BALNEOTHERAPY AND HORMESIS FOR OSTEOARTRITIS PAIN HEALING

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Abstract

Balneotherapy is an ancient therapy that is still popular today. Thermal mineral water is used for this therapy. Some positive effects of mineral baths on human health have been demonstrated. These positive effects are probably due to the combined mechanical, thermal and chemical effects of mineral water and mud. The combination of balneotherapy and physiotherapy was more effective in improving pain, physical function and walking speed in advanced knee osteoarthritis than physiotherapy alone. Hormesis is a type of cellular response to the low dose of toxin and is considered an adaptive compensatory process after an initial disturbance of homeostasis. There are several factors that can be considered hormetins, e.g. heat and thermal water. This mini-review summarizes the improvements in the treatment of osteoarthritis by balneotherapy and hormesis.

Keywords: Balneotherapy, Thermal water, Hormesis, Osteoartritis

Abbreviations

BT	Balneotherapy
OA	Osteoartritis
RA	Rheumatoid arthritis
FM	Fibromialgy
OARSI	Osteoartritis Research Society International
HT	Hidrotherapy
EULAR	European League Against Rheumatism
MMP	Matrix metaloproteinaze
CRP	C-reactive protein
PGE2	Prostaglandine E2
LTB4	Leukotriene B4
ACTH	Adrenocorticotropic hormone
SNS	Sympathetic nervous system
TS	Heat shock
BTS	Heat shock protein

Introduction

Balneotherapy (BT) refers to bathing in natural mineral or thermal water (e.g. mineral baths, sulfur baths, Dead Sea baths), the use of mud packs or both (Verhagen, et al., 2015). BT and mud therapy have always been used empirically to treat numerous diseases. Baths are considered an integral part of traditional medicine in many cultures and countries, e.g. in: France, Italy, Spain, Portugal, Germany, Austria, Switzerland, Turkey, Poland, Czech Republic, Hungary, Romania, Russia, Israel, Japan and others. Cures are now an important part of the public health systems of many countries in Europe and beyond (Protano, et al., 2023).

BT is an effective, well-tolerated and complementary approach in the treatment of various pathologies, especially those related to chronic inflammation, such as cardiovascular, respiratory, gastrointestinal, endocrine and neurological diseases and, above all, skin and rheumatic diseases (Forestier, et al., 2017). In recent decades, a growing number of studies (including high-quality meta-analyzes and systematic reviews) have reported the beneficial effects of BT, including mud therapy, on various clinical outcomes in patients with osteoarthritis (OA) (Espejo-Antúnez, et al, 2013; Liu, et al, 2013; Forestier, et al, 2016), rheumatoid arthritis (RA) (Santos, et al, 2016; Tékus, et al, 2018), fibromyalgia (FM) (Ablin, et al, 2013 ; Naumann Sadaghiani, 2014; Schitter, et al, 2022) and other rheumatic diseases (Gálvez, et al, 2018). Of all these pathologies, OA is most commonly treated with balneological interventions (Gálvez, et al., 2018). The beneficial effect is probably due to the combined mechanical, thermal and chemical action of mineral water and mud (Tékus, et al., 2018). As these therapies have only a few or no side effects, they are particularly relevant for OA patients, who are usually elderly patients at risk of side effects related to multimorbidity and polypharmacy (Gálvez, et al., 2018). The Osteoarthritis Research Society International (OARSI) guidelines state that BT is appropriate in OA patients with comorbidities when treatment options are limited (McAlindon, et al., 2014).

The purpose of this term paper is to introduce BT and OA, present the beneficial effects of BT in patients with OA, and describe the ways in which BT affects OA symptoms.In addition, the usage of hormesis is introduced as promising healing technique.

Joint imflammation

Osteoarthritis (OA) is a degenerative process of articular cartilage associated with hypertrophic bone changes (Tékus, et al., 2018). OA is a common chronic degenerative disease associated with pain and a weakened state with progressive damage to the articular cartilage, moderate inflammatory changes in the tissue in and around the joints and, in more severe cases, the formation of osteophytes and bone cysts (Loeser, et al., 2016). OA is the most common joint disease and the main cause of pain and mobility impairment in older people. OA is the result of complex mechanical, biological, molecular and enzymatic interactions that ultimately lead to degeneration of the joint tissue and affect the entire joint (Man Mologhianu, 2014).

