud with the assistance of a warm shower (taken under the water in temperatures of 37-38 ºC).
2. The patient gets dried of immediately and rests for half an hour to an hour.
3. Afterward, the patient either takes a light walk or receives a massage, or is taken into an adequate exercise program, if necessary.

Main peloid actions:

- ➢ cardiovascular system - stimulation of cardiovascular reactions with accentuation of hemodynamics by central and peripheral mechanisms. Immediate mobilization of blood deposits and their involvement in the general circulation takes place; cutaneous vasodilation → increases cardiac output (45)
- ➢ nervous system - sedative or exciting effects on the CNS and SNV by sedating pain receptors (46).
- ➢ The mud bath determines the increase of the antimicrobial defense capacity by increasing the

phagocytic power of the leukocytes - highlighted by the changes of the opsono-cytophagic index

- digestive: determines the balance of gastric secretion, increases biliary secretion
- renal: decreases renal secretion and diuresis (when perspiration is stimulated)
- tissue: tissue hydrophilicity changes → increases resorption capacity (chronic inflammation, bursitis)
- immune system - regulation of immunoglobulin values (47), an increase of non-specific immunity (9)(48).
- The endocrine system. The enzymatic and metabolic changes that appeared in the endocrine glands after peloidotherapy differ according to the specific secretion of the gland, according to the functional stage in which the gland is located, and are related to the type of therapeutic application. Under the action of mud, there is a harmonic stimulation in all glands in the sense of increasing the enzymatic and synthetic activity while maintaining the specificity of each. Correlated with the activity of endocrine functional harmonization is the stimulation of the activity of the hypothalamic-pituitary-adrenal axis translated by optimizing the plasma levels of β-endorphins. Glands with internal secretion - ovarian, pituitary function are stimulated.
- The endocrine mechanism is also involved in inducing the anti-inflammatory (49) effects of pelotherapy by modulating the activity of the hypothalamic-pituitary-adrenal axis and by the general balancing of the endocrine balance, persistent effects, and post-cure.
- Reactivity to chemical mediators - acetylcholine and adrenaline - as well as to ions correlated with vegetative activity - Ca, Mg, K - is increased after the external cure with mud, and the vegetative tone tends regulation/normalization, which leads to remediation of vegetative stigmas.

Therapeutic effects of mud (50)

Through its composition and thermopexy properties, the mud determines:

- ✓ stimulation of peripheral mechanoreceptors - triggers reflex mechanisms with favorable effects;
- ✓ subsequently follows skin vasodilatation (neurohumoral phase, with input made directly through the thermal factor) - benefits the absorption of elements present in the mud;
- ✓ bacteriostatic and bactericidal effects (51)(34)
- ✓ exchanges of energy and substances (thermoregulation of peripheral circulation, excretion, stimulation of skin repair processes) (2);
- ✓ general thermoregulation stress resulting in related optimized adaptive physiology and or therapeutic-rehabilitative responses (2);
- ✓ vitamin D synthesis;
- ✓ regulating the balance of homeostasis through immune, endocrine, and neurovegetative mechanisms (47)(52);
- ✓ better oxygenation of tissues (an increase of SO2% in peripheral blood, O2 binding capacity, and oxy-hemoglobin).

The thermal effect of peloidotherapy determines:

- ✓ pain relief (53);
- ✓ decreased muscle contractions (54);
- ✓ anti-inflammatory effects - the higher the application temperature, the higher the tonic immuno-stimulatory and cardiovascular effects, the application is possible due to the special mud property of thermopexy.

All of these develop local and general remote effects, such as analgesic effect, anti-inflammatory, muscle relaxant, detoxifying, neuroendocrine, to regulate immunity (55) and because the (including) mud based thermotherapy acts, as well, by enhancing the elasticity of the conjunctive-collagen major musculo-entheso-articular constituents – respectively through reducing their stiffness, which is associated to many conditions affecting such structures and/or to (just) aging – this, together with the above mentioned muscle decontracturant and analgesic effects, results also in an important link to facilitating rehabilitation: with more supple, relaxed and pain freer segments of the body, is a biological state prone to better outcomes of kinesiotherapy/ physical exercise, with consequent augmented functional mobility recover, and thus, an overall improvement of the quality of life, too.

Pharmacodynamic properties

Being a biological material used in human therapy, the analysis is performed according to the methods indicated in the "Romanian Pharmacopoeia" with some additions taken from the working methods used for soil analysis. The obtained result is presented in the form of the physicochemical analysis bulletin.

When applying peloids, a series of processes take place at the level of the skin:

- ✓ sensitive reception of mud qualities/properties and their transmission to the upper stages of integration and control;
- ✓ exchange of energy and substance with the peloid environment;
- ✓ fulfillment of adaptive functions: circulatory (peripheral circulation of thermoregulation), secretory (sweating), protective (keratinogenesis, melanogenesis, hydrolipid film formation);
- ✓ integration of skin - mud application effects in the general physiology of the body: thermoregulation, vitamin D synthesis, optimization of homeostatic balances: immune, endocrine, and neurovegetative of the body (17).

Applying mud to the entire surface of the skin triggers local tissue and general functional reactions, inhibiting or activating some enzyme systems and intermediate metabolites. The mud spa treatment produces favorable effects that persist for a long time by changing the ability to respond adaptively to various stimuli.

This procedure is a demanding one as the application time, density and temperature are higher, respectively the higher the salt concentration of the dilution saltwater. Even in healthy, robust patients, this procedure is especially demanding for the cardiovascular system. That is why it is contraindicated especially in hyper and hypertensive patients.

Peloiodotherapy is indicated for the following conditions:

- degenerative rheumatism with different locations: spine (spondylosis, simple discopathy, chronic lumbago (56), peripheral (coxarthrosis, gonarthrosis) (57)
- osteoartritis (58)(59)(60)(61)(62)(63)(64)(65)(66)(67),
- inflammatory rheumatism (54)
- ab-articular rheumatism (68)
- fibromyalgia (69)(70)
- musculoskeletal disorders (MSDs) (71)(72)
- post-traumatic sequelae (73)
- carpal tunnel syndrome (74)
- central and peripheral nervous system damage (75)
- psoriasis (76)(34)
- chronic eczema, chronic wounds (77)
- chronic urticaria
- obesity (78)
- pituitary dwarf
- rickets or children's weakness
- gynecological chronic inflammation, secondary sterility, post-tuberculosis sequelae

The ability of therapeutic mud to effectively restore reproductive function has long been known and does not cause doubt. In mud resort centers for the treatment of infertility applications and mud baths, vaginal and rectal tampons with mud heated to the desired temperature.

The effect of mud therapy will be more visible if it is combined with physical therapy (79) and gynecological massage, with medical microclyms, reflexology, and homeopathy.

Mud treatment is indicated for patients with chronic inflammatory processes of different origins, with chronic adnexitis and peri-adnexitis, with different adhesions, with parameterized residues, with chronic endocervicitis and colitis, with some forms of infertility, with miscarriage.

Mud treatment is useful in case of insufficiency of ovarian function and mild forms of uterine underdevelopment. Patients with severe genital lesions at Trichomonas may go for a spa treatment. Amenorrhea and dysmenorrhea - menstrual disorders - are also indications for mud therapy.

Contraindications

- febrile/infectious or acute/subacute conditions - other than those for which the treatment is performed;
- cardiovascular diseases;
- respiratory diseases: exacerbation of COPD, asthma with recent seizures, bronchiectasis, recent respiratory infections;
- dermatological diseases: bedsores, suppurative wounds, eczema in the developmental stage, psoriatic erythroderma.

Mud therapy is contraindicated if the patient suffers from asthma, diabetes, ulcers, any form of cancer, or hepatitis, kidney, or cardiovascular disease.

2. METHOD

Search Strategy. To fundament the above-mentioned data synthesis we have achieved a related systematic literature review and meta-analysis. Accordingly, we have searched for relevant *open access* works, in 6 international databases: including Cochrane[1], Elsevier[2], NCBI/PubMed[3], NCBI/PMC[4], PEDro[5] , and ISI Web of Knowledge/Science[6], published from January 2015 until December 2020. The contextually quested key words combinations/ syntaxes used in this respect were: "Pelotherapy /Peloidotherapy /Mud-therapy /Fango-therapy AND Rehabilitation".

