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Efficacy and Safety of Balneotherapy using Diverse Natural Resources in Lithuania: A Multicenter Study

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Abstract: Background: Balneotherapy or spa therapy, with its multimodal effects, has shown clinical efficacy in treating various pathological conditions. However, further studies are needed to assess its impact on mental health and to evaluate treatment safety. **This study aimed** to evaluate the effectiveness of different natural resources of the Lithuanian medical spa for stress-related disorders and skin health and to disclose the safety profile of using natural resources. **Methodology**. We performed a multicenter randomized controlled single-blinded study in 6 Lithuanian medical spas. The 1- 2-week treatment combining mineral water, therapeutic mud, and salt procedures was provided for the 364 participants with moderate stress levels and the effect was evaluated using surveys, instrumental, and laboratory measures. **Results**. The findings highlighted that the effects of BT using different natural resources significantly improve mental and skin health, as well as contribute to overall health status for up to 6 months. A significant reduction of anxiety, depression, and fatigue as well as improvement in sleep, skin moisture, subjective skin state, and integrative outcomes was achieved in all centers after treatment, while stress and saliva cortisol, working speed, skin oiliness, and elasticity improved in a few centers. A positive result was related to the duration of the treatment, and possibly- to the features of natural resources. Mineral water most commonly caused side effects; it varied among centers, however, they were predominantly local, mild, and transient. **Conclusions**. Balneotherapy using natural resources is effective for the enhancement of mental and skin health. Further research is necessary for a better understanding of the role of different natural resources on health status and safety profile.

Keywords: balneotherapy, health, mental state, mineral water, natural resources, peloids, peloidotherapy, safety, spa therapy, skin

1. Introduction

Natural resources are essential components of living and inanimate nature. They include the energy of the sun and the depths of the Earth, minerals (oil, metals, peat), air, climate, water, soil, herbals, forests, wildlife, and landscape. Some of the most used resources used in balneotherapy (BT) are clay, peat, and underground water. The use of various mineral waters and peloids as therapeutic agents has a longstanding tradition in

many countries from ancient Egyptian, Roman, and Greek cultures, Egypt, and Israel [1], [2], [3]. In Europe, the following healing resources are recognized: healing mineral waters (for drinking, breathing, baths, or active procedures); healing gases (radon, H_2S, CO_2 in water sources); sea therapy; healing mud; healing climate; Kneipp therapy [4], etc.

In an era dominated by modern medical interventions, there is a resurging recognition of the need for natural holistic, and sustainable alternative treatment approaches. BT is an effective complementary method based on stimulating and adapting the body in the management of various low-grade inflammations and stress-related pathologies, especially rheumatic and metabolic conditions [5], [6], and generally employs mineral, or thermal waters, and gases [7], [8] from natural springs, peloids (mud), and other traditional remedies for the treatment of different pathological conditions, such as dermatological, rheumatological, gastroenterological, pulmonary, cardiovascular, gynecological, metabolic, neurological, psychiatric, endocrine, and even Covid-19 [9], [10], [11], [6], [12], [13], [14], providing analgesic, anti-inflammatory (limiting the production of the central proinflammatory cytokines, prostaglandins), antioxidative, sedative, and muscle-rejuvenating effects, reducing heat shock proteins and adipokines [15], [16], [17], [18], [19], [20]. The mechanism of action of BT is still not fully clear [21]. It has been proposed that numerous factors in natural resources like mineral water and peloids, such as mechanical, thermal, and chemical effects, play a combined role in the effectiveness [22], [23]. The environment, density, buoyancy, specific gravity, viscosity, hydrostatic pressure, temperature, and dissolved substances of mineral water affect the balneotherapy [24]. The pressure of the mud on the body surface and the osmotic changes in the skin lead to the softening and resolution of pathological products, as well as other features [25], [26]. Non-specific (hydrotherapeutic) mechanisms depend on the physical properties of the water and are well-known [27]. In contrast, specific (chemical) properties depend on the organic and inorganic compounds as well as on the microorganisms present in mineral water or peloids, which are challenging to verify [28], [29], [30].

Stress has become a ubiquitous and prevalent challenge worldwide, affecting individuals across diverse cultures and lifestyles. The fast-paced nature of modern life, coupled with various socio-economic factors, has contributed to the escalating prevalence of stress-related mental disorders (anxiety, depression, fatigue, cognitive function impairment). Moreover, the COVID-19 pandemic has dramatically affected people's lives around the world through threats to physical health, lifestyle changes, increased stress, and increased threats to mental health and well-being [31], [32]. Stress expression encompasses physical, emotional, mental well-being, and behavioral changes [33]. Chronic stress promotes the development of anxiety and depression [34] and dementia [35], and has bidirectional relationships with fatigue [36] and sleep quality [37]. There is an intricate relationship between stress and skin conditions: stress, whether chronic or acute, can act as a trigger or an exacerbating factor for various skin conditions [38], [39]. Conditions such as eczema, psoriasis, acne, and hives have been linked to heightened stress levels. The physiological response to stress, including the release of stress hormones, may contribute to inflammation, imbalances in the immune system, and impaired skin barrier function. Conversely, skin conditions can also induce stress due to their visible nature, impacting self-esteem.

Most scientific studies worldwide have shown positive effects of BT on musculoskeletal diseases and skin regeneration [40], [41], [42], [43], [44], [5], as well as other diseases and general health indicators [45], [46], [47].

In recent years studies have reported positive effects of balneotherapy related to relieving stress, fatigue, mood disorders, and burnout [48], [49], [50], [51]. They also showed improved quality of life, sleep, psycho-emotional well-being, and mental activity [52]. [53], [54], [55], [56].

Overall, mental and skin health has significant individual and societal implications, yet research attention and effective natural treatment methods are lacking. In the pursuit of medical treatments, the importance of embracing safe and natural products has garnered increased attention. Studies on BT treatments vary, hindering conclusive findings on their benefits. Diverse methodologies and results also obstruct clear assessments of natural resource effectiveness and safety. Further research is needed to understand the full impact on mental and physical health and to develop effective treatment approaches. The composition of water and peloid varies from region to region and may be associated with different effects upon usage, which should be clarified for integrating balneotherapy in the treatment programs together helping to develop sustainable medical balneal tourism [57], [58], [59]. Lithuania is among the leading and well-known countries throughout Europe for medical spas and is rich in natural resources. However, scientifically based studies regarding the combined therapeutic effect and safety of different natural resources for the treatment of different disorders are still limited.

The aims of this study were, firstly, to study the effectiveness of different natural resources of the Lithuanian medical spa for the reduction of stress-related disorders and improvement of skin conditions; and secondly, to disclose safety issues in using natural resources.

2. Methods

Study design and ethics

The multicenter randomized controlled single-blinded (for researchers) interventional study was made from January through September 2023 in 6 medical spa centers: Gradiali (Palanga), Atostogų parkas (Kretingos reg), Egle (Druskininkai), Draugystė (Druskininkai), Tulpė (Birštonas), Versmė (Birštonas) in Lithuania (Fig.1).

