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Natural Therapeutic Resources in Translational and Integrative Medicine: From Chemical Characterization to Clinical Integration

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ABSTRACT

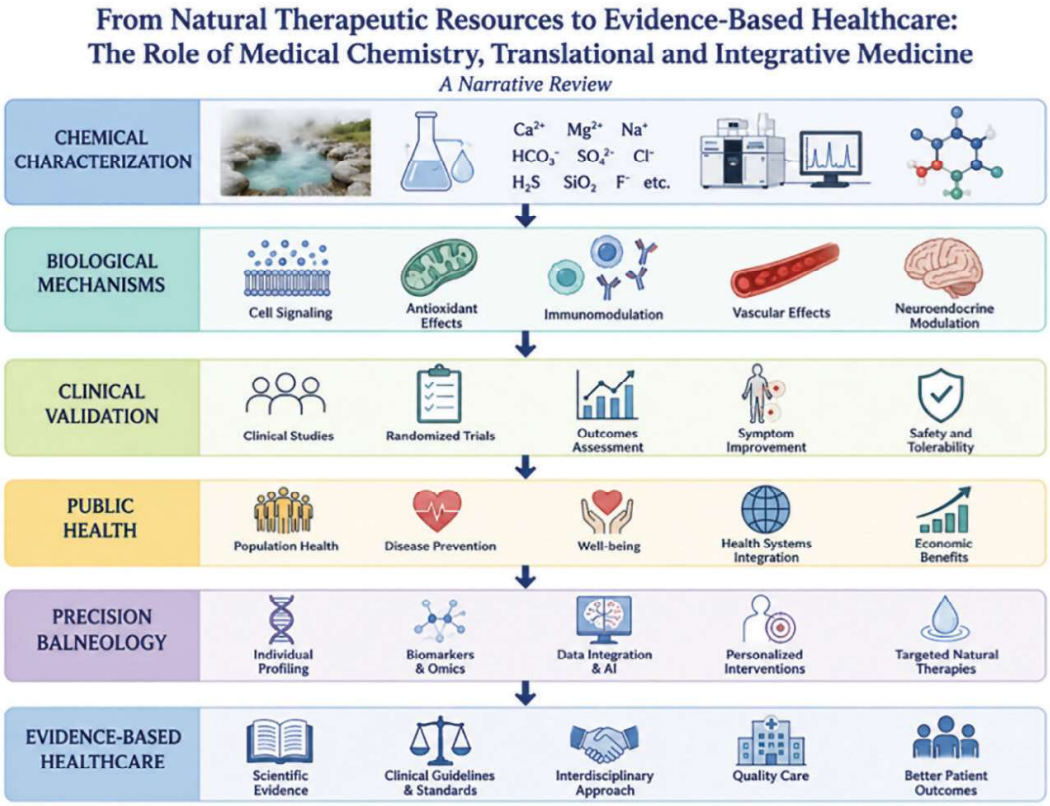
Natural therapeutic resources, including mineral waters, thermal springs, therapeutic muds, and bioactive natural compounds, play an important role in health promotion, disease prevention, and rehabilitation. Despite their long-standing application, the systematic integration of their chemical characterization, biological mechanisms of action, and clinical efficacy remains limited, restricting their evidence-based implementation in modern healthcare systems.

The present study aims to provide a comprehensive analysis of the chemical and biological foundations of natural therapeutic resources and to propose a novel translational-integrated conceptual framework for their evidence-based implementation in contemporary healthcare. The study is based on an interdisciplinary synthesis of current evidence from medical chemistry, biochemistry, balneology, translational medicine, integrative medicine, and public health.

This paper introduces a novel conceptual framework that bridges the chemical characterization of natural therapeutic resources with their molecular and physiological mechanisms of action, clinical evidence, and integration into public health practice. Particular attention is given to the ionic composition, trace element profiles, dissolved gases, and bioactive constituents of mineral waters and other natural therapeutic factors, together with the biological mechanisms underlying their therapeutic effects. The role of translational medicine in transforming molecular and experimental findings into clinical applications is discussed, as well as the contribution of integrative medicine to achieving an evidence-based synergy between natural and conventional therapeutic approaches. The proposed framework may serve as a foundation for future standardization, personalized balneological interventions, and evidence-based policy development in natural therapeutic resource management.

The analysis demonstrates that the effective and safe clinical implementation of natural

therapeutic resources requires standardized translational strategies, interdisciplinary collaboration, and the incorporation of personalized medicine principles. The proposed conceptual framework provides a scientific foundation for the standardization, evidence-based application, and effective integration of natural therapeutic resources into contemporary healthcare systems. Collectively, the proposed framework contributes to advancing translational and integrative medicine by establishing a systematic bridge between chemical characterization, mechanistic evidence, clinical validation, and public health implementation of natural therapeutic resources.