The eligible articles were analyzed in detail regarding pathologies addressed by mud therapy/ rehabilitation – following a (Preferred Reporting Items for Systematic Reviews and Meta-Analyses – **PRISMA**[7] – type filter/ selection methodology – see Fig. 1) with additional country scientific relevance specified for this therapeutic method. The meta-analysis proceeded was designated to estimate the prevalence of various pathologies in the use of mud therapy/ rehabilitation.

Inclusion and Exclusion Criteria

Any relevant article that reported clinical or physical/chemical or biological information regarding peloids/mud therapy/ rehabilitation was included in the analysis. All articles with any design (reviews, randomized controlled trials, non-randomized controlled trials, case-control studies, cross-sectional studies), if eligible according to the above-mentioned selection methodology, were included.

Articles were excluded if they didn't reach – using a weighted, own, PEDro inspired scoring classification – at least a score of 4 – "fair quality" or mare points.

3. RESULTS

Our search identified, first, **394** articles. Based on the successive filtering stages and, respectively, on the

[1] https://www.cochrane.org/
[2] https://www.elsevier.com/
[3] https://pubmed.ncbi.nlm.nih.gov/
[4] https://www.ncbi.nlm.nih.gov/pmc/
[5] https://pedro.org.au/
[6] http://apps.webofknowledge.com/WOS_GeneralSearch
[7] http://www.prisma-statement.org/

classification criteria of the Physiotherapy Evidence Database (PEDro), we finally identified/retained and analyzed **68** articles (see Fig. 1).

Although, in principle, a rigorous method – and we have followed the PRISMA type paradigm – there still might be some missing works of our related article selection. On the other hand, to augment/ consolidate our documentation base, we have used also **40** papers freely found in the literature, and even – aiming, too, at an as exhaustive knowledge underpinning as possible – derogatively, we have also considered some articles which, probably being very new, couldn't yet have reached the PEDro threshold score we have settled.

Meta-analysis (80)

Afferent with the final step, we have done also a related Meta-analysis, **26** studies were included in this step, which count **15123** human subjects in total. The smallest sample size was **32** and the largest was **6281**. The meta-analysis (80) investigated the beneficial effects of mud therapy on specific indicated diseases.

Our obtained **forest plot**, also known as a **blobbogram**, is a graphical display of estimated results from several scientific studies addressing the same question, along with the overall results. Sometimes trials are just looking at different concepts. Statistical heterogeneity is apparent only after the analysis of the results. Heterogeneity may be judged graphically (by looking at the forest plot) and be measured statistically. In a forest plot from the systematic review, the error bars for each trial include the summary result, which suggests that statistical heterogeneity is not a problem and that the message is a consistent one (fig 3). To determine whether significant heterogeneity exists, a P-value high for the $\chi 2$ test of heterogeneity is good news because it suggests that the heterogeneity is insignificant and that one can go ahead and summarise the results (81).

4. Relevant topical data regarding mud therapy in, Physical and Rehabilitation Medicine (PRM) and Balneology

In vivo experimental models (82) based on murine osteoarthritis or rheumatoid arthritis, to establish the actions of Hévíz mineral water and mud, Hungary (83) or Jeju Magma-Seawater, Korea (82) – by a modern methodological approach using functional tests and morphological analysis – provided favorable Evidence-Based data of Complementary and Alternative Medicine effects of these natural therapeutic-rehabilitative factors, that can be observed clinically in OA patients, too. Articular diseases are the most frequent causes of chronic pain and related disability. For instance, rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation and progressive structural joint damage. Osteoarthritis is a degenerative process of the articular cartilage associated with hypertrophic changes in the bone (84). The new insights in the pathogenesis of osteoarthritis (OA) reveal the implications of adipocytokines. In the last years, balneological research was directed towards the study of specific inflammatory cytokines' involvement in musculoskeletal disorders. Correlations between peloid therapy and inflammatory pathways, at a molecular level, are established and new insights into the world of chondrocytes and osteoblasts are brought to light (85).

Peat obtained from Taean-gun, Chungcheongnam-do, Korea, can be considered as a therapeutic option for pain relief of knee OA patients. Although short-term peat intervention did not have significant effects on serum cartilage oligomeric matrix protein, long-term follow-up assessment using several parameters, including pain and OA biomarkers (86), is needed. The reduction in knee joint varus/valgus range of motion and the increase in gait velocity after peat intervention are meaningful results as effects of peat intervention on gait parameters (87).

Experts agree that the Spa therapies are effective in controlling the symptoms and objective signs of disease in patients with musculoskeletal disorders, as well as in ensuring a decrease in the recruitment of NSAIDs and analgesics (88).

The hormetic effects of balneotherapy are related to different factors. The main factor that is common to all types of mineral-medicinal waters and muds is heat.

The anti-aging properties of mud therapy (69) are an exciting concept for prevention and slowing the aging process throughout the entire body and other dermatological diseases. Therapeutic spas and baths offer an atmosphere of health and physical fitness by their chemical, thermal, mechanical, and endocrine actions. They also provide relaxation and stress relief. Mud therapy is effective individually or as a complement to other medical therapies. Recently, the concept of thermal mud therapy has been changing. During the aging process, endocrine changes result in a decline in endocrine function involving the responsiveness of tissues as well as reduced hormone secretion from peripheral glands. This is coupled with modifications in the central mechanisms controlling the temporal organization of hormone release, with a dampening of circadian hormonal and non-hormonal rhythms. Compared to younger individuals, healthy older individuals have alterations in body composition and a decline in functional status: decreased muscle mass, increased fat mass, and decreased strength. Even with healthy aging, there are changes in endocrine systems, including estrogen (menopause), testosterone (andropause), growth hormone/insulin-like growth factor-I axis (somatopause), hypothalamic-pituitary-thyroid axis, hypothalamic-pituitary-cortisol axis, and dehydro-epiandrosterone and its sulfate (adrenopause) (89).

H_2S – which is also a biochemical component within the mud, as well as radon (90) – induces a wide range of

physiological responses such as blood pressure modulation, neuromodulator in the brain and within the vasculature, protective against ischemic reperfusion injury, and anti-inflammatory reactions (36). H2S is an endogenous gasotransmitter, and, as such, it can be absorbed by numerous routes; it can penetrate the skin and mucosae and can therefore act at the cell level both in the skin (29) and in internal organs. Organic components of muds were demonstrated to have biological effects contributing to the healing mechanisms, but their medical significance is not still fully understood (91).

Techirghiol sapropelic mud is one of the natural therapeutic factors of medical use in Romania, being represented by the deposit on the bottom of lake Techirghiol; it has been and still is a subject to ongoing medical research because of the need of its medical use for scientific evidence-based medicine (92). One of the interesting papers regarding Techirghiol mud's post-resorptive effects, refer to the plasmatic level variations of leptin show a different response depending on the balneal application type. Warm mud application leads to a significant decrease of the leptin level which translates into the remission of inflammation and rheumatic pain. Cold mud application as a contrasting therapy leads to an increase of the leptin values at the end of the treatment, an increase that is not statistically significant. The lack of leptin variation in the case of the group that underwent constant therapy is due to the thermoregulation function that is highly strained during the cold application, while the thermal comfort during baths neutral from a thermal point of view stabilizes the hypothalamus function and does not request major neuroendocrine answers. Recent data indicate that the hypothalamus is targeted by leptin actions, leptin which crosses the hematoencephalic barrier and interacts with the leptin receptor in the arcuate nucleus of the hypothalamus, thereby controlling the thyroid-stimulating hormone, the melanocyte-stimulating hormone, and gamma-aminobutyric acid, which will eventually modulate the metabolic answers of the body (93).