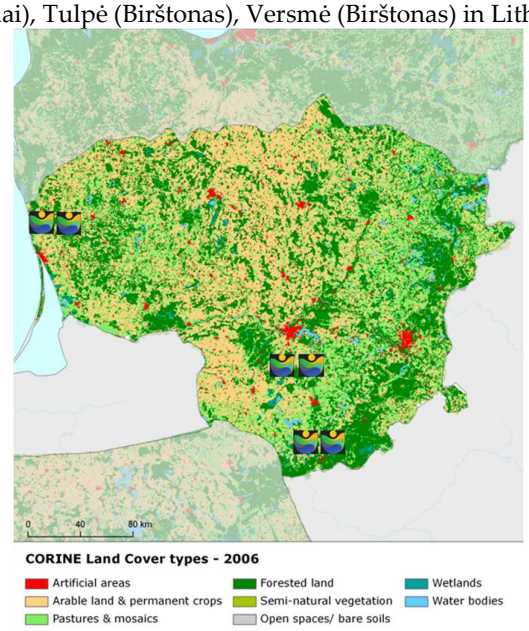

Figure 1. The location of medical spas participated in the study.[32].

 - sites of the tested mineral water.

This study was conducted according to the guidelines of the Declaration of Helsinki and it adheres to Good Clinical Practice (GCP) guidelines and other relevant regulations, and following the biomedical study protocol approved by Kaunas Regional Research Ethics Committee (permission code BE-2-87 (28-11-2022). The study was registered in ClinicalTrial.gov (Identifier: NCT06018649). The information about the planned study and the participants being recruited was disseminated throughout Lithuania, and all terms, and descriptions of the study were available on the Klaipeda University site together with

the registration form. All the participants signed the informed consent with the information about the study's aim, terms, and description of this study before fulfilling the electronic registration form. Detailed information about biomedical research and an opportunity to ask questions and receive answers was given, and signing informed consent in paper form was carried out at the research center before the examination (T0), participants received a copy of the Informed Consent Form. According to the signed consent, participants could discontinue participation in the study at any time without giving any reason. The coded data will be stored in the University for the period provided for in the legislation. Research centers were committed to respect and protect the privacy and personal data of each data subject. The privacy policy was prepared in accordance with Regulation (EU) 2016/679, Directive 95/46/EC, personal legal protection of the Republic of Lithuania law, and other legal acts protecting the information that they collect, use, and store.

Participants and resources

Inclusion criteria were the age of 18–65 years, with moderate stress intensity (> 3 points (10, VAS), or moderate stress management <7 (10, VAS). The *exclusion criteria* were uncontrolled/decompensated systemic diseases (hematological, endocrine, rheumatological, renal, cardiovascular, digestive, pulmonary), active infection, malignant tumors, surgery or significant trauma in the past year, applied balneotherapy treatment during 3 months, pregnancy/lactation, bleeding, severe mental and physical health problems.

The person who was responsible for the selection of participants according to inclusion and exclusion criteria analyzed the data provided and contacted possible participants (if needed) and according to participants' preferred treatment location and possibilities to reach the research center daily (within a radius of about 100 km) allocated them to Klaipeda and Druskininkai clusters. The lists of potential participants were drawn up after the initial assessment of the information provided, and participants were invited for the initial examination in research sites (T0). The number of persons assessed for eligibility was 1137.

Sampling was a probabilistic nest (cluster), in which each research participant's entry into the sample was multi-stage, criterion-based. Persons who met eligibility criteria were allocated to Klaipeda (2 research centers) and Druskininkai (4 research centers) clusters, coded and randomly assigned to one of six groups with different *treatment modes*: 6-day ambulatory BT treatment (6ABT), 11-day ambulatory BT treatment (11ABT), 11-day ambulatory BT treatment with nature therapy procedure (11ABTNT), 11-day inpatient treatment (11BTS), 11-day nature therapy procedure (11NT), and control group (11C) by a statistician using computer program after the initial examination (T0) at the study centers. The study utilized the SPSS function "Random sample of cases," which selects a subset of cases either based on an approximate percentage or an exact number. All selected participants were randomized into groups using a predetermined SPSS method, ensuring unbiased allocation to different experimental conditions or treatment arms. The parameters of age, sex, and baseline stress level analyzed by a Pearson χ^2 or ANOVA, Tukey's honesty test, had no significant difference between the six groups. The researchers/assessors performing the examination did not know which group the subject belonged to.

The *sample size* required for statistically significant comparisons of the rehabilitation effect of the means of quantitative variables before and after the procedures was calculated by the G*Power program [33] according to the data of the authors' previous published studies [34]. For an estimated sample size of 0.32, 0.4, and 0.5, the group size would be 79, 52, and 34 subjects, respectively.

A total of 364 participants received treatment at the centers. The *participants' characteristics* based on the screening questionnaire in research centers are given in Table

A1. No difference in gender (chi-square p=0.178), education (p=0.281), marital status (p=0.310), profession (p=0.093), mode of work (0.085), work experience (p=0.241), salary (p=0.262), working hours (p=0.214), resting hours (p=0.858), and in post-covid condition (p= 0.792) were found. The participants differ in living place (more of Centers 5 and 6 lived in the city, p=0.031) and ill with COVID-19 (participants of Centers 5 and 6 were more ill during the last 6 months, p=0.046). The participants' groups in centers differ in age between Centers 5 and 4 (mean difference -6.95, p =0.016), and Centers 1 and 4 (mean difference -7.43, p=0.042). The least stress was in Center 6, with the best skin condition- in Center 5 (a significant difference between Centers 1 and 5 (p=0.033). There were no differences according to stress management.

The 6 groups with different treatment modes were allocated to 6 medical spas (Centers) with different natural resources (Table 1). Four centers provided one mode of procedure to their allocated participants, and two centers provided mixed modes since there was no possibility of organizing the separate modes.

Table 1. The characteristics of treatment modes in research centers and some constituents of natural resources.

Centers	1	2	3	4	5	6
Treatment modes in Centers	11ABTNT	11BTS	6ABT	11ABT	6ABT, 11ABTNT, 11BTS	6ABT, 11ABT, 11BTS)
Natural resources used in the study						
Mineral waters, TDS, mg/l	55221	35837	21667	22213	16750	82445
pH	6.53	6.84	7.49	7.27	7.54	5.71
Main minerals by amounts	Cl-Na-Ca-SO4-Mg-K-Br-HCO3-Fe	Cl-Na-Ca-SO4-Mg-HCO3-K-B	Cl-Na-Ca-SO4-Mg-HCO3-K-Br	Cl-Na-Ca-SO4-Mg-K-Br-F	Cl-Na-SO4-Ca-Mg-K-HCO3-Br	Cl-Na-Ca-Mg-SO4-K-Br-Fe-B
Water procedure/dilution with tap water	1:1, bath	1:2, bath	Natural, bath	Natural, pool	1:1, pool	Natural, pool
Peloids	Peat, wrapping	Peat, wrapping	Sapropel, wrapping	Peat, diluted with mineral water, bath	Sapropel, wrapping	Sapropel, wrapping
pH	7	8,3	6,9	6,4	6,6	6,7
TDS, mg/l	20007	1780	53	50	141	38,5
Main minerals by amounts	Ca-Fe-Cl-Mg	Ca-Fe-Mg-Mn-Si	Ca-Fe-Mg	Ca-S-Mg	Ca-Fe-Mg	Ca-Fe-Mg-NO3-Mn-Si
Dry residue, mg/l	24140	2425	385	385	347	238
Organic material, %	70,73	14,32	91,96	78,54	91,17	81,92
Degree of fragmentation, %	81,36	100	76,07	73	79,44	75,91
Humic acid content, %	2,25	1,22	14,65	/	6,54	28,25
Fulvic acid content, %	17,9	0,98	11,68	/	14,09	3,25
Salt procedure	Aerosols, Himalayan salt	Salt room	Aerosols, mineral water	Salt room	Salt room	Salt room

According to certified laboratory results, natural resources had some differences in amounts of different substances (see Table 1). TDS of mineral waters were 17- 82 g/l (high mineralization (3,4,5)- brines (1,6); main minerals established in all centers were Cl (6,1), Na (6,1,2), Ca (6,1,2), SO4 (1, 4), Mg (6,4,1), K (6,1), HCO3 (3,5), Fe (1), Br 46 (3-4) to 270 (6)

mg/l. The mineral water with natural composition was used for the bath and pools in Centers 3,4,6; Centers 1, 2, and 5 diluted mineral water with hot tap water.