OA is considered one of the most common musculoskeletal disorders and one of the ten most disabling diseases in industrialized countries. Globally, an estimated 7% of the world's population (more than 500 million people) suffer from OA, with a much higher risk among women. The number of people affected by this disease increased by 48% between 1990 and 2019. However, in 2019, OA was the 15th leading cause of years lived with disability (Hunter, et al., 2020). In the United States, OA affects more than 32.5 million adults and is considered one of the most expensive diseases to

treat (CDC, 2020). The extent of OA is directly proportional to age, especially in individuals aged 75 to 79 years. Men are more commonly affected than women until the fifth decade of life, but the trend reverses after menopause, with the latter having a higher prevalence (Protano, et al., 2023).

OA can affect any movable joint, but some specific forms of the disease have a selective localization such as gonarthrosis (also called OA of the knee), OA that affects one or both knees. The global age-standardised prevalence of knee OA was 3.8% and was higher in females comapred to males (Cross, et al., 2014).

OA therapy includes conservative (pharmacological and non-pharmacological) or surgical approaches (Kulisch, et al., 2014). The aim of therapy is to relieve pain, maintain joint mobility and maximize joint and overall function. The main non-pharmacological conservative treatment consists of some physical measures such as rehabilitation, assistive devices, exercises to increase muscle strength, flexibility and endurance, patient education about yoga through suggestions for daily living and thermotherapy, which includes massage, HT, mud therapy and BT (Rausch Osthoff, et al., 2018; Kolasinski, et al., 2020; Bernetti, et al., 2020). Several studies have compared BT with other standard OA treatments and found that BT has greater long-term effects on quality of life in people with severe disabilities by reducing joint pain and stiffness and increasing limb mobility (Fioravanti, et al., 2017). Due to its numerous positive effects, BT is recommended in the OARSI guidelines as a complementary non-pharmacological treatment for gonarthrosis, coxarthrosis and polyarticular OA (Bannuru, et al., 2019). In addition, due to its positive effects on OA, BT is also listed in the EULAR (European League Against Rheumatism) recommendations for healthcare professionals' approach to pain management in inflammatory arthritis and OA (Geenen, et al., 2018).

Balneotherapy

In medical hydrology and physical medicine, bath therapy encompasses a range of techniques based on the healing effects of water, including balneotherapy (BT) and hydrotherapy (HT) (Gomes, et al., 2013). Different types of mineral water may be used in this therapy, just above 31 ºC (Verhagen, 2007). Some beneficial effects of mineral baths compared to no treatment were demonstarted.

Exercises in warm (tap) water are commonly referred to as "hydrotherapy" or "aquatic therapy" (Verhagen, et al., 2015). BT is a set of methods and practices that use medically and legally recognized mineral thermal waters, muds and natural gasses from natural sources (e.g. CO_2, H_2S) for therapeutic purposes in the premises of thermal spas, based on scientific evidence (Gomes, et al., 2013; Fioravanti, et al., 2015b). Muds (or peloids) are mature mud suspensions composed of a complex mixture of fine-grained materials of geological origin, mineral water and, usually, organic compounds from biological metabolic activity. Mud therapy or pelotherapy is therefore a balneological procedure that consists of the external application of mud for therapeutic purposes (Gomes, et al., 2013).

Histrory of balneotherapy

The term "balneotherapy" comes from the Latin word balneum (bath). The term is classically used in (Eastern) European countries when natural mineral or thermal waters are used for bathing, drinking and inhalation (Verhagen, et al., 2015). One of the basic elements of BT is the use of (natural) mineral and thermal waters just above 31 ºC, gasses and peloids (including dressings - local application of peloids). In most European countries, BT often takes place in centers with thermal or sea baths (Gutenbrunner, et al., 2010). In Homeric times, baths were mainly used for cleansing and refreshment. At the time of Hippocrates, bathing was not only seen as a simple hygienic measure. It was considered useful for the treatment of most diseases. The Romans used the water to treat orthopedic diseases, but after the Roman era the baths were no longer used. The baths were rediscovered in the sixteenth century. The baths were rediscovered in the nineteenth century and since then bath therapy has been used continuously to treat musculoskeletal conditions. BT is most commonly prescribed to patients with any form of arthritis, including ankylosing spondylitis. Positive effects are also mentioned in the treatment of other diseases, such as psoriasis (Verhagen, et al., 2015).

