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 pathways 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,
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 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.

Fango therapy - 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): H2S, CO2, NH4, CH4, O2, Rn (8)

Hydrogen sulfide (H2S) 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 H2S are vasodilation and promoting new vessel growth (36).
Humic substances are generally considered to have solution, obtaining the alkaline extract of soluble humates. 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).

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 37°C, and for those with inflammatory rheumatic diseases below 36°C. The duration of the bath is 20’ - 40’. The bath must be followed by a shower at 37° - 38°C 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 38° - 46°C 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 39° - 40°C for 2 hours or vaginal irrigation with mud dissolved in lake water and heated to 37°C (43).

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 hydroxy (mineral mud) are used only for packaging, those with medium hydroxy (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)

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 °C).
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
Through its composition and thermopexy properties, the therapeutic effects of mud determine:

- Physicochemical analysis bulletin. The obtained result is presented in the form of the physicochemical analysis bulletin.

- 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:

- Sensible perception 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.

Peliodotherapy is indicated for the following conditions:
- degenerative rheumatism with different locations: spine (spondylosis, simple discopathy, chronic lumbago (56), peripheral (coxarthrosis, gonarthrosis) (57)
- inflammatory rheumatism (54)
- ar-bo-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 Cochrane1, Elsevier2, NCBI/PubMed3, NCBI/PMC4, PEDro5, and ISI Web of Knowledge/Science6, 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 – PRISMA7 – 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

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3 https://www.cochrane.org/
2 https://www.elsevier.com/
5 https://pedro.org.au/
6 http://apps.webofknowledge.com/WOS_GeneralSearch
7 http://www.prisma-statement.org/
Articular cartilage associated with hypertrophic changes and damage. Osteoarthritis is a degenerative process of the synovial inflammation and progressive structural joint damage. 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.

### 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 dehydroepiandrosterone and its sulfate (adrenopause) (89). H2S – 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, rheopexy, 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). Osteoarthritis 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”.

7. Funding

This research did not receive any specific grant from funding public, commercial, or not-for-profit agencies.

8. Acknowledgments

This study, being a systematic review, did not require written consent from the patients involved.

All authors have equally contributed to this article.

9. Declaration of interests

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

Figures and tables

TABLE 1 Step I: numerical search results.

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We searched for the following set of keywords in 6 international databases: “Mud therapy”, “Pelodotherapy”, “Pliotherpay”, “Fango therapy”, “Mud therapy” + “rehabilitation”, “Pelodotherapy” + “rehabilitation”, “Pliotherpay” + “rehabilitation”, “Fango therapy” + “rehabilitation”.

Next we removed the duplicates (i.e., same article found in different databases).

We excluded all articles that are not published in ISI Thomson Reuters indexed journals.

Next we applied a custom set of selection criteria PEDro inspired.

Full-text analysis for eligibility was performed on the remaining articles and 6 articles were excluded with reasons.

The articles that satisfied all the previous filtering criteria / PRISMA steps were selected for qualitative synthesis.

The articles that satisfied all the previous filtering criteria / PRISMA steps and include data related to pathologies/country of patients treated by mud therapy, were selected for meta-analysis.

**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**

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<th>Study</th>
<th>Year</th>
<th>N. total patients</th>
<th>OA</th>
<th>Rheumatoid arthritis</th>
<th>Osteoporosis</th>
<th>Arthritic symptoms</th>
<th>Low Back Pain</th>
<th>Musculoskeletal disorders</th>
<th>Control</th>
<th>Romania</th>
<th>Spain</th>
<th>Hungary</th>
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10
**Figure 2:** Pathologies and Country frequencies in mud therapy studies (see LEGEND in Table 3)

### Table 3: Studies

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<td>Morer (5) 2016</td>
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<tr>
<td>Yucesoy (52) 2018</td>
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<tr>
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<tr>
<td>Aksoy (43) 2017</td>
<td>0.524 (0.400, 0.647)</td>
<td>33/63</td>
</tr>
<tr>
<td>Kim (78) 2020</td>
<td>0.537 (0.394, 0.689)</td>
<td>22/41</td>
</tr>
<tr>
<td>Ionescu (76) 2017</td>
<td>0.500 (0.356, 0.644)</td>
<td>23/46</td>
</tr>
<tr>
<td>Lopez (92) 2019</td>
<td>0.000 (0.000, 0.001)</td>
<td>0/1390</td>
</tr>
<tr>
<td>Xiang (55) 2016</td>
<td>1.000 (0.998, 1.000)</td>
<td>1010/1010</td>
</tr>
<tr>
<td>Gálvez (57) 2018</td>
<td>0.966 (0.949, 1.000)</td>
<td>36/36</td>
</tr>
<tr>
<td>Iliescu (90) 2018</td>
<td>0.437 (0.425, 0.449)</td>
<td>2744/6291</td>
</tr>
<tr>
<td>Varzatly (60) 2019</td>
<td>0.348 (0.251, 0.445)</td>
<td>32/92</td>
</tr>
<tr>
<td>Kirby (81) 2019</td>
<td>0.982 (0.963, 1.000)</td>
<td>60/60</td>
</tr>
<tr>
<td>Hou (94) 2020</td>
<td>0.390 (0.369, 0.427)</td>
<td>440/1106</td>
</tr>
</tbody>
</table>

**Overall (I²=99.99%, P<0.001)** 0.544 (0.400, 0.687) 7372/15123

**Binary Random-Effects Model**

<table>
<thead>
<tr>
<th>Metric: Proportion</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>Std. error</th>
<th>p-Value</th>
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<tr>
<td>Estimate</td>
<td>0.544</td>
<td>0.687</td>
<td>0.073</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>tau^2</td>
<td>Q(df=25)</td>
<td>Het. p-Value</td>
<td>I²</td>
</tr>
<tr>
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<td>0.138</td>
<td>1447636.745</td>
<td>&lt;0.001</td>
<td>99.995</td>
</tr>
</tbody>
</table>

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

**References:**


32. Özuku K, Göral H, Karagülle M, Barut Y, Eröksüz R, Karagülle MZ. Balneological outpatient treatment for


95. 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).
97. Couteau Céline, Coiffar L. Phycocosmetics and Other Marine Cosmetics, Specific Cosmetics Formulated Using Marine Resources Céline. 2020;