Peloids' pH was 6.4- 8.3- low acidic (4), neutral (1,3,5,6), alkaline (2); TDS varied between 38.5 (6) to 20007 (1); % organic material was 14 (2) to 92% (3,5); main minerals were Ca (2,1,6), Fe (1,2,6), Mg (2,1,6); the highest amount of humic acid was in Centers 3 and 6, lowest- in 1-2 centers, fulvic- Centers 1 and 5, lowest- in Center 2. Although Centers 3 and 5 used sapropel from the same supplier, some parameters still differed. Peloids were used for wrapping in Centers 1,2,3,5,6; in Center 4 mud baths were given.

Study outcomes

Primary study outcome – effectiveness of BT on mental and skin state, secondary - overall effectiveness and safety of BT procedures.

Study instruments

The mental and skin health status of participants was measured before (T0) and after treatment (T1). The interview about changes in complaints, objective status, and usage of medicines was made by medical doctors after treatment (T1). Participants' opinions about overall therapeutic effectiveness, and positive body changes were made after treatment (T1), after 3 months (T2), and after 6 months (T3). Adverse events were collected, described by participants using prospective assessments (prespecified symptom inventories) which can offer greater sensitivity and consistency in detecting side effects of specific treatments, and monitored by doctors of physical medicine and rehabilitation. The list of the side effects was given to researchers after treatment (T1) (N=308).

The instruments for the evaluation of BT treatment's complex effect on stress were saliva cortisol and perceived stress scale (PSS-10). Saliva cortisol- a marker of brain health- is a simple and more accurate method than blood cortisol. Saliva contains only the free active part of hormones and transport molecules do not interfere with the test. The test was made in a certified laboratory (Germany). Laboratory method: Enzyme Immunoassay (ELISA), device: Tecan Evolyzer, the name of the kit: Cortisol Saliva Elisa Tecan; REF: RE52611, Quantitation as functional sensitivity: 0,005 μg/dl (with a precision of 20 %), inter- assay: range between 10,1 % and 19,5 % (CV: 13,2 %), intra-assay: range between 3,2 % and 6,1 % (CV: 4,3 %). Higher cortisol numbers indicate higher stress levels. Stress as a general entity was subjectively measured using the Perceived Stress Scale (PSS-10) [60] which is one of the most widely used scales for measuring the perception of stress. It can also be used to monitor stress during the implementation of stress management strategies [61]. Individual scores on the PSS can range from 0 to 40, with higher scores indicating higher perceived stress: 0-13 is considered as low stress; 14-26- moderate stress, and 27-40 - high perceived stress.

The CESD-R is a screening test for depression and depressive disorder. The CESD-R measures symptoms defined by the American Psychiatric Association [62], the total CESD-R Score is calculated as a sum of responses to all 20 questions (0-80). We have used the scale as a continuous variable. Anxiety was measured using a shortened five-item Spielberger State-Trait Anxiety Inventory- STAI-20 version- STAI-5 [63]. For STAIS was a question: How do you feel right now, STAIT- How do you generally feel; STAIS-5 ≥10 or/and STAIT-5 ≥14 can be considered potentially clinically anxious. We have used the scale as a continuous variable. Fatigue was measured using a 10-item Fatigue Assessment scale (FAS) [64]. The total score ranges from 10 to 50, with a higher score indicating more severe fatigue. Scores above 22 represent significant fatigue [65]; between 22 and 34 indicates mild-to-moderate fatigue; 35 or more indicates severe fatigue. Sleep quality was measured using a self-administered single-item sleep quality scale (SQS) where 0 stands for terrible, 1-3 for poor, 4-6 for fair, 7-9 for good, and 10- excellent sleep [66]. Integrative outcomes were measured using the Arizona Integrative Outcomes Scale which reflects on the sense of well-being, considering physical, mental, emotional, social, and spiritual

condition. The score is marked on the line from „worst you have ever been (0) to best you have ever been (10) [67]. To objectively measure cognitive functions, we utilized a series of RehaCom selection tests, including assessments for working memory, working speed, attention, and visual field. RehaCom stands as a computerized system designed for cognitive function therapy, with its effectiveness substantiated by clinical studies.

Overall subjective skin condition was measured using a questionnaire on a 10-point scale, where 0 means very bad, and 10- excellent skin condition. The objective skin state (skin moisture, oiliness, elasticity) was measured using an IMATE skin test pen, model M-6602 (China) on the middle of right upper arm outer surface. The referenced values for the hand are moisture 25-35, oil 41-52, and elasticity 50-65.

The following assessment was used to assess complaints and medicine (antihypertensives, antiarrhythmics, painkillers, sedatives) usage: 1- reduced, 2- no change, 3- increased; to determine the objective status shift and respondent's opinion regarding overall therapeutic effectiveness of procedures after treatment: 1- improved, 2- no change, 3- worsens; to assess the remaining effect of procedures after 3 and 6 months: 1- remains effect, 2- effect lost.

The frequencies of adverse reactions are typically determined during clinical trials from the information reported by trial participants [68]. The method used in our trial was prospective comprehensive symptom checklists prepared by researchers with a list of symptoms, their frequency, duration, and need for treatment for mineral water, peloid, and salt procedures. The overall safety of the whole complex treatment was measured using a 5-point Likert scale, where 1 stands for extremely safe, and 5- for unsafe treatment.

Procedures

The same BT complex was prescribed in all centers: 20 min of tap water pool with light exercises, mineral/geothermal water bath- 34-36° 20 min, sapropel wrapping- 20 min, salt therapy- 25 min. For Centers 1 and 5 the nature therapy procedure was as follows: a 45-minute walk in nature (forest or seaside), a complex of simple strength and breathing low-intensity exercises, sensory impulses (landscape, forest smells- aromatherapy, natural sounds of nature, collecting nature's goodies, mindfulness therapy, heliotherapy. The first procedure was provided by a kinesiotherapist, all others had to be performed by the participant independently with accurate instructions given. The description of the BT complex is provided in Table A2. Participants were told to not make significant changes to their lifestyle during the study period.

Statistical analysis

Descriptive data were presented as means and standard deviations (SD) graphically by means and 95% CI. Independent 2-tailed t-tests for continuous variables and Chi-square test, chi-square statistic to compare variables frequencies in each rehabilitation group, and z-test for categorical variables were used to examine between categories. Analysis of variance (ANOVA) with Tukey HSD post-hoc multiple comparison tests were used to assess the differences between mean values of variables across the study groups. Comparison of variable means at the treatment beginning (T0), and end (T1) was performed using Paired-Samples t-test. When the conditions of normality of the variables were not met, the differences between the values of the variables in the rehabilitation groups were evaluated by applying the Friedman non-parametric test. Sample size-adjusted effect sizes (Cohen's d statistic) were calculated for power analysis. Descriptors for magnitudes of d = 0.01 to 2.0, as initially suggested by Cohen and expanded by Sawilowsky were used [69]. The correlation between two parametric or nonparametric variables was made using Pearson's or Spearman's r, which can vary from −1 to 1, with −1 indicating a perfect negative linear relation, 1 indicating a perfect positive linear relation, and 0 indicating no linear relation between two variables. A p-value <0.05 denoted

statistical significance. Analyses were performed with the SPSS (Statistical Package for the Social Sciences for Windows) version 28.0 SPSS Inc., Chicago, IL.