5. DISCUSSION

The use of mud by humans for medicinal and wellness purposes is most probably as old as mankind. Balneotherapy is an effective complementary approach in the management of several low-grade inflammations and stress-related pathologies, especially rheumatic and metabolic conditions. However, despite the demonstrated clinical and symptomatic benefits of these therapies, their role in modern medicine is still controversial, mainly because the biological mechanisms underlying these benefits have not yet been completely elucidated. In the context of these pathologies, further studies are necessary to clarify the mechanisms of effects involving the stress response and, consequently, its interaction with the inflammatory response (42).

Thermal muds have been used in many spas for the treatment of different diseases (medical uses) as well as to clean and beautify the skin, in different forms/wellness such as mud baths, masks, and cataplasms (94). DPSIR (Drivers-Pressures-State change-Impacts-Responses) (95) framework can be used also to analyze touristic activities, including mud uses, to identify a set of key indicators with weightings for health tourism destinations by using an advanced analytic hierarchy process (AHP) method, derived from the official, academic, and professional opinions of the experts (96).

Yet, in the literature, mineralogical and chemical compositions and the possible toxicity of the peloids (97) need to be investigated and compared with some limits to determine whether they have any health benefits and potential applications for pelotherapeutic treatments (26).

On the other hand, the therapeutic Euganean thermal mud is a unique product of the Euganean Thermal District (Italy) that represents the largest and oldest thermal center in Europe (54). The application of the therapeutic mud, whose beneficial effects have been documented since Ancient Roman times, is recognized by the Italian Health System as a healing treatment for arthro-rheumatic diseases. The beneficial mud is obtained by a specific maturation procedure that can be considered as an ancient biotechnological process. This process is now coded by a protocol to be followed to obtain the "Mature Mud AOC" certification. The mud maturation process begins when virgin clay, obtained from the lakes of Arquà Petrarca (Padova, Italy), is laid in open-air tanks or silos of the different thermal Spas, and maintained there for a period of at least two months, constantly covered by a layer of flowing thermal water, at the indicated temperature of 38–40 ◦C. This maturation procedure allows a microbial community, mainly represented by cyanobacteria, to grow on the mud surface. Microorganisms, embedded in a thick polysaccharidic matrix, generate a green biofilm that indicates the correct mud maturation. Before using the mud for therapies, this is mixed and put in tanks in which thermal water at nearly 60 ◦C is present, to reduce the natural microbial load and maintain the fluidity of the product (98).

Additionally, Techirghiol represents ancient golf of the Black Sea, with sapropelic mud extracted from the lake, associated with marine climatic characteristics in a combined heliomarin and thalassotherapy cures. In BRST are treated patients with a wide range of diseases, most of them with osteoarticular and neurological pathology, both adults and children. Yearly, in Balneal and Rehabilitation Sanatorium from Techirghiol, are admitted more than ten thousand patients. The patients are admitted for a period of 12 days up to 30 days and they receive complex rehabilitation treatment: hydro-kinetic-therapy in the salted water of the pool, alternated with warm mud baths or hot mud wrapping, or cold mud ointment, and then

swim in the lake, completed with massage, electrotherapy, and kinesiotherapy. All patients underwent an initial clinical examination and then the physician filled up a questionnaire, which includes personal data, information about the disease requiring admission if the patient has in the medical history any balneal treatment and what were the results, and finally the group of affections to which fit the existing symptoms (99).

Delivery of drugs on/into/through the skin enables either local or systemic actions and improvement of poor biopharmaceutics profiles of drugs administered via other administration paths, and becomes a useful strategy in situations in which other administration routes are not possible or inadvisable. Pelotherapy is the topical administration of hot-muds or peloids, with optimal rheological and thermal properties composed of clay minerals and mineral-medicinal water aimed at treating arthro-rheumatic issues, bone-muscle traumatic damage, and dermatological pathologies. Most of the important properties attributed to clays for dermo-cosmetic applications are related to their surface properties (surface area, cation exchange capacity, layer charge, among others); rheological properties (thixotropy, rheopecty, viscosity, plasticity); and other physical and mechanical properties including particle size and shape, color, softness, opacity, reflectance, iridescence, and so on (21).

The paucity of evidence about cost-effectiveness and economic evaluation of conservative, non-pharmacological and non-surgical rehabilitative interventions for the range of lower limb musculoskeletal complaints is a concern for one found study (100).

Balneotherapy could be beneficial in treating patients suffering from low back pain, but there is still not enough quality scientific evidence (101).

Mud produces important beneficial effects including anti-inflammatory and anti-microbial activity which might explain in part the therapeutic properties of mud packs against chronic inflammatory skin disorders. Besides, treatment of keratinocytes with mud extract led to a significant increase of ATP levels as well as mRNA expression of genes involved in cell protection and longevity. The mud could serve as a natural anti-oxidant and moisturizing anti-aging agent with important cosmeceutical applications (34).

Kinesiotherapy (therapeutic exercises including stretching, isotonic, isometric, and isokinetic strengthening), is effective in improving pain, joint stiffness, functional mobility and muscle strength in patients with knee OA. There are new data that emphasize the efficiency of the combined effect of geotherapy with kinesiotherapy in reducing pain for patients with osteoarthritis (102).

6. Conclusions

This paper overviews the current state-of-the-art knowledge in the approach of peloidotherapy in rehabilitation, with a focal point on the therapeutic properties of peloids. Most of the thermal spas around the world recommend their mud baths or local mud cataplasm applications, as they recognize therapeutic results through their anti-inflammatory, analgesic, and antiseptic effects on musculoskeletal and dermatologic pathologies, which are increasingly supported by clinical trials (103). Guidelines and studies reviewed are recognizing the beneficial effects and mechanisms of action of mud therapy (12). Osteoarthrosis is the most addressed pathology (104)(105).

The works we have evaluated show that almost half of the thereof included patients originate from Romania.

Our systematic review and meta-analysis have emphasized an additional, corollary, conclusion, too: the often connected/ synergistic, therapeutic, and rehabilitative effects of the balneary interventions (46), including mud procedures based, prove and strengthen the Romanian successfully paradigm of a unitary/ sole specialty: Physical and Rehabilitation Medicine & Balneology – and this is reflected also in the new focus and title of our publication ”Balneo and PRM Research Journal”.

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9. Declaration of interests

Authors declare no competing interests. The approval of the Ethics Commission of „Bagdasar-Arseni Hospital” in Bucharest (N.O. 9910/17.03.2021) was obtained for this article.

Figures and tables

TABLE 1 Step I: numerical search results.

Articles	Keywords	Web of Science	Cochrane	Elsevier	PubMed	PMC	PEDro	Total
Articles found in the first phase	"Mud therapy"	44	1	7	69	41	15	177
	"Peloidotherapy"	13	4	2	7	5	0	31
	"Pelotherapy"	52	2	2	14	29	0	99
	"Fango therapy"	0	1	0	0	0	0	1
	"Mud therapy" + "rehabilitation"	11	1	5	20	21	0	58
	"Peloidotherapy" + "rehabilitation"	2	0	1	3	2	0	8
	"Pelotherapy" + "rehabilitation"	3	0	0	4	13	0	20
	"Fango therapy" + "rehabilitation"	0	0	0	0	0	0	0
	TOTAL	125	9	17	117	111	15	394