BT is based on the beneficial effects of natural thermo-mineral waters, gases and peloids. The effects of BT are attributed to the atmosphere of thermomineral water, its density, specific gravity, hydrostatic pressure, buoyancy, viscosity, temperature and the effects of dissolved substances (Gutenbrunner, et al., 2010). The authors Gálvez, et al. (2018) state that BT is a clinically effective complementary approach in the treatment of low-grade inflammatory and stress-related pathologies. BT is one of the oldest forms of treatment for osteoarthritis patients. Nowadays, individually tailored combinations of non-pharmacological and pharmacological treatment are used to achieve the best results. In several countries, especially in Central Europe, drug therapies are used as part of non-pharmacological treatment (Hanzel, et al., 2018).

Effect of balneotherapy in patients with osteoarthritis

Arthritic diseases are the most common causes of chronic pain and disability (Tékus, et al., 2018).

The biological mechanisms by which immersion in mineral medicinal water and the application of mud alleviate the symptoms of many pathologies are not yet fully understood, but it is known that neuroendocrine and immunological responses to BT, including humoral and cell-mediated immunity, are involved in these mechanisms of action. . This leads to anti-inflammatory, analgesic, antioxidant, chondroprotective and anabolic effects along with neuroendocrine and immunological regulation in various diseases (Gálvez, et al., 2018). The positive effect of BT is probably due to the combined mechanical, thermal and chemical effects of mineral water and mud (Tékus, et al., 2018).

BT causes local and general physiological effects in the organism, which are carried out by physical mechanisms, mainly related to thermal therapeutic effects. Temperature plays a central role in the effects of BT. Mineral healing waters and mud are usually applied hot, as they are excellent for heat transfer, can

store heat and release it slowly, so that these treatments can be considered thermotherapeutic interventions. The special feature of BT is that its beneficial effect on the body is not only due to the physical properties of the mineral healing water and mud, but also to their chemical and biological composition. On the other hand, in other spa treatments where ordinary tap water is used, such as HT, only the physical properties of the water (temperature, hydrostatic pressure, hydrodynamics, buoyancy, viscosity, electrical conductivity, etc.) are responsible for the beneficial effects (Gomes, et al., 2013).

While the physical therapeutic effects of BT are well known, the chemical-biological effects are difficult to identify and evaluate. Indeed, thermotherapeutic effects are the basis of BT treatment as a result of the increased application temperature, which is usually in the range of 38 to 42 ◦C (Naumann Sadaghiani, 2014). Irrespective of this, the absorption of biologically active inorganic and organic substances through the skin also plays a role in the effectiveness of BT. In vitro and in vivo studies have shown that some water-soluble minerals can penetrate human skin and appear to be a key mechanism responsible for improving some clinical outcomes in both BT and mud therapy, implying that these beneficial effects are not exclusively related to the action of heat (Sarsan, et al., 2012). Mineral water or mud treatments had better and longer improvements in e.g. osteoarthritis, osteoporosis compared to baseline and non-mineral similar treatments (Morer C. et al, 2017)

Studies on the effect of thermal water from Hungary on mice artificially infected with OA showed that thermal water as wellas the combined treatment of water and mud significantly reduced mechanical hyperalgesia and knee edema in an OA model. Neither healing water nor mud treatment improved the deep structural bone and joint damage in the animal models (Tékus, et al., 2018). Based on these results, it could be concluded that BT is an effective complementary treatment to reduce pain and swelling in degenerative joint disease. Research by authors Tékus, et al. (2018) confirmed the anti-nociceptive and anti-inflammatory effects of thermal water and mud treatment in patients with degenerative diseases. The exact molecular mechanism of BT is not yet fully understood, but its efficacy has also been confirmed in human studies (Gálvez, et al., 2018). A randomized, controlled, single-blinded follow-up study showed that BT reduced pain, function and quality of life in patients with knee OA and that it is a potentially beneficial treatment modality for patients with this condition (Kulisch, et al., 2014). A study by Sahin-Onat et al. (2015) found that a combination of BT and physiotherapy was more effective in improving pain, physical function and walking speed in advanced knee OA than physiotherapy alone.