3. Results

The changes in mental, skin states, and integrative outcomes parameters in research centers are shown in Table A3.

The effectiveness of balneotherapy on stress

After implementing the BT procedures, there was a noteworthy reduction in **saliva cortisol** levels observed in **two centers**: Centers 5 (with a 36% reduction from baseline and a medium effect size) and 6 (with a 22% reduction and a small effect size). However, no significant changes in cortisol levels were recorded in the remaining centers.

According to PSS-10, **stress** was moderate in all centers before treatment. It reduced significantly **in five** of six centers: in Centers 4 (medium effect), 2,3, 5, and 6 (small effect). No significant effect on stress level was in 1 center. The mean change in scale ranged from 2.5-3.4 points. The change in center 4 was qualitative: moderate stress level changed to low-stress level.

The effectiveness of balneotherapy on fatigue and mental disorders

The baseline mild-to-moderate **fatigue** level was reduced in **all centers** by 3.2-4.2 points with large (Center 3), medium (Centers 1,2,5, and 6), and small (Center 4) effect sizes. Although the change in Center 4 had a small effect qualitative change of fatigue to a normal level was achieved.

State anxiety was reaching a clinically anxious state in 1, 3, and 4 Centers before treatment. **State- and trait anxiety** were reduced in **all centers** after treatment: state- by 1.5-3.8 points with medium (Centers 5 and 6) to very large (Center 3), while trait- by 2.1-3.5 points with medium (Center 1) to very large (Centers 2, 3, and 4) effect size. State-anxiety reduction reached a qualitative change: from potentially clinically anxious to a normal state in Centers 1, 3, and 4.

Subthreshold depression symptoms had respondents from 1 and 3 Centers before treatment. **Depression** was reduced in **all centers** by 5.6-18.1 points with the medium (Centers 1,5, and 6) to large (Centers 2-4) effect size. The change in 1 and 3 centers was qualitative- after treatment symptoms no longer had **clinical significance for depression.**

The baseline sleep quality was fair in all except Center 3. **Sleep** was improved in **all centers** by 1.3-2 points (10, VAS) with medium (Center 5) to very large (Center 4) effect size, from 21% (Center 3) to 32% (Center 1) from the initial level. The positive qualitative changes (from fair to good) were reached after treatment in five centers.

When evaluating changes in objective cognitive functions, a significant change after treatment was obtained in the **working speed** - a significant speed reduction was observed in Center 3 (very large effect), and speed acceleration – in **two centers**: Center 5 and 6 (small effect).

The effectiveness of balneotherapy on skin state

The **overall skin health** according to the respondent's opinion was better after the course of the procedures in **all centers** by 1.1-2.5 points (10, VAS): the biggest effect size was in Center 4 (very large effect), followed by Centers 3, 1 (large effect), 2, 5, and 6 (medium effect). The improvement was 18% (6)- 47% (3) from baseline mean.

Skin moisture was increased in respondents in **all centers** by 1-6.5 points with small (Centers 3, 5, and 6), large (Centers 1 and 2) to very large (Center 4) effect sizes from 3% (Center 5) to 22% (Center 2) from the baseline level. **Skin oiliness** significantly reduced by 1.2-2.3 points in respondents of Center 1 (medium effect), 2, and 4 (large effect) up to 4% (Center 2) from baseline. No significant change in Centers 3,5, and 6 was revealed. **Skin elasticity** significantly increased by 0.7-3.8 points in respondents of Center 5 (small effect), Center 1 (medium effect), Center 2 (large effect), and Center 4 (very large effect) centers up to 8% (Center 2) from the baseline level.

The positive qualitative changes of objective skin state according to reference values were identified. Specifically, skin oiliness (which was increased in the beginning in all centers) reduced to the normal range in Centers 1 and 2; skin elasticity reached normal levels in both **Centers 1 and 2**.

The balneotherapy effect on integrative outcomes and overall health in research centers

Integrative outcomes score changed significantly in **all centers** positively after treatment by 1-3.5 points (10, VAS) with medium (Centers 2 and 6) to very large (Center 3) effect size. The mean improvement was from 16% (Center 2) up to 61% (Center 1) from the baseline level.

A positive treatment outcome was observed for participants' complaints, objective condition, and medication usage in all research centers. After the procedures, **complaints** decreased the most by up to 94% in Center 2; a small increase in complaints was identified in Center 5, and in 10% of Center 1 participants complaints persisted. The **objective condition** improved in 87-100% of cases- changed the most for visitors of Center 2, and to a lesser extent for those in Centers 5 and 6; the most significant reduction in **medication usage** was seen in Center 5 (Figure 2).

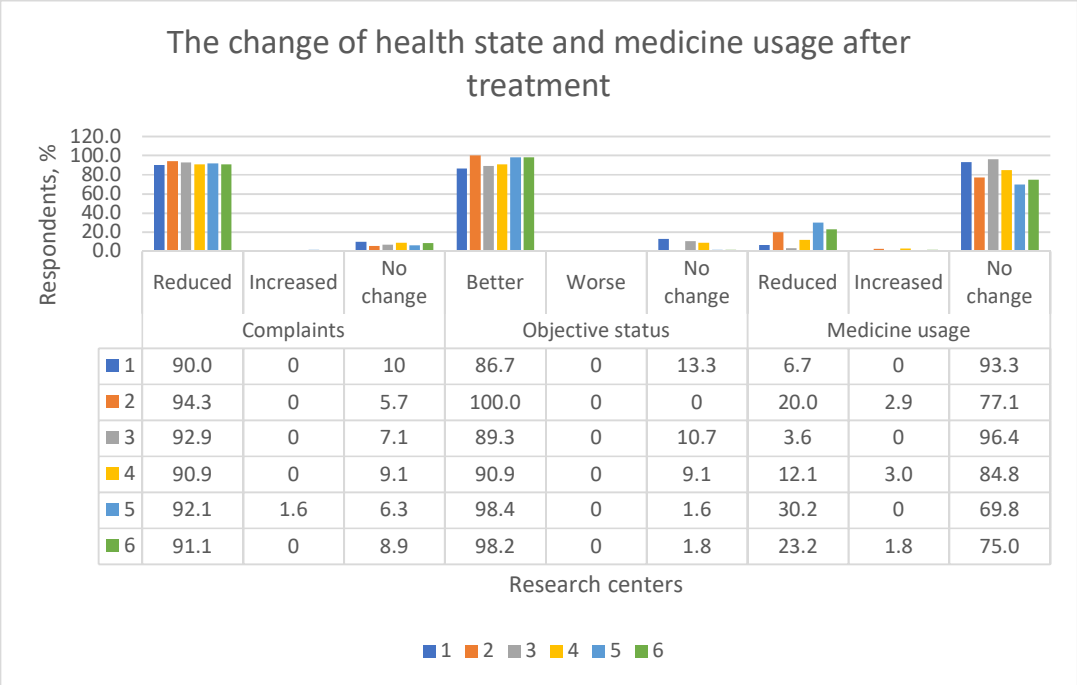

Figure 2. The change in respondent's complaints, objective status, and drug usage after treatment.