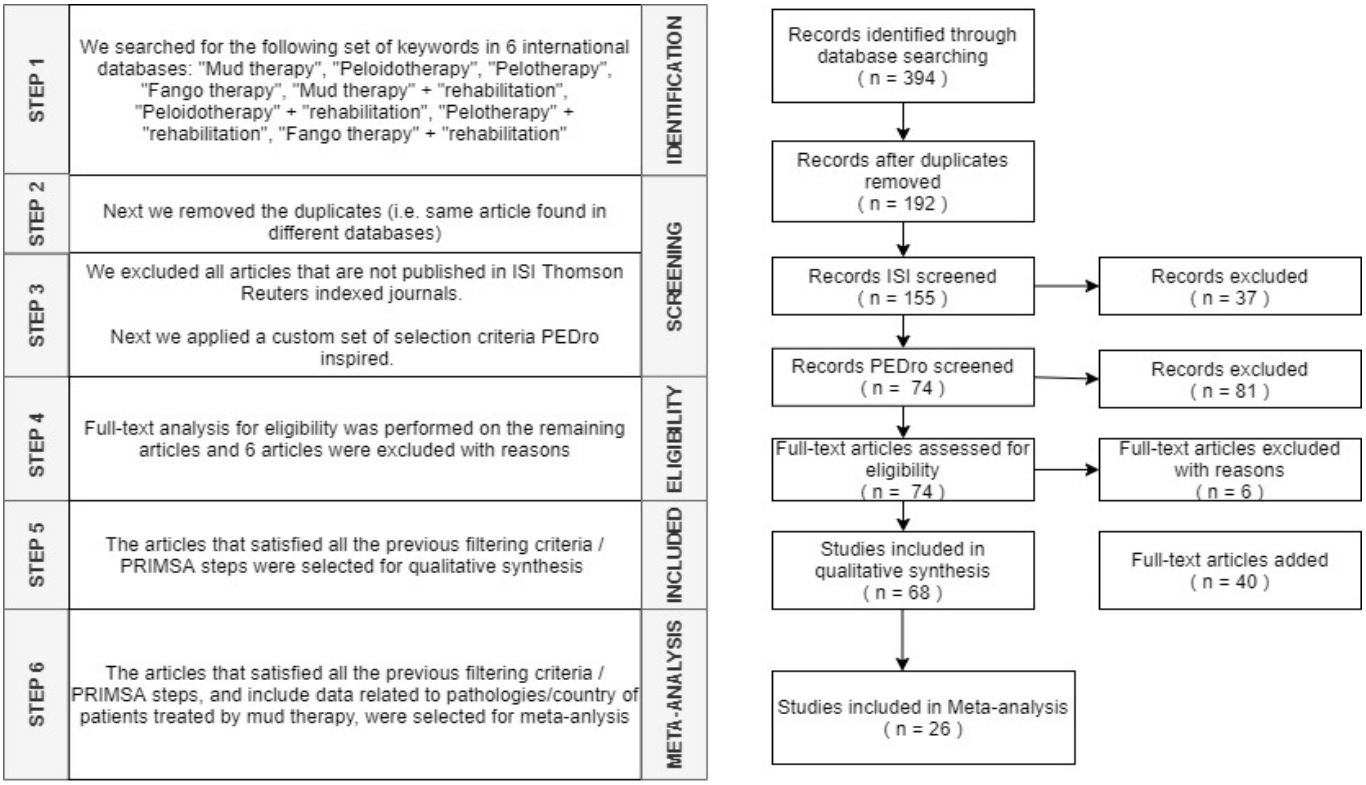


Figure 1: Flow-chart depicting the literature search and selection strategy. After applying the inclusion and exclusion criteria

TABLE 2 OpenMeta-Analyst source files related to pathologies/country patients treated by mud therapy

Study	Year	N - total patients	OA	Rheumatoid arthritis	Osteoporosis	Algic symptoms	Low Back Pain	Musculoskeletal disorders	Control	Romania	Spain	Hungary	Turkey	France	Italy	OTHER COUNTRY
AXIS LEGEND			1	2	3	4	5	6	7	1	2	3	4	5	6	7
Karagülle (3)	2015	404	0	0	0	0	404	0	202	0	0	0	0	360	0	44
Morer (5)	2016	1118	599	308	64	0	147	0	535	0	0	397	156	0	0	721
Fioravanti (55)	2015	95	95	0	0	0	0	0	46	0	0	0	0	0	95	0
Fioravanti (106)	2015	103	53	0	0	0	0	0	50	0	0	0	0	0	103	0
Yücesoy (57)	2018	139	0	0	0	0	139	0	139	0	0	0	139	0	0	0
Forestier (58)	2016	2233	1721	0	0	0	0	0	512	0	132	117	330	642	378	634
Özkuk (32)	2017	50	50	0	0	0	0	0	50	0	0	0	50	0	0	0
Pascarelli (107)	2016	103	53	0	0	0	0	0	50	0	0	0	0	0	103	0
Eröksüz (70)	2019	50	0	0	0	0	0	50	50	0	0	0	50	0	0	0
Gungen (44)	2016	59	34	0	0	0	0	0	25	0	0	0	59	0	0	0
Valckenaere (108)	2018	185	0	0	0	92	0	0	93	0	0	0	0	185	0	0
Gyarmati (83)	2017	47	47	0	0	0	0	0	24	0	0	47	0	0	0	0
Tenti (31)	2020	212	212	0	0	0	0	0	212	0	0	0	0	0	212	0
Cantista (7)	2020	120	60	0	0	0	0	0	60	0	0	0	0	0	0	120
Alfier (102)	2020	48	48	24	0	0	0	0	24	0	0	0	0	0	0	48
Hahm (53)	2020	32	0	0	0	0	16	0	16	0	0	0	0	0	0	32
Aksoy (47)	2017	63	33	0	0	0	0	0	30	0	0	0	63	0	0	0
Kim (87)	2020	41	22	0	0	0	0	0	19	0	0	0	0	0	0	41
Ionescu (85)	2017	46	23	0	0	0	0	0	23	46	0	0	0	0	0	0
López (101)	2019	1390	0	0	0	0	1390	0	0	0	0	71	81	1192	0	46
Xiang (60)	2016	1010	1010	0	0	0	0	0	0	0	132	53	236	451	80	58
Gálvez (62)	2018	36	36	0	0	0	0	0	36	0	36	0	0	0	0	0
Iliescu (99)	2018	6281	2744	0	0	0	2273	0	0	6281	0	0	0	0	0	0
Varzaityte (65)	2019	92	32	0	0	0	0	0	60	0	0	0	0	0	0	92
Király (66)	2019	60	60	0	0	0	0	0	60	0	0	60	0	0	0	0
Hou (104)	2020	1106	440	0	0	0	0	0	411	0	121	53	151	451	290	50
TOTAL		15123	7372	332	64	92	4369	50	2727	6327	421	798	1315	3281	1261	1886
%		100	48.75	2.20	0.42	0.61	28.89	0.33	18.03	41.84	2.78	5.28	8.70	21.70	8.34	12.47