Balneotherapy and immune system

Balneotherapy or spa treatment is commonly known for the various forms of using medicinal waters and their effects on the human body. In this section the effect on immune system would be inspected more in detail. Over the last two decades, numerous studies have investigated immunological mechanisms of action that suggest anti-inflammatory effects that may underlie the clinical benefits of BT. In various pathologies associated with mild inflammation, particularly rheumatic diseases, BT and mud therapy have been reported to lead to a reduction in serum concentrations of the proinflammatory cytokines TNF-α and IL-1β, the regulatory cytokine IL-6, and an increase in the anti-inflammatory growth factor IGF -1 (Gálvez, et al., 2018). Similar results were shown in the research (Ortega, et al., 2017) on a comprehensive evaluation of the effect of mud therapy on the cytokine profile of OA patients. The data showed a drastic decrease in unhealthily elevated systemic levels of IL-1β, TNF-α, IL-8, IL-6 and TGF-β, confirming the anti-inflammatory effects of mud therapy (Ortega, et al., 2017). Mud therapy can also reduce circulating levels of adipokines, adiponectin and resistin in OA (Fioravanti, et al., 2015a). All of these cytokines and adipokines are important mediators of inflammation and cartilage metabolism (Berenbaum, et al., 2013), and their modulation by BT leads to anti-inflammatory chondroprotective effects that may play a beneficial role in rheumatic diseases such as OA. Similarly, matrix metalloproteinases (MMPs) are involved in cartilage degradation. Serum MMP-3 levels have decreased following mud therapy in OA patients, either as a direct effect of the intervention or as a result of a reduction in pro-inflammatory mediators such as cytokines that stimulate MMP secretion, suggesting that mud therapy contributes to the integrity of the extracellular matrix (Gargiulo, et al., 2014). In addition, C-reactive protein (CRP) levels, which increase in response to inflammation, are lowered in patients with rheumatic and cardiovascular diseases after BT (Oyama, et al., 2013). Prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) are other important mediators of inflammation. There is evidence that BT and mud therapy reduces circulating levels of these biomarkers in patients with rheumatic diseases (Gálvez, et al., 2018). It is known that the inflammatory response plays a key role in the development and maintenance of many pathological pain conditions. As part of the inflammatory response, some proinflammatory cytokines such as IL-1β, IL-6 and TNF-α are strongly involved in the inflammatory and neuropathic pain process. They can directly modulate neuronal activity in the peripheral and central nervous system and stimulate the production of other mediators associated with inflammation and pain, such as substance P and PGE2, contributing to hyperalgesia and allodynia (Gálvez, et al., 2018). In this way, the reduction in the levels of these mediators after BT may also be related to the analgesic effects of the treatment, as shown by the simultaneous reduction in pain sensation (Ortega, et al., 2017).

The hypothalamic-pituitary-adrenal axis (stress axis) is activated in response to various stressors, including hyperthermia, and leads to the release of β-endorphin, a peptide with morphine-like analgesic effects, adrenocorticotropic hormone (ACTH) and cortisol. The latter is particularly important due to its anti-inflammatory effect and its ability to inhibit the production of most cytokines. At the same time, activation of the sympathetic nervous system (SNS) by stressors stimulates the release of catecholamines. After BT,

when hyperthermia occurs, systemic ACTH, cortisol, growth hormone and prolactin levels increase in patients with various pathologies, including inflammatory pathologies (Gálvez, et al., 2018).

The authors Ortega, et al. (2017) reported on neuroendocrine immune regulation in OA patients undergoing mud therapy. In these patients, there was an increase in the concentration of circulating cortisol, which contributes to the reduction of elevated systemic levels of inflammatory cytokines in this pathology (Ortega, et al., 2017). This suggests that the effects of BT on the neuroendocrine system are mainly due to the heat stress caused by the application of elevated temperatures. Heat stress triggers a cellular response, the heat shock response (HSR), in which heat shock proteins (HSPs) are synthesized and released. Maintaining the response to TS by repeated mild heat stress leads to hormetic effects in the organism. In this way, the response to TS and BTS could play a role in the beneficial effects of BT (Scapagnini, et al., 2014). However, the optimal intensity, duration and interval of heat stimulation for clinical use, especially in diseases associated with inflammation and stress, have yet to be determined (Gálvez, et al., 2018).

Hormesis

The hormonal effects of BT are due to various factors. The most important factor common to all types of mineral healing waters and mud is heat. Other factors are specific biochemical components of the water, such as hydrogen sulfide (H_2S) and radon. The results of several studies show that the beneficial effects of BT and HT are consistent with the concept of hormesis, thus supporting the role of hormesis in hydrothermal treatment (Gálvez, et al., 2018). While severe heat stress leads to cell damage and cell death, mild heat stress induces a response to TS that protects cells and organisms from severe damage, allows the resumption of normal cellular and physiological activities, and leads to a higher degree of thermotolerance. An important aspect of stress responses is that they can lead to higher levels of stress tolerance and greater resistance to subsequent stress damage from more than one type of stress. In this way, mild heat stress can protect against oxidative stress or toxin damage (Scapagnini, et al., 2014).