Comparing changes in complaints between research centers, there were no significant differences among the centers (ANOVA 0.987). Significant differences between groups were observed in objective condition and medication usage changes (ANOVA 0.03 and 0.014, respectively). Medication usage in Center 5 was significantly lower than in Center 3 ($p=0.039$).

After treatment, 91-100 % of participants stated that the procedures were effective; the majority - from Centers 1, 3, and 5. After 3 months, the effect persisted in 70-100% of cases. The most significant effect persisted for Centers 2 and 6 participants, after six months 47-74% still felt the effect, most of them from Center 2. The longest impact was observed in Center 2, and the shortest duration was noted in Center 3 (Figure 3).

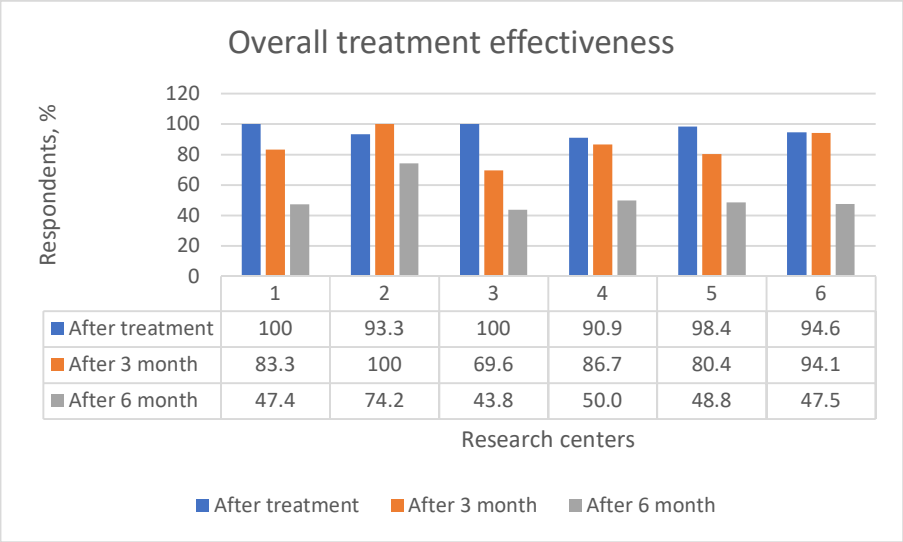

Figure 3. The respondent's opinion regarding the treatment's overall effectiveness.

Participants' opinions on **effectiveness** among research centers were evaluated. There was no difference between centers in the post-treatment period (ANOVA 0.214). However, after 3 months, there was a difference between centers (ANOVA 0.008; Center 2 vs 3, p=0.013, Center 6 vs 3, p=0.055), while changes between centers remained consistent after 6 months (ANOVA 0.206).

The safety of different procedures using natural resources

The participants assessed the side effects of mineral water, mud, and salt procedures. In their opinion, **mineral water** caused adverse effects in 12 (Center 4) to 43% (Center 2). Side effects from **peloid** procedures were reported by 7 (Center 3) to 23% (Center 2) of participants. **Salt procedures** resulted in side effects from 4 (Center 5) to 13% (Center 2) of participants (Figure 4).

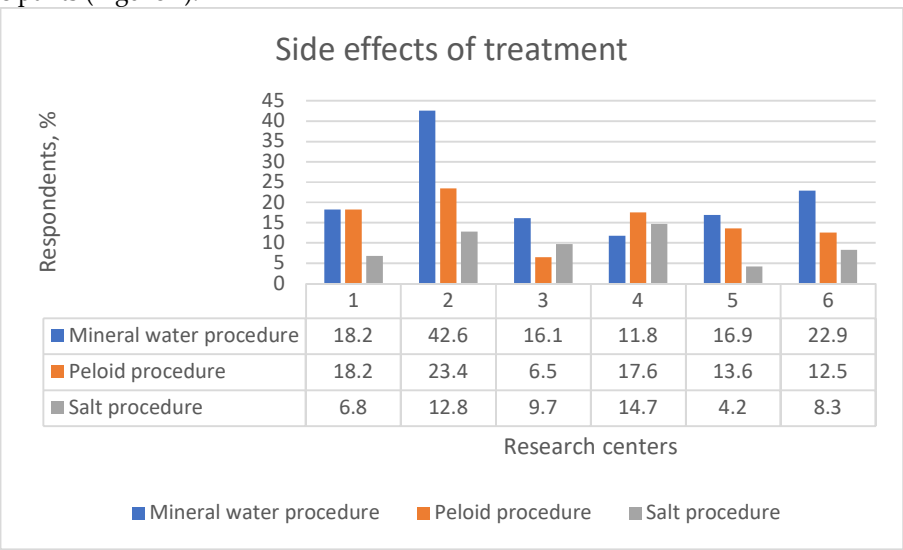

Figure 4. The reported side effects of procedures.

Comparing the side effects of mineral water among centers, a significant difference was found (ANOVA p=0.005): Center 2 vs 5 (p=0.039), Center 2 vs 4 (p=0.004), and Center 2 vs 3 (p=0.042). In contrast, there were no significant changes in the frequency of side effects of mud and salt procedures between research centers (ANOVA p=0.434 and 0.538, respectively).

The detailed frequency of side effects of mineral water, peloids, and salt procedures for the participants is presented in Table A4. Most commonly, drowsiness, fatigue, thirst, skin itching, dryness, and redness were observed during the mineral water procedures. According to the complaints, the safest water and salt procedures were conducted in Center 5, while the safest mud procedures occurred in Center 6. Treatment for heart palpitations and blood pressure was required for one person in Center 6, while treatment for skin redness, itching, and rash was necessary in Center 5.

In 60% (Center 6) to 95% (Center 2) of cases, the duration of side effects of mineral water procedures was short (minutes-hours). In four centers, the effects lasted for several days (mostly 20% - Center 1), while in Centers 4-6, up to 15% (6 participants) continued after the end of the treatment (Figure 5).

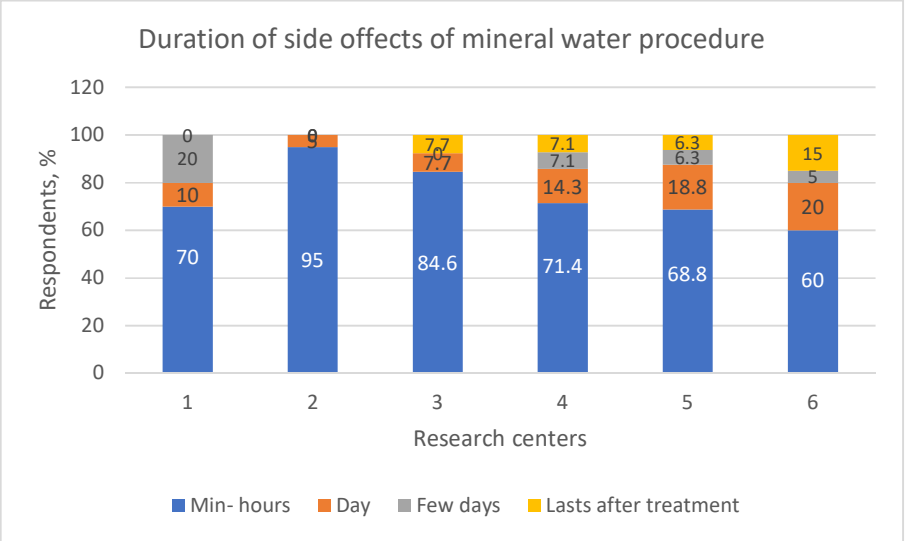

Figure 5. The duration of side effects of mineral water in research centers.