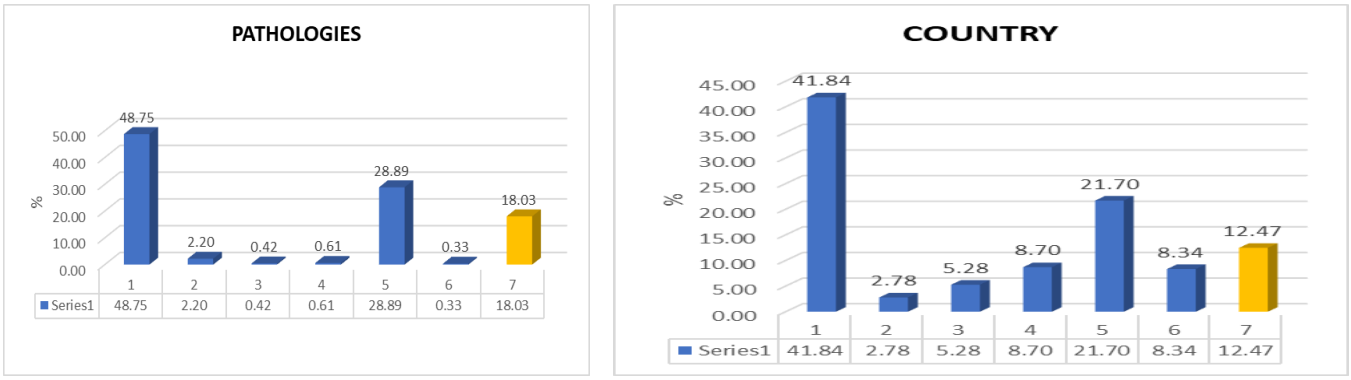
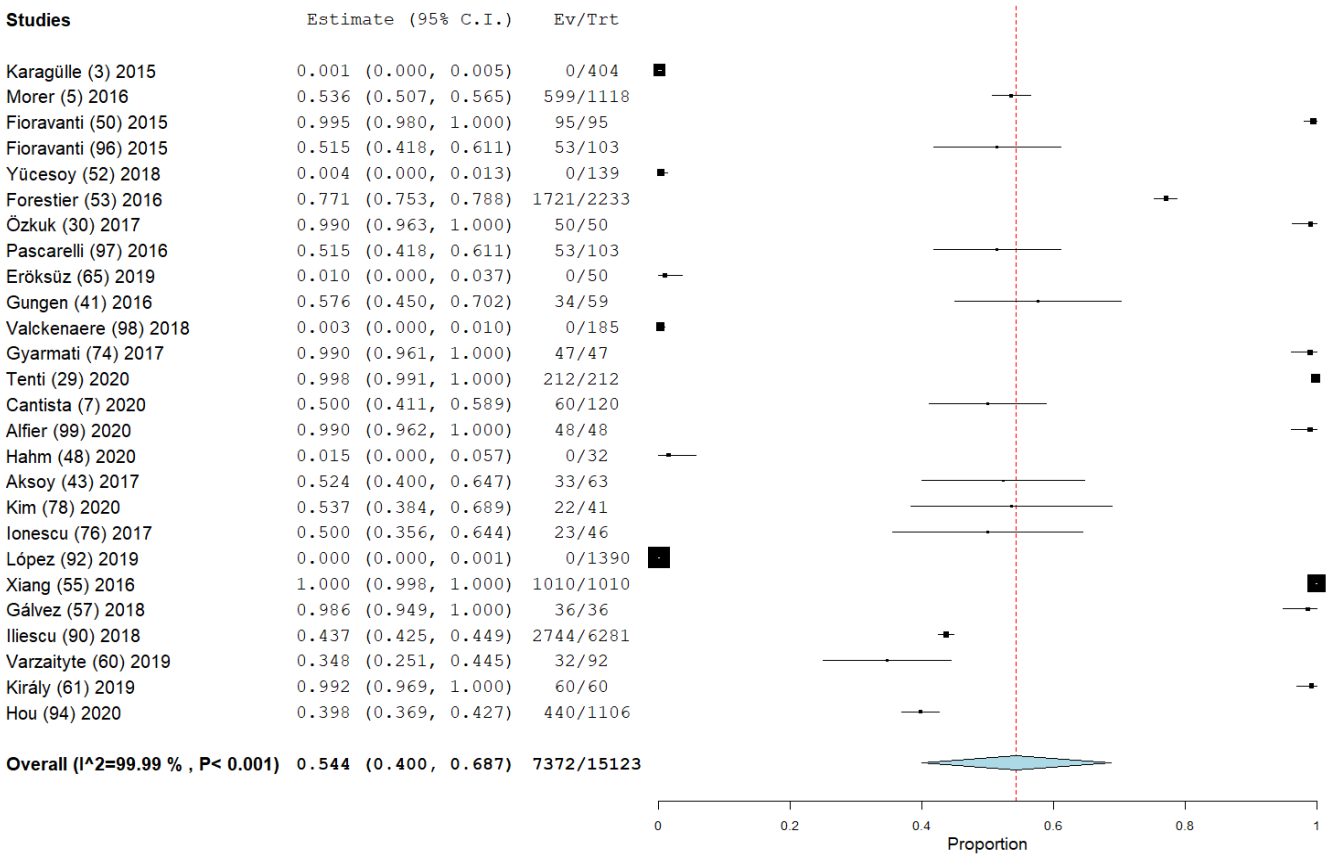


Figure 2: Pathologies and Country frequencies in mud therapy studies (see LEGEND in Table 3)



Binary Random-Effects Model

Metric: Proportion
Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
0.544	**0.400**	**0.687**	**0.073**	**< 0.001**
Heterogeneity	**tau^2**	**Q(df=25)**	**Het. p-Value**	**I^2**
	0.138	**1447636.745**	**< 0.001**	**99.995**

Figure 3: Studies **Heterogeneity** - forest-plot (80)

References:

1. Valeriani F, Margarucci LM, Spica VR. Recreational use of spa thermal waters: Criticisms and perspectives for innovative treatments. Int J Environ Res Public Health. 2018;15(12).
2. Kamioka H, Nobuoka S, Iiyama J. Overview of systematic reviews with meta-analysis based on randomized controlled trials of balneotherapy and spa therapy from 2000 to 2019. Int J Gen Med. 2020;13:429–42.
3. Karagülle M, Karagülle MZ. Effectiveness of balneotherapy and spa therapy for the treatment of chronic low back pain: a review on latest evidence. Clin Rheumatol. 2015;34(2):207–14.
4. Kim MH, Choi G, Elzatahry A, Vinu A, Choy Y Bin, Choy JH. Review of clay-drug hybrid materials for biomedical applications: Administration routes. Clays Clay Miner. 2016;64(2):115–30.