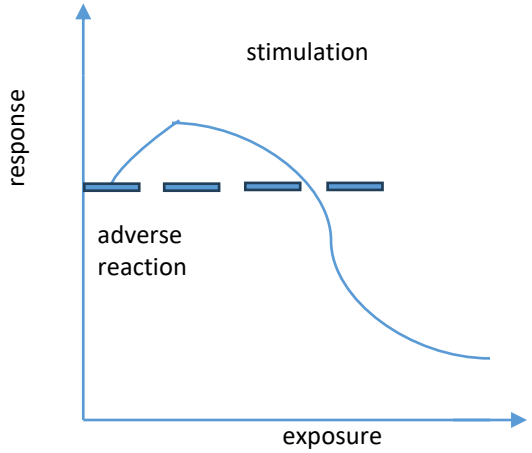

Figure 1: Response in dependence of exposure time

Hormesis is a biphasic dose-response phenomenon where low doses of stressor or toxin can have a beneficial effect on an organism, contrary to the traditional understanding of dose-response relationships (Calabrese, et al., 2007). Higher doses result in an inhibitory or toxic effect. This response to low doses of stress is considered an adaptive compensatory process or an adaptive and stress response after an initial disturbance of homeostasis that increases the organism's ability to withstand more severe stress (Mattson, 2008).A hormetin is defined as a condition that may be potentially hormetic in a physiological sense by activating or regulating one or more cellular and molecular stress response pathways that protect against a similar but more severe stress (Rattan Demirovic, 2010). There are several conditions and factors that can be considered hormetins, in addition to chemicals and toxins, these can include: biological hormetins such as infection, hypoxia/ischemia, endogenous metabolites, dietary caloric restriction, intermittent fasting, and micronutrients; psychological hormetins such as mental challenges and meditation; and physical hormetins such as exercise, heat, and radiation (Ortega, 2016). In fact, repeated mild heat stress affects various parameters of cellular senescence and other functional characteristics such as differentiation, wound healing and angiogenesis. These hormetic effects result in an important biological response that leads to an overall improvement of the living system (Gálvez, et al., 2018). In this context, thermotherapeutic strategies such as BT and HT can be considered as potential hormonal interventions.

Hormetic effect of radon

Mineral healing waters containing radon are radioactive and can also be regarded as a therapeutic hormonal strategy. Therapy with radon-containing healing water consists of the intake of radon by inhalation or by transcutaneous absorption of radon dissolved in water. This therapy is used for many inflammatory diseases, including arthritis, asthma, bronchitis and psoriasis (Gálvez, et al., 2018). Although ionizing radiation has been shown to be carcinogenic at high doses, it has biologically beneficial effects at low doses by initially causing minor molecular damage, which then leads to the activation of one or more stress response pathways, triggering adaptive mechanisms that can prevent adverse health effects (Gutenbrunner, et al., 2010). Radiation-induced hormetic response mechanisms include activation of DNA repair, scavenging of free radicals,

elimination of damaged cells through apoptosis, synthesis of stress proteins and stimulation of the immune response (Gálvez, et al., 2018). Some older studies have shown positive effects of BT with radon in OA patients. They had improvements in antioxidant and immune function as well as changes in pain-related biomarkers (Yamaoka, et al., 2004a; b). Treatment with radon-rich medicinal water at optimal radon concentration would be beneficial as an adjunct treatment for rheumatic diseases such as OA (Calabrese Calabrese, 2013). In addition, a randomized clinical study (Annegret and Thomas, 2013) showed significantly better long-term pain reduction after radon therapy for rheumatic diseases. Compared to treatment without radon, BT with radon was superior in terms of pain relief, improvement in function, reduction in the use of anti-inflammatory drugs and analgesics and the persistence of these benefits in the longer term (Annegret and Thomas, 2013).