During the peloid procedure, most participants complained of drowsiness, fatigue, thirst, skin itching, and dryness. Treatment was required for skin redness and itching in one participant from Center 5 (Table A4).

The side effects of peloids lasted short in 63% (center 6) to 89% (center 1) of cases. For a few days, the effect persisted in 14% of participants in Center 3, 11% in Center 1, and Center 4, it continued even after the procedures in 8% of participants (Figure 6).

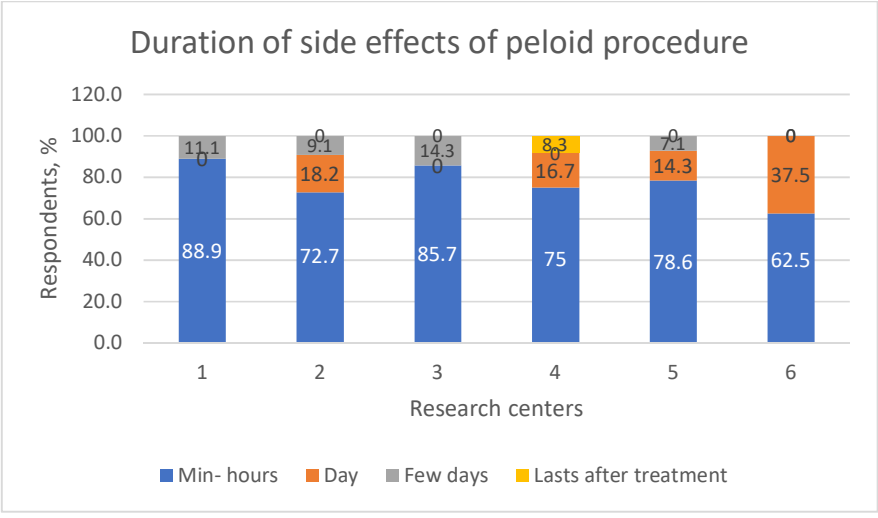

Figure 6. The duration of side effects of peloid procedures in research centers.

The highest number of side effects of salt therapy occurred in Center 4, while the lowest was in Center 5 of the study. The most common effects were thirst, dry mouth, cough, and drowsiness (Table A4).

The side effects of salt therapy lasted very briefly in 71-100% of cases (see Fig). In centers 4-6, they persisted up to 25% for several days, while in center 3, they continued even after the procedures.

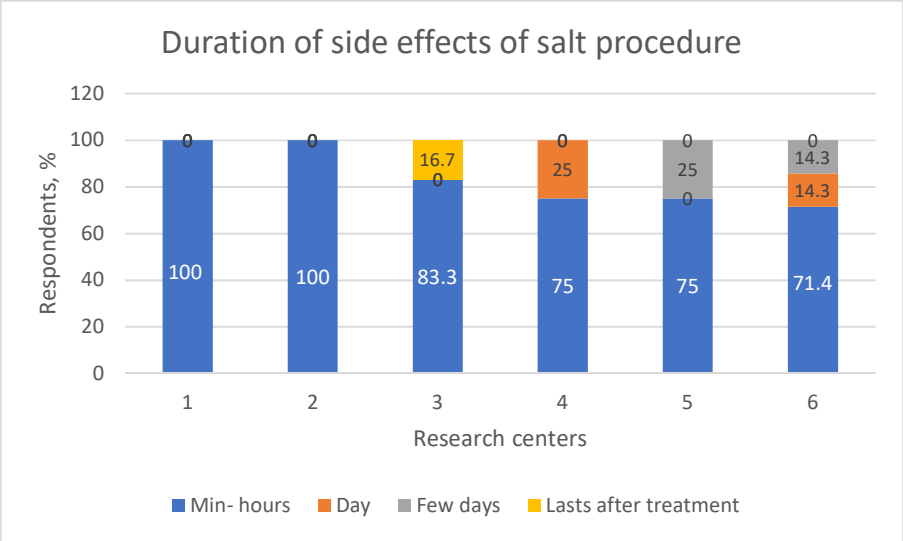

Figure 7. The duration of side effects of salt procedures in research centers.

After the treatment, the participants assessed the **overall safety** of the procedures. 76% (Center 3) to 94% (Center 1) of participants rated the overall safety of the procedures as exceptionally safe; up to 6% (Centers 4-6) of participants rated all procedures as potentially safe (Figure 8). When comparing the overall assessment of procedure safety among the research centers, no significant difference was found (ANOVA p=0.453).

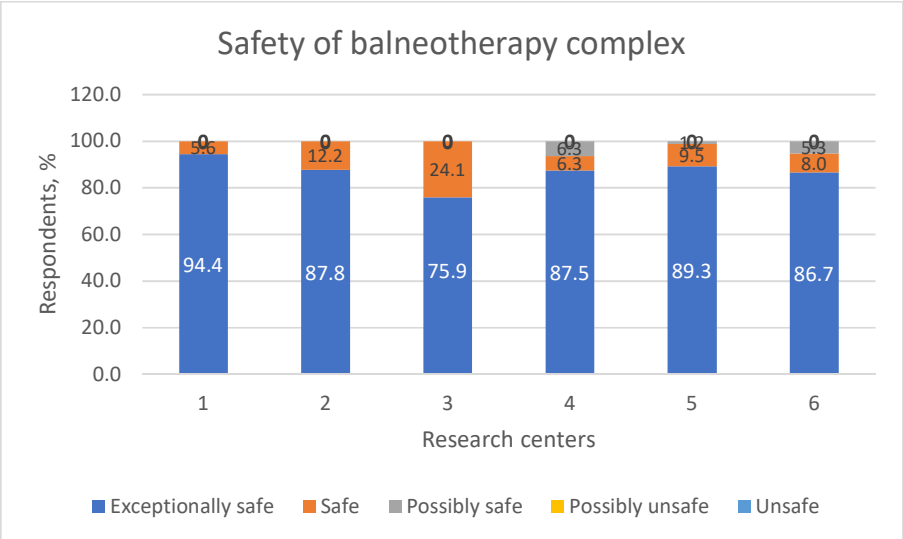

Figure 8. The evaluation of the safety of BT complex in research centers.

In summary, the overall safety of the BT procedures at Center 1, which included 11 days of ambulatory BT and nature therapy, was rated highest by participants. Additionally, the side effects of peloid and salt procedures there were the shortest in duration. At Center 2, where participants underwent 11 days of inpatient BT treatment, the highest number of adverse effects were reported for mineral water and mud procedures, although these typically lasted only a short time. The

procedures at Center 3, consisting of 6 days of ambulatory BT, were rated the lowest in terms of overall safety. In Center 4, mineral water procedures were deemed the safest, but salt procedures had the most side effects. Salt procedures in Center 5 were considered the safest, with mineral water procedures also generally safe. Lastly, the sapropel procedures at Center 6 resulted in the fewest adverse effects.

For one participant in the Center 6 center, the treatment was halted after three days due to a deterioration in overall well-being, increased weakness, and dyspnea, even though the ECG changes present before the treatment remained unchanged.

Correlation between effectiveness and safety

Assessing correlations between the investigated indicators revealed a significant relationship between **skin condition, stress, and adverse events** (Table A5). Higher intensity of stress before and after treatment was associated with more initial skin problems, poorer stress management, more significant skin-related issues, and worse overall evaluation of procedure safety after treatment. Good initial stress management was linked to better initial skin condition, more frequent use of skin care products, lower stress intensity before and after treatment, better stress management, and more frequent use of moisturizers both before and after treatment.