5. Morer C, Roques CF, Françon A, Forestier R, Maraver F. The role of mineral elements and other chemical compounds used in balneology: data from double-blind randomized clinical trials. Int J Biometeorol. 2017;61(12):2159–73.
6. Masiero S, Litwocenko S, Agostini F. Rehabilitation in an Italian thermal setting: a new therapeutic strategy for patients with musculoskeletal disability—the results of an Italian survey. Int J Biometeorol. 2020;64(6):951–4.
7. Cantista P, Maraver F. Balneotherapy for knee osteoarthritis in S. Jorge: a randomized controlled trial. Int J Biometeorol. 2020;64(6):1027–38.
8. Gomes C de SF. Healing and edible clays: a review of basic concepts, benefits and risks. Environ Geochem Health. 2018;40(5):1739–65.
9. Gálvez I, Torres-Piles S, Ortega E. Effect of mud-bath therapy on the innate/inflammatory responses in elderly patients with osteoarthritis: a discussion of recent results and a pilot study on the role of the innate function of monocytes. Int J Biometeorol. 2020;64(6):927–35.
10. Verhagen Arianne P, Bierma-Zeinstra Sita MA, Boers Maarten, Cardoso Jefferson R, Lambeck Johan, de Bie Rob de VHC. Balneotherapy (or spa therapy) for rheumatoid arthritis (Review). 2015;
11. Bawab A Al, Bozeya A, Abu-Mallouh S, Abu Irmaileh B, Daqour I, Abu-Zurayk RA. The Dead Sea Mud and Salt: A Review of Its Characterization, Contaminants, and Beneficial Effects. IOP Conf Ser Mater Sci Eng. 2018;305(1).
12. Bernetti A, Mangone M, Alviti F, Paolucci T, Attanasi C, Murgia M, et al. Spa therapy and rehabilitation of musculoskeletal pathologies: a proposal for best practice in Italy. Int J Biometeorol. 2020;64(6):905–14.
13. Bullitta S, Re GA, Manunta MDI, Piluzza G. Traditional knowledge about plant, animal, and mineral-based remedies to treat cattle, pigs, horses, and other domestic animals in the Mediterranean island of Sardinia. J Ethnobiol Ethnomed. 2018;14(1):1–26.
14. Ma'or Z, Halicz L, Portugal-Cohen M, Russo MZ, Robino F, Vanhaecke T, et al. Safety evaluation of traces of nickel and chrome in cosmetics: The case of Dead Sea mud. Regul Toxicol Pharmacol [Internet]. 2015;73(3):797–801. Available from: http://dx.doi.org/10.1016/j.yrtph.2015.10.016
15. Baldovin T, Amoruso I, Caldara F, Buja A, Baldo V, Cocchio S, et al. Microbiological hygiene quality of thermal muds: A pilot study in pelotherapy facilities of the euganean thermal district (ne italy). Int J Environ Res Public Health. 2020;17(14):1–15.
16. Liguori G, Di Onofrio V, Gallè F, Liguori R, Nastro RA, Guida M. Occurrence of Legionella spp. in thermal environments: Virulence factors and biofilm formation in isolates from a spa. Microchem J [Internet]. 2014;112:109–12. Available from: http://dx.doi.org/10.1016/j.microc.2013.09.023
17. Antonelli M, Donelli D. Mud therapy and skin microbiome: a review. Available from: https://doi.org/10.1007/s00484-018-1599-y
18. Carretero MI. Clays in pelotherapy. A review. Part I: Mineralogy, chemistry, physical and physicochemical properties. Vol. 189, Applied Clay Science. Elsevier Ltd; 2020. p. 105526.
19. Awad ME, López-Galindo A, Setti M, El-Rahmany MM, Iborra CV. Kaolinite in pharmaceutics and biomedicine. Vol. 533, International Journal of Pharmaceutics. Elsevier B.V.; 2017. p. 34–48.
20. Morrison KD, Misra R, Williams LB. Unearthing the Antibacterial Mechanism of Medicinal Clay: A Geochemical Approach to Combating Antibiotic Resistance. Sci Rep. 2016;6(August 2015):1–13.
21. Viseras C, Carazo E, Borrego-Sánchez A, García-Villén F, Sánchez-Espejo R, Cerezo P, et al. Clay minerals in skin drug delivery. Clays Clay Miner. 2019;67(1):59–71.
22. Tran Thi Man, Tran Thi Lan·, Nguyen Anh Duong PLA. Assessment of the usability of Tam Bo bentonite (Di Linh - Lam Dong) for peloid. Vietnam J Earth Sci. 2020;42(4):384–94.
23. Sánchez-Espejo R, Cerezo P, Aguzzi C, López-Galindo A, Machado J, Viseras C. Physicochemical and in vitro cation release relevance of therapeutic muds "maturation." 2015; Available from: http://dx.doi.org/10.1016/j.clay.2015.08.007
24. Drobnik J, Stebel A. Central European ethnomedical and officinal uses of peat, with special emphasis on the Tołpa peat preparation (TPP): An historical review. 2019; Available from: https://doi.org/10.1016/j.jep.2019.112248
25. García-Villén F, Sánchez-Espejo R, Carazo E, Borrego-Sánchez A, Aguzzi C, Cerezo P, et al. Characterisation of Andalusian peats for skin health care formulations. 2017; Available from: https://doi.org/10.1016/j.clay.2017.12.017
26. Çelik Karakaya M, Karakaya N. Chemical composition and suitability of some Turkish thermal muds as peloids. Turkish J Earth Sci. 2018;27(3):191–204.
27. Pozo M, Armijo F, Maraver F, Zuluaga P, Ejeda JM, Corvillo I. Variations in the texture profile analysis (TPA) properties of clay/mineral-medicinal water mixtures for pelotherapy: Effect of anion type. Minerals. 2019;9(3):11–3.
28. Martínez-Villegas N, Suárez Muñoz M, González-Hernández P, Melián Rodríguez C, Barrios Cossio J, Hernández Díaz R, et al. Inorganic and organic characterization of Santa Lucía salt mine peloid for quality evaluations. Environ Sci Pollut Res. 2020;27(14):15944–58.
29. Carbajo JM, Maraver F. Salt water and skin interactions: new lines of evidence. Int J Biometeorol. 2018;62(8):1345–60.
30. Calin MR, Radulescu I, Ion AC, Capra L, Almasan ER. Investigations on chemical composition and natural radioactivity levels from salt water and peloid used in pelotherapy from the Techirghiol Lake, Romania. Environ Geochem Health [Internet]. 2020;42(2):513–29. Available from: https://doi.org/10.1007/s10653-019-00382-8
31. Tenti S, Manica P, Cheleschi S, Fioravanti A. Sulfurous-arsenical-ferruginous balneotherapy for osteoarthritis of the hand: results from a retrospective observational study. Int J Biometeorol. 2020;1561–9.
32. Özkuk K, Gürdal H, Karagülle M, Barut Y, Eröksüz R, Karagülle MZ. Balneological outpatient treatment for

patients with knee osteoarthritis; an effective non-drug therapy option in daily routine? Int J Biometeorol. 2017;61(4):719–28.
33. Sergio Cardoso da Silva P, Koyaishi Torrecilha J, Flávio de Macedo Gouvea P, Francis Máduar M, Maria Barros de Oliveira S, Antonio Scapin M. Chemical and radiological characterization of Peruíbe Black Mud. 2015; Available from: http://dx.doi.org/10.1016/j.clay.2015.09.016
34. Spilioti E, Vargiami M, Letsiou S, Gardikis K, Sygouni V, Koutsoukos P, et al. Biological properties of mud extracts derived from various spa resorts. Environ Geochem Health. 2017;39(4):821–33.
35. Costantino M, Izzo V, Conti V, Manzo V, Guida A, Filippelli A. Sulphate mineral waters: A medical resource in several disorders. J Tradit Complement Med [Internet]. 2020;10(4):320–6. Available from: https://doi.org/10.1016/j.jtcme.2019.04.004
36. Carbajo JM, Maraver F. Sulphurous mineral waters: New applications for health. Evidence-based Complement Altern Med. 2017;2017.
37. Hoteteu M, Munteanu C, Ionescu EV, Almășan RE. Bioactive substances of the Techirghiol therapeutic mud. Balneo Res J. 2018;9(1):05–10.
38. Barhoumi T, Bekri-Abbes I, Srasra E. Physicochemical characteristics and suitability of curative pastes made of Tunisian clay minerals and thermal waters for use in pelotherapy. Comptes Rendus Chim [Internet]. 2019;22(2–3):126–31. Available from: https://doi.org/10.1016/j.crci.2018.11.006
39. Hernández AC, Awad ME, Meléndez W, González G, López-Galindo A, Sánchez-Espejo R, et al. Colloidal and thermal behaviors of some venezuelan kaolin pastes for therapeutic applications. Minerals. 2019;9(12):18–22.
40. Armijo F, Maraver F, Pozo M, Isabel Carretero M, Armijo O, Ángel Fernández-Torán M, et al. Thermal behaviour of clays and clay-water mixtures for pelotherapy. 2016; Available from: http://dx.doi.org/10.1016/j.clay.2016.02.020
41. Glavaš N, Mourelle ML, Gómez CP, Legido JL, Rogan Šmuc N, Dolenec M, et al. The mineralogical, geochemical, and thermophysical characterization of healing saline mud for use in pelotherapy. Appl Clay Sci. 2017;135:119–28.
42. Maraver F, Armijo F, Fernandez-toran MA, Armijo O, Ejeda JM, Vazquez I, et al. Peloids as Thermotherapeutic Agents. 2021;
43. Stier-Jarmer M, Frisch D, Oberhauser C, Immich G, Kirschneck M, Schuh A. Effects of single moor baths on physiological stress response and psychological state: a pilot study. Int J Biometeorol. 2017;61(11):1957–64.
44. Gungen GO, Ardic F, Findikoglu G, Rota S. Effect of mud compress therapy on cartilage destruction detected by CTX-II in patients with knee osteoarthritis. J Back Musculoskelet Rehabil. 2016;29(3):429–38.
45. Naumann J, Sadaghiani C, Bureau N, Schmidt S, Huber R. Outcomes from a three-arm randomized controlled trial of frequent immersion in thermoneutral water on cardiovascular risk factors. BMC Complement Altern Med [Internet]. 2016;16(1):1–8. Available from: http://dx.doi.org/10.1186/s12906-016-1241-7
46. Barassi G, Obrero-Gaitan E, Irace G, Crudeli M, Campobasso G, Palano F, et al. Integrated Thermal Rehabilitation: A New Therapeutic Approach for Disabilities. Adv Exp Med Biol-Clinical Exp Biomed [Internet]. 2020;8:29–38. Available from: https://doi.org/10.1007/5584_2019_465
47. Kasapoğlu Aksoy M, Altan L, Eröksüz R, Metin Ökmen B. The efficacy of peloid therapy in management of hand osteoarthritis: a pilot study. Vol. 61, International Journal of Biometeorology. 2017. p. 2145–52.
48. Masiero S, Maccarone MC, Magro G. Balneotherapy and human immune function in the era of COVID-19. Int J Biometeorol. 2020;64(8):1433–4.
49. Ortega E, Gálvez I, Hinchado MD, Guerrero J, Martín-Cordero L, Torres-Piles S. Anti-inflammatory effect as a mechanism of effectiveness underlying the clinical benefits of pelotherapy in osteoarthritis patients: regulation of the altered inflammatory and stress feedback response. Int J Biometeorol. 2017;61(10):1777–85.
50. Bergamaschi B, Marzola L, Radice M, Manfredini S, Baldini E, Vicentini CB, et al. Comparative study of spa mud from “bacino idrominerario omogeneo dei colli euganei (B.i.o.c.e.)–italy” and industrially optimized mud for skin applications. Life. 2020;10(6):1–19.
51. Gomes CF, Gomes JH, da Silva EF. Bacteriostatic and bactericidal clays: an overview. Environ Geochem Health [Internet]. 2020;42(11):3507–27. Available from: https://doi.org/10.1007/s10653-020-00628-w
52. Metin Ökmen B, Eröksüz R, Altan L, Meliha &, Aksoy K. Efficacy of peloid therapy in patients with chronic lateral epicondylitis: a randomized, controlled, single blind study. Available from: http://www.random.org/.
53. Hahm SC, Shin HJ, Lee MG, Lee SJ, Cho HY. Mud Therapy Combined with Core Exercise for Chronic Nonspecific Low Back Pain: A Pilot, Single-Blind, Randomized Controlled Trial. Evidence-based Complement Altern Med. 2020;2020.
54. Cozzi F, Galozzi P, Ciprian L, Zanatta E, Polito P, Oliviero F, et al. Mud-bath treatment of seronegative spondyloarthritis: experience at the Euganean Thermal Area. Int J Biometeorol. 2020;64(6):937–41.
55. Fioravanti A, Giannitti C, Cheleschi S, Simpatico A, Pascarelli NA, Galeazzi M. Circulating levels of adiponectin, resistin, and visfatin after mud-bath therapy in patients with bilateral knee osteoarthritis. Int J Biometeorol. 2015;59(11):1691–700.
56. Forestier R, Suehs C, Françon A, Marty M, Genevay S, Sellam J, et al. Usual care including home exercise with versus without spa therapy for chronic low back pain: Protocol for the LOMBATHERM’ study, a multicentric randomised controlled trial. Trials. 2020;21(1):1–12.
57. Yücesoy H, Geçmen İ, Adıgüzel T, Karagülle M, Karagülle MZ. Efficacy of balneological outpatient treatment (hydrotherapy and peloidotherapy) for the management of chronic low back pain: a retrospective study. Int J Biometeorol. 2019;63(3):351–7.
58. Forestier R, Erol Forestier FB, Francon A. Spa therapy and knee osteoarthritis: A systematic review. Ann Phys Rehabil Med. 2016;59(3):216–26.