Hormetic effect of hydrogen sulfide

The active molecule in sulphur and sulphate mineral healing waters is hydrogen sulphide H_2S, hormetin, which can actively penetrate the skin. While high concentrations of H_2S are extremely toxic, low concentrations are tolerated and have potential cytoprotective effects with anti-inflammatory and antioxidant applications (Carbajo and Maraver, 2017). H_2S has important physiological functions as an endogenous cell signaling molecule in the regulation of inflammation and oxidative stress (Jin, et al., 2015; Olas, 2017). In vitro research by the authors Braga, et al. (2013) demonstrated the antioxidant and anti-inflammatory effects of sulfate thermal water. Fioravanti, et al. (2013) demonstrated that sulfate thermal water inhibits nitric oxide (NO) production and apoptosis in chondrocytes of OA patients. There is also evidence that H_2S treatment reduces interleukin secretion in OA patients (Sieghart, et al., 2015). H_2S also blocks the production of inflammatory cytokines (IL-8, IL-1β, TNF-α, IL-6 and IL-10) and balances the formation of reactive oxygen species (Burguera, et al., 2020). From all these studies, it can be concluded that BT with water rich in H_2S (in low concentrations, as found in natural sources) can exert hormetic therapeutic effects in various pathological conditions related to inflammation. The hormonal effects of sulfurous thermal water may be due to the synergistic action of two different hormetins: H_2S and heat (Gálvez, et al., 2018).

Disadvantages

Every mineral healing water and mud in the world have different characteristics, physical properties and chemical compositions. Despite mounting evidence, it is difficult to analyze the specific effects of each mechanism and chemical component separately. Depending on the predominant ions and gasses, mineral healing waters can be divided into chlorinated, sulphated, bicarbonated, ferrous, carbonated, sulphuric, and radioactive waters (Monasterio, et al., 2016). It is known that different diseases generally require remedies with different chemical compositions to achieve therapeutic results (Gálvez, et al., 2018). However, the exact components best suited to each pathology and the ideal concentration of each element required for optimal biological and clinical outcomes are not yet fully understood. It is plausible to assume that the mechanism of action is the result of a complex synergistic combination of several factors (Morer, et al., 2017).

Furthermore, there are no precise data on the side effects and complications of BT. This applies in particular to rare side effects. Adverse effects may include skin rash, infections and accidents, such as slipping on wet surfaces near the bathroom (Verhagen, et al., 2015).

The treatment environment is also an important factor in treatment outcomes. It was steted state that many factors may contribute positively to the reported effects, e.g. changes in the environment, "spa scenery", absence from (domestic) work commitments, physical and mental relaxation, physical therapy, etc. (Verhagen, et al., 2015) Thus, the potential benefits of the spa could also be attributed to the effects of factors unrelated to the water-therapy itself.

The evaluation of the effectiveness of BT often has weaknesses that can lead to a high risk of bias. For example, there is often a lack of data presentation and information about the study design, particularly strategies to avoid bias. Therefore, a solid analysis of the effectiveness of BT cannot be presented. Quality of life assessments are also often not provided. This is surprising as one of the aims of BT or therapy for patients with chronic diseases in general is to improve health-related quality of life. The follow-up period also appears to be quite short. The heterogeneity of the 'balneotherapy' intervention was also noted(Verhagen, et al., 2015). BT sometimes referred to treatment with tap water or to mineral baths, carbon dioxide baths, Dead Sea baths, sulphur baths or combinations of all of these. Sometimes it also involved treatment with the mud itself. It is therefore difficult to determine which form of BT is most effective, indicating the need for further research.

Conclusion

Balneotherapy is an effective complementary approach in the treatment of many mild inflammatory and stress-related diseases, especially rheumatic diseases. Most studies report positive effects of balneotherapy. However, despite the proven clinical and symptomatic benefits of balneotherapy, its role in modern medicine remains controversial, mainly because the biological mechanisms underlying these benefits are not yet fully understood. Further research is needed to elucidate the mechanisms of balneotherapy efficacy that are related to the stress response and consequently to the inflammatory response. Due to the diversity and heterogeneity of balneotherapy modalities, water and mud composition and application protocols, it is difficult to determine the exact intervention to achieve optimal biological and clinical outcomes in different pathologies. In hormesis, the ideal temperature and concentration of different bioactive chemical elements (as well as the number and duration of treatments and the intervals between each treatment) must be determined in order to trigger hormetic responses without causing harmful or toxic effects. Clearly, further research is needed to understand the hormonal mechanisms of efficacy. There-

fore, balneotherapy can be administered by health professionals on the basis of scientific evidence supporting its use.

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CONFLICT OF INTERESTS

The authors declare that no conflict of interests exist.

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ETHICAL APPROVAL

The study was not performed on humans or animals. The study used anonymized data in accordance with applicable health data legislation and General Data Protection Legislation.

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