Bigger skin problems after treatment were associated with higher stress levels before and after treatment, poorer stress management after treatment, adverse effects of mineral water, and medication use after treatment. Lower stress intensity after treatment was linked to better management, medication use, and a better overall assessment of procedural effectiveness.

More adverse effects occurred from mineral water and mud therapy in those with skin problems before treatment. Although initial skin problems did not affect the overall safety evaluation of the procedures, they did impact persistent complaints and objective conditions. Adverse events did not have an impact on the use of skincare products. The occurrence of adverse effects from all-natural resources was related to their association with the overall safety evaluation of the procedures. (Table 5).

4. Discussion

The essence of each treatment is to reduce health complaints as quickly, effectively, and safely as possible, improve health conditions, decrease medication intake, and ensure that the effects are long-lasting. With this study, we aimed to know whether different natural resources used in BT are responsible for different effects on stress-related disorders as well as skin conditions, and safety.

The study results indicate that all treatment modes significantly improve most of the studied mental and skin status parameters, as well as providing positive changes in integrative outcomes, complaint levels, objective condition, and medication usage, while the overall therapeutic effectiveness remains up to 6 months. It is difficult to unequivocally state which treatment complex with different resources in each research center is more effective. In most cases, the effect varies by the effect size or the change from the baseline condition but remains significant regardless of the differences in treatment duration or the nature of procedure allocation. The shortest duration of treatment effectiveness was noted in Center 3 where the 1-week outpatient treatment mode was provided. Fluctuations in individual indicators across all centers may be influenced by the utilization of different resources, treatment durations, and outpatient-inpatient modalities.

The best **effect on stress** reduction was achieved: for the reduction of saliva cortisol- in Centers 5 and 6 (mixed mode of procedures), and for subjective stress - in Center 2 (2-week inpatient procedures). The mineral water of Center 5 had the most HCO3, pH 7,5; peloid had a large amount of organic material, fulvic acid, HCO3, and calcium. The mineral water of Center 6 had the biggest TDS, magnesium, calcium, and bromide; peloid- calcium, silica, and humic acid. The sapropel from Center 2 has a lot of magnesium and calcium. Perhaps the anti-stress effect is related to the presence of magnesium, calcium, bromine, bicarbonate, and humic acids in the resources, rather than to total mineralization, which varies significantly among the centers. The treatment at Center 2, and partly at Centers 5 and 6, was inpatient; relaxation

from work duties could help with stress reduction, as could the seaside climate at Centers 5 and 6. Similar results on the effect on the BT effect in distress and mental state were achieved in our previous trial, when 10 days of treatment with 15 min 108 g/l geothermal water bath reduced pain and general, physical, and mental fatigue, improved stress management, mood, and cognitive functions with effect size from 0.8 to 2.3 [70]. The cortisol in saliva reduced as well relaxation effect was achieved after 25 min. of BT intervention and the authors concluded BT compared to progressive muscular relaxation was more beneficial concerning subjective relaxation effects and similarly beneficial with regard to a decrease in salivary cortisol [71]. The decrease of salivary cortisol concentration was seen between pre- and post-moor 20 min bath in week 1 (Z = -3.355, p = 0.0008), together with the improvement of mood state [72]. The main findings of the systemic review suggested that BT is a useful method for the management of stress conditions and may have the potential to influence cortisol levels in healthy subjects improving stress resilience with the same potential to influence cortisol levels in sub-healthy and ill subjects [73]. Conversely, an elevation of blood cortisol was reported in some other trials because of hyperthermia-induced activation of the HPA axis and SNS in healthy subjects [74], [6] or the change in serum cortisol levels after treatment was not statistically significant (p=0.683) [75].

The mental state- symptoms of anxiety, depression, fatigue, and sleep- significantly improved in all Centers with the biggest effect sizes in Centers 2-4. From the objective parameters of cognitive function changed only working speed: improvement was seen after 2 weeks in Centers 5 and 6- could be cortisol reduction had an impact on it. Other studies have shown positive results on mental state after mineral water procedures: 12-day BT program in medium mineralization, bicarbonate, sulfate, sodium, and magnesium water improved pain, mood state, sleep, and depression [51]; 15 sessions of 20 min BT improved PSQI and the NHP-Sleep scales in obese with no significant effect on cortisol [76], also confirmed in a systematic review [77]; 10 days of 20 min BT using 20, 40 and 60 g/l baths improved sleep with the 40 g/L group showing the most lasting improvement after 3 months of follow-up [78]; 4 weeks of 15-minute baths in bicarbonate-containing water improved sleep and vigor-activity [52]; 8 week BT showed advantage over pharmacotherapy in treatment of generalized anxiety disorder [79]; 5 months of spring BT improved emotions, sleep, and fatigue with effect size from 0.096 to 1.302 [49]. Studies have shown that peloid therapy can activate antioxidative mechanisms, resulting in reduced stress and improved sleep quality [80]. A meta-analysis of seventeen eligible studies with 977 participants made by Koroglu, S et al. found that BT reduces depression (SMD: 0.53) and anxiety (SMD: 0.46) scores in adult individuals [48] while in the meta-analysis of fibromyalgia patients depression (Beck depression scale) was reduced at two weeks (SMD = −0.35), three (SMD=−0.23), (grade: moderate, low) and six months (SMD = −0.45; grade: moderate) [54].

The best effect on skin condition was in Centers 4 (2-week outpatient BT), 2 (2-week inpatient treatment), and 1 (2-week outpatient BT with NT). The resources of those centers had TDS of 12-22 g/l, low acidic-neutral pH, sulfur, magnesium, calcium, silica, chloride, manganese, and bicarbonate which could be beneficial to the skin. Thanks to the knowledge and practice so far, BT may be an effective adjunctive therapy for inflammatory and autoimmune skin diseases [42]. A systematic review also shows a clear improvement in signs and symptoms of psoriasis and eczematous diseases after the use of mineral water [81]. Study results are in line with our previous results of reduction of an overall number of skin complaints (p=0,001), as well as improvement of skin moisture (p<0,05) and elasticity (p=0,016) after 10-15 days of 15-20 min geothermal water baths [82]. The recent prospective cohort study provided that 95.2% of cases of eczematous dermatitis and 58.8% of cases of non-specific skin issues were improved after 3-7 days BT for once daily and after 30 days of bathing the 90% PASI score reduced to a score of one [83]. A literature review on the role of BT for skin diseases stated that psoriasis and atopic dermatitis are frequently treated by BT with a high rate of success, although other diseases such as pruritus, lichen

ruber planus, acne vulgaris, and seborrheic dermatitis can benefit from the anti-inflammatory and antiproliferative activity of BT also [13].

In our study the most significant overall effectiveness after the treatment course was reported by participants from Centers 1, 3 (1-week outpatient BT), and 5, with the highest improvement for those from Centers 2 and 6 after 3 months, and for those from Centers 2 after 6 months. This indicates that both 1- and 2-week BT effectively improve health, but longer-lasting effects are provided by the 2-week treatment, especially when inpatient.