59. Fraioli A, Mennuni G, Fontana M, Nocchi S, Ceccarelli F, Perricone C, et al. Efficacy of spa therapy, mud-pack therapy, balneotherapy, and mud-bath therapy in the management of knee osteoarthritis. A systematic review. Biomed Res Int. 2018;2018.
60. Xiang J, Wu D, Li J. Clinical Efficacy of Mudpack Therapy in Treating Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Studies. Am J Phys Med Rehabil. 2016;95(2):121–31.
61. Gay C, Guiguet-Auclair C, Pereira B, Goldstein A, Bareyre L, Coste N, et al. Efficacy of self-management exercise program with spa therapy for behavioral management of knee osteoarthritis: Research protocol for a quasi-randomized controlled trial (GEET one) 11 Medical and Health Sciences 1103 Clinical Sciences 11 Medical and Healt. BMC Complement Altern Med. 2018;18(1):1–9.
62. Gálvez I, Torres-Piles S, Ortega E. Innate/inflammatory bioregulation and clinical effectiveness of whole-body hyperthermia (balneotherapy) in elderly patients with osteoarthritis. Int J Hyperth [Internet]. 2018;35(1):340–7. Available from: https://doi.org/10.1080/02656736.2018.1502896
63. Schiphof D, van den Driest JJ, Runhaar J. Osteoarthritis year in review 2017: rehabilitation and outcomes. Osteoarthr Cartil [Internet]. 2018;26(3):326–40. Available from: https://doi.org/10.1016/j.joca.2018.01.006
64. Stanciu Liliana-Elena, Ionescu Elena-Valentina, Oprea Carmen AE-R. Rehabilitation in Osteoporosis - therapeutic chalenge? Balneo Res J [Internet]. 2020;11(4):501–6. Available from: http://bioclima.ro/Balneo388.pdf
65. Varzaityte L, Kubilius R, Rapoliene L, Bartuseviciute R, Balcius A, Ramanauskas K, et al. The effect of balneotherapy and peloid therapy on changes in the functional state of patients with knee joint osteoarthritis: a randomized, controlled, single-blind pilot study. Int J Biometeorol. 2020;64(6):955–64.
66. Király M, Kővári E, Hodosi K, Bálint P V., Bender T. The effects of Tiszasüly and Kolop mud pack therapy on knee osteoarthritis: a double-blind, randomised, non-inferiority controlled study. Int J Biometeorol. 2020;64(6):943–50.
67. Bennell KL, Hall M, Hinman RS. Osteoarthritis year in review 2015: Rehabilitation and outcomes. Osteoarthr Cartil [Internet]. 2016;24(1):58–70. Available from: http://dx.doi.org/10.1016/j.joca.2015.07.028
68. Angioni M.M., Denotti A., Pinna S., Sanna C. MF, Dessole G., Loi A. CA. Spa therapy induces clinical improvement and protein changes in patients with chronic back pain. Reumatismo. 2019;71(3):119–31.
69. Maeda T, Kudo Y, Horiuchi T, Makino N. Clinical and anti-aging effect of mud-bathing therapy for patients with fibromyalgia. Mol Cell Biochem [Internet]. 2018;444(1–2):87–92. Available from: http://dx.doi.org/10.1007/s11010-017-3233-4
70. Eröksüz R, Erol Forestier FB, Karaaslan F, Forestier R, İşsever H, Erdoğan N, et al. Comparison of intermittent and consecutive balneological outpatient treatment (hydrotherapy and peloidotherapy) in fibromyalgia syndrome: a randomized, single-blind, pilot study. Int J Biometeorol. 2020;64(3):513–20.
71. Lanhers C, Pereira B, Gay C, Hérisson C, Levyckyj C, Dupeyron A, et al. Evaluation of the efficacy of a short-course, personalized self-management and intensive spa therapy intervention as active prevention of musculoskeletal disorders of the upper extremities (Muska): A research protocol for a randomized controlled trial. BMC Musculoskelet Disord [Internet]. 2016;17(1):1–9. Available from: http://dx.doi.org/10.1186/s12891-016-1353-8
72. Albadi I, Ciobotaru C, Stoica S, Onose G. News on spasticity and possibilities to control it through hydro-/thermo-/kinesio-therapeutic means – synthetic and systematic literature review. Proc Rom Acad, Ser B. 2020;22(3):148–161.
73. Mikhaylenko V, Fedorchenko R, Komissarova O, Plakida A. The effectiveness of ergo- and psychotherapy in the process of sanatorium-resort treatment of spinal patients. Balneo Res J. 2020;(Vol.11, 4):485–90.
74. Metin Ökmen B, Kasapoğlu Aksoy M, Güneş A, Eröksüz R, Altan L. Effectiveness of PELOID therapy in carpal tunnel syndrome: A randomized controlled single blind study. Int J Biometeorol. 2017;61(8):1403–10.
75. Koziolkin O. A., MiedviedkovaS. O. LiakhovaI. M. Malakhova S. M. LisovaO. O. COO. Complex treatment of patients with vertebral thoracalgia using manual therapy and physical rehabilitation. Zaporozhye; 2019. p. 595–601.
76. Golušin Z, Jovanović M, Magda N, Stojanović S, Matić M, Petrović A. Efekti balneoterapije u Banji Rusanda kombinovane sa kalcipotriolom na plak psorijazu. Vojnosanit Pregl. 2015;72(11):1010–7.
77. García-Villén F, Faccendini A, Miele D, Ruggeri M, Sánchez-Espejo R, Borrego-Sánchez A, et al. Wound healing activity of nanoclay/spring water hydrogels. Pharmaceutics. 2020;12(5).
78. Gowda S, Mohanty S, Saoji A, Nagarathna R. Integrated Yoga and Naturopathy module in management of Metabolic Syndrome: A case report. J Ayurveda Integr Med [Internet]. 2017;8(1):45–8. Available from: http://dx.doi.org/10.1016/j.jaim.2016.10.006
79. Fidut-Wrońska J, Latosiewicz R, Chmiel J, Chołuj K, Pikto-Pietkiewicz K. Inclusion of pelotherapy in the treatment of patients with lumbar discopathy treated with low-frequency magnetic field and kinesitherapy. Heal Probl Civiliz. 2018;12(2):126–31.
80. Viechtbauer W. Conducting meta-analyses in R with the metafor. J Stat Softw. 2010;36(3):1–48.
81. John Fletcher. What is heterogeneity and is it important? Br Med J. 2006;333(7558):83–6.
82. Kim CG, Lee DG, Oh J, Lee YH, Lee YJ, Song PH, et al. Effects of Balneotherapy in Jeju Magma-Seawater on Knee Osteoarthritis Model. Sci Rep. 2020;10(1):1–14.
83. Gyarmati N, Kulisch Á, Németh A, Bergmann A, Horváth J, Mándó Z, et al. Evaluation of the effect of Hévíz mud in patients with hand osteoarthritis: A randomized, controlled, single-blind follow-up study. Isr Med Assoc J. 2017;19(3):177–82.
84. Tékus V, Borbély, Kiss T, Perkecz A, Kemény, Horváth

J, et al. Investigation of Lake Hévíz Mineral Water Balneotherapy and Hévíz Mud Treatment in Murine Osteoarthritis and Rheumatoid Arthritis Models. Evidence-based Complement Altern Med. 2018;2018.
85. Ionescu E V., Tica I, Oprea C, Iliescu DM, Petcu LC, Iliescu MG. Adiponectin correlation with bioclinical benefits of using natural therapeutic factors in knee osteoarthritis. Acta Endocrinol (Copenh). 2017;13(3):308–13.
86. Saberi Hosnijeh F, Bierma-Zeinstra SM, Bay-Jensen AC. Osteoarthritis year in review 2018: biomarkers (biochemical markers). Osteoarthr Cartil [Internet]. 2019;27(3):412–23. Available from: https://doi.org/10.1016/j.joca.2018.12.002
87. Kim M, Lee KH, Han SH, Lee SJ, Kim CG, Choi JH, et al. Effect of Peat Intervention on Pain and Gait in Patients with Knee Osteoarthritis: A Prospective, Double-Blind, Randomized, Controlled Study. Evidence-based Complement Altern Med. 2020;2020.
88. Paoloni, Marco, Bernetti Andrea, Brignoli Ovidio, Coclite Daniela, Fraioli Antonio, Masiero Stefano, Napoletano Antonello, Quirino Nicola, Rengo Franco Ruosi Carlo , Ugo Viora9 MV and SV. Appropriateness and efficacy of Spa therapy for musculoskeletal disorders. A Delphi method consensus initiative among experts in Italy. Ann Ist Super Sanità. 2017;53(1):70–6.
89. Stanciu LE, Pascu EI, Ionescu E V., Circo E, Oprea C, Iliescu MG. Anti-ageing potential of techirghiol mud therapy through the modulation of pituitary-adrenal axis activity. J Environ Prot Ecol. 2017;18(2):728–36.
90. Gálvez I, Torres-Piles S, Ortega-Rincón E. Balneotherapy, immune system, and stress response: A hormetic strategy? Int J Mol Sci. 2018;19(6).
91. Cheleschi S, Gallo I, Tenti S. A comprehensive analysis to understand the mechanism of action of balneotherapy: why, how, and where they can be used? Evidence from in vitro studies performed on human and animal samples. Int J Biometeorol. 2020;64(7):1247–61.
92. Stanciu LE, Oprea C, Pascu EI, Circo E, Iliescu MG, Ionescu E V., et al. Impact of contrast therapy with techirghiol sapropelic mud on blood elements of elder patients. J Environ Prot Ecol. 2018;19(2):923–32.
93. Ionescu E V., Oprea C, Almasan ER, Stanciu LE, Iliescu MG. Biological variation under balneal treatment of serum level of leptin in relation with body mass index in case of patients suffering from knee osteoarthritis. J Environ Prot Ecol. 2017;18(1):375–85.
94. Murakami S, Goto Y, Ito K, Hayasaka S, Kurihara S, Soga T, et al. The Consumption of Bicarbonate-Rich Mineral Water Improves Glycemic Control. Evidence-based Complement Altern Med. 2015;2015.
95. Dolbeth M, Stålnacke P, Alves FL, Sousa LP, Gooch GD, Khokhlov V, et al. An integrated Pan-European perspective on coastal Lagoons management through a mosaic-DPSIR approach. Sci Rep. 2016;6(March 2015):1–12.
96. Lee CW, Li C. The process of constructing a health tourism destination index. Int J Environ Res Public Health. 2019;16(22).
97. Couteau Céline, Coiffar L. Phycocosmetics and Other Marine Cosmetics, Specific Cosmetics Formulated Using Marine Resources Céline. 2020;
98. Zampieri RM, Adessi A, Caldara F, Codato A, Furlan M, Rampazzo C, et al. Anti-inflammatory activity of exopolysaccharides from Phormidium sp. ETS05, the most abundant cyanobacterium of the therapeutic euganean thermal muds, using the zebrafish model. Biomolecules. 2020;10(4).
99. Iliescu MG, Profir D, Surdu O, Marin V, Demirgean S, Almasan RE, et al. Statistical view through balneal activity in Techirghiol medical area. J Environ Prot Ecol. 2018;19(1):382–91.
100. Fenocchi L, Riskowski JL, Mason H, Hendry GJ. A systematic review of economic evaluations of conservative treatments for chronic lower extremity musculoskeletal complaints. Rheumatol Adv Pract. 2018;2(2):1–15.
101. López PC. Balneotherapy treatment for patients suffering from low back pain. Balneo Res J. 2019;10(10.2):167–73.
102. Alfieri FM, Barros MCC, Carvalho KC de, Toral I, Silva CF da, Vargas e Silva NC de O. Geotherapy combined with kinesiotherapy is efficient in reducing pain in patients with osteoarthritis. J Bodyw Mov Ther. 2020;24(1):77–81.
103. Bastos CM, Rocha F, Cerqueira Â, Terroso D, Sequeira C, Tilley P. Assessment of clayey peloid formulations prior to clinical use in equine rehabilitation. Int J Environ Res Public Health. 2020;17(10).
104. Hou C, Liang L, Chu X, Qin W, Li Y, Zhao Y. The short-term efficacy of mud therapy for knee osteoarthritis: A meta-analysis. Medicine (Baltimore). 2020;99(17):e19761.
105. Salca A, Stoica N, Dogaru G. Treatment of knee OSTEOARTHRITIS in Spa Health resorts: where do we stand? Balneo Res J. 2015;6(3):184–94.
106. Fioravanti A, Bacaro G, Giannitti C, Tenti S, Cheleschi S, Gui\delli GM, et al. One-year follow-up of mud-bath therapy in patients with bilateral knee osteoarthritis: a randomized, single-blind controlled trial. Int J Biometeorol. 2015;59(9):1333–43.
107. Pascarelli NA, Cheleschi S, Bacaro G, Guidelli GM, Galeazzi M, Fioravanti A. Effect of mud-bath therapy on serum biomarkers in patients with knee osteoarthritis: Results from a randomized controlled trial. Isr Med Assoc J. 2016;18(3–4):232–7.
108. Chary-Valckenaere I, Loeuille D, Jay N, Kohler F, Tamisier JN, Roques CF, et al. Spa therapy together with supervised self-mobilisation improves pain, function and quality of life in patients with chronic shoulder pain: a single-blind randomised controlled trial. Int J Biometeorol. 2018;62(6):1003–14.