Natural resources used in the study were rich in Cl, Na, Ca, Mg, HCO3, S, K, Br, Mn, Si, and organic material. Possibly, the distinct healing properties of water and peloid procedures arise from the diverse combination of minerals and organic components present in the natural resources. This showcases the interconnected relationship between these elements and their impact on therapeutic outcomes. The essential functions of the most important bio-essential chemical elements found in mineral water and peloids used in therapies are described in earlier works [1], [28]. The trace elements in mineral-medicinal waters that affect the skin: are calcium [84], sulfur, magnesium, chloride, copper, chromium, fluorine, manganese, zinc, nickel, and silicon [85]. The primary functions and therapeutic effects of minerals, medicinal waters, and peloids were described in earlier scientific papers [86], [87]. Mineral-rich waters, such as those high in sulfur [88], magnesium, or silica, have been associated with various health benefits: sulfur-rich waters are believed to have anti-inflammatory and skin-rejuvenating properties [89], while magnesium is known for its muscle-relaxing effects [90]; clay with a high silica content may have exfoliative and detoxifying properties. Some natural water sources contain organic components like algae or plant extracts, which can add to therapeutic benefits. The organic matter in mud or clay can contribute to its therapeutic effects. Organic components may have anti-inflammatory or skin-conditioning properties. Certain natural waters and clays may contain beneficial microorganisms, such as probiotics, which can positively influence skin health and the immune system. We have studied pathogenic bacteria as required by hygiene standards in water but not all microorganisms. Microorganisms present in mud or clay can interact with the skin in a way that promotes a healthy microbial balance. This has the potential to positively affect conditions like acne or eczema. The presence of microorganisms in peloids can modify mineral reactions and prevent the toxicity of pathogenic microorganisms [2].

A treatment-related adverse event is one that is not present at baseline but occurs after initiation of treatment, regardless of attribution [68]. During our study, more frequent adverse events associated with mineral water and mud procedures were identified, possibly linked to the self-questionnaires used. Variations in the frequency of side effects between centers could be related to different resources used or their specific components, which could be evaluated in further experimental studies. It's important to note that adverse events mostly lasted briefly and were primarily local reactions with a general relaxing effect. Participants commonly experienced drowsiness, fatigue, thirst, skin itching, dryness, and redness. In most cases (water 60-95%, mud 63-83%, salt 71-100%), the side effects were short-term, with the need for treatment for 2 participants (0.5%) on skin issues, heart palpitations, and blood pressure, and discontinuation of treatment for 1 (0.3%). It is not possible to precisely determine why the water procedure at Center 2 (water was similar to Center 5) and the peloid procedure (characterized by alkaline pH, high ash content, most manganese, and least organic matter) resulted in the highest number of adverse events. Additionally, this may be due to participants' pre-existing skin problems, as correlation analysis showed that those with skin issues before treatment experienced more adverse effects from mineral water and mud therapy.

Following the study, we identified correlations between skin conditions, stress, and side effects. According to Pearson and Spearman correlation, no significant relationships were found between treatment effectiveness and side effects. The study also highlighted that individuals with pre-existing skin problems were likelier to experience undesirable

effects from mineral water and mud treatments. However, these effects did not impact the use of skincare products. We can observe that the most common adverse effects of all resources occur in the same individuals, possibly in those who are more sensitive and have initial skin problems. We recommend assessing and correcting the person's skin condition (for mineral water and mud procedures), blood pressure (for all procedures), and pulse (for mineral water and salt procedures) before starting procedures with natural resources. It is advisable to inform the patient about potential adverse effects and recommend monitoring their condition (skin, blood pressure, pulse) to facilitate timely treatment. Before using BT (especially with higher mineralization or a more intensive treatment course), it is vital to regulate blood pressure and cardiac activity and adhere to BT treatment indications and contraindications. It is necessary to warn the patients about local side effects like skin redness, dryness, and itchiness. During the procedures, it is recommended to drink more water, avoid overheating, and contact a specialist if there are any unpleasant side effects. For a better impact of procedures using natural resources, the initial condition of the skin, and the level of stress should consider.

It is difficult to compare our determined adverse effects with other author studies. Typically, studies conclude that BT treatment is deemed safe, or generally safe, causing minimal or negligible adverse effects [91], emphasizing that none of the participants withdrew from the study due to adverse reactions [92]. However, it's crucial to acknowledge potential adverse reactions. The frequency of accidents during bathing is low, with minimal side effects like skin irritation reported. Possible adverse reactions include skin irritation, itching, infections (e.g., Pseudomonas folliculitis), exfoliative dermatitis, hypotension, scalds, thermal reactions, headaches, and others [93]. Treatment in the Dead Sea does not worsen blood pressure, and there's evidence of improvement [94], no significant changes in heart failure indicators were observed. Bathing in water with a high salt concentration is safe, effective, and pleasant for healing and recovery [41]. BT is considered truly safe when used appropriately, even for pregnant women [64]. Side effects are generally mild. Special warnings would be pregnancy as BT with sudden or prolonged exposure to high temperatures might be potentially unsafe; insufficient reliable information is available for breastfeeding; BT is potentially safe for children when used appropriately, with no reports of severe side effects in scientific studies.

Because of its effectiveness and potential safety, BT should be more frequently prescribed for chronic diseases and conditions that require multidisciplinary therapeutic intervention. It should also be combined with primary and secondary prevention strategies, involving medication, physical therapy, hydrotherapy, and climate therapy. Natural resources are the wealth of the country. Natural healing waters, therapeutic gases, and peloids have many properties that are useful in the prevention, treatment, and rehabilitation of various diseases. Using natural resources such as mineral or geothermal water, therapeutic mud, sun, air, forest, and landscape, as procedures in resorts and spas could help restore or improve our physical and mental health. Promoting mental health and well-being is an important area related to the Sustainable Development Goal (3.4) by 2030 [96].

Study limitations

Despite a large sample size and numerous valuable findings, our study has limitations and biases. The groups at the centers varied in size and exhibited differences in initial levels of stress and skin condition. This variation arose due to randomization based on different treatment modalities, with groups being divided among research centers thereafter. In the research centers, various resources and treatment modalities were employed, complicating comparisons between centers and the generalizability of results. It's challenging to attribute treatment outcomes or adverse effects to specific resources due to the use of a combination of procedures. Additionally, fully assessing the safety profile of these procedures is hindered by instances where the same individual reported multiple

symptoms, and in many cases, complaints were either not confirmed by a physician as adverse events or the participants did not seek medical attention.

5. Conclusion

The usage of various natural resources in BT significantly improves mental and skin health and contributes to a reduction in overall health issues, creating a holistic improvement in individuals' health.

Recognizing the detrimental impact of chronic stress on physical and mental well-being, there is a growing emphasis on adopting comprehensive strategies to mitigate its effects. A systematic approach to evaluate the efficacy of natural resources is needed, incorporating rigorous scientific methodologies. Moreover, developing international standards for utilizing natural resources in healthcare and wellness is imperative to ensure consistency and reliability in their application. Collaboration among researchers, policymakers, and industry experts is essential to establish guidelines and regulations governing the responsible use of natural resources for therapeutic purposes. Public awareness campaigns should be initiated to educate individuals about the proper utilization of natural resources and to promote a balanced and sustainable approach to their exploitation. Encouraging interdisciplinary research and fostering collaboration between different scientific disciplines will contribute to a more holistic understanding of the therapeutic properties of natural resources, and to developing effective and targeted approaches to harnessing the therapeutic potential of natural resources. Despite challenges, the field of balneology holds promise for holistic healthcare, but its scientific recognition remains insufficient compared to its potential contributions to integrative medicine.

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Institutional Review Board Statement: The study was conducted following the Declaration of Helsinki, approved by the Kaunas Regional Research Ethics Committee (permission code BE-2-87), and registered in ClinicalTrial.gov (Identifier: NCT06018649).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: data supporting reported results can be found in the Klaipeda University database.

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Conflicts of Interest:

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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