Graphical Abstract

Graphical Abstract. Conceptual overview of the proposed translational-integrated framework illustrating the progression from chemical characterization of natural therapeutic resources through biological mechanisms and clinical validation to evidence-based healthcare implementation. The graphical abstract summarizes the multidisciplinary workflow proposed in this review and highlights the integration of medical chemistry, translational medicine, precision balneology, and public health.

KEYWORDS: natural therapeutic resources; balneology; translational medicine; integrative medicine; medical chemistry; personalized medicine

1. INTRODUCTION

Natural therapeutic resources, including mineral waters, thermal waters, therapeutic muds (peloids), and various bioactive natural compounds, have been used for centuries for health promotion, disease prevention, and rehabilitation **(Nasermoaddeli & Kagamimori, 2005; Fioravanti et al., 2011; Karagülle & Karagülle, 2022).** In modern healthcare, where increasing attention is directed toward natural, minimally invasive, and patient-centered therapeutic approaches, these

resources have regained considerable medical and public health importance **(World Health Organization, 2013).**

Despite their widespread use, scientific evaluation of the efficacy and safety of natural therapeutic resources remains fragmented. Existing studies frequently focus on individual aspects—chemical composition, biological activity, or clinical outcomes—while comprehensive integration of these domains remains limited. Furthermore, the lack of standardization, uncertainties regarding therapeutic dosing, and the limited availability of high-quality clinical evidence continue to restrict their evidence-based incorporation into contemporary healthcare systems **(Cheleschi et al., 2020; Karagülle & Karagülle, 2022).**

Addressing these limitations requires a translational medicine approach, which facilitates the effective translation of discoveries from fundamental sciences into clinical practice. Such an approach enables systematic integration of the chemical characterization of natural therapeutic resources with their biological mechanisms and clinical outcomes **(Woolf, 2008; Rubio et al., 2010; National Center for Advancing Translational Sciences, 2024).** At the same time, integrative medicine provides a framework for combining evidence-based natural therapies with conventional medical interventions to achieve patient-centered healthcare **(World Health Organization, 2013; Snyderman & Yoediono, 2021).**

Among natural therapeutic resources, balneological factors, particularly mineral waters, represent highly complex natural systems characterized by diverse ionic compositions, trace elements, dissolved gases, and bioactive constituents. These physicochemical characteristics determine their biological activity and therapeutic potential **(Cheleschi et al., 2020; Fioravanti et al., 2011).** Consequently, understanding the mechanisms underlying their clinical effects requires an interdisciplinary perspective that integrates medical chemistry, biochemistry, clinical medicine, balneology, environmental sciences, and public health **(Karagülle & Karagülle, 2022).**

The present study aims to provide a systematic analysis of the chemical and biological foundations of natural therapeutic resources and to evaluate their translational integration into contemporary medical practice. Beyond reviewing current scientific evidence, this paper proposes a novel translational-integrated conceptual framework that systematically links chemical characterization, molecular mechanisms, biological responses, clinical implementation, and public health applications. The proposed framework seeks to bridge existing gaps between laboratory research and evidence-based clinical practice, providing a scientific basis for the standardization, clinical validation, and future integration of natural therapeutic resources into modern healthcare systems.

To the best of our knowledge, few previous reviews have attempted to comprehensively integrate medical chemistry, balneology, translational medicine, integrative medicine, and public health into a unified conceptual framework for natural therapeutic resources.

2. THEORETICAL BACKGROUND

2.1. Classification of Balneological Resources

Natural therapeutic resources comprise a diverse group of balneological factors that differ in their origin, physicochemical characteristics, and biological mechanisms of action. Their classification is based on physical parameters, chemical composition, and therapeutic applications, providing the foundation for standardized evaluation, scientific characterization, and evidence-based clinical use **(Nasermoaddeli & Kagamimori, 2005; Karagülle & Karagülle, 2022).**

The principal categories of balneological resources include mineral waters, thermal waters, and therapeutic muds (peloids), all of which are widely utilized in balneology, rehabilitation

medicine, preventive medicine, and spa therapy. Although these resources differ in composition and physical properties, they share the common characteristic of exerting therapeutic effects through complex interactions between chemical, physical, and biological factors **(Fioravanti et al., 2011; Cheleschi et al., 2020).**

Mineral waters are primarily classified according to their dominant chemical constituents and ionic composition. They are characterized by varying concentrations of sodium (Na^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), bicarbonate (HCO_3^-), sulfate (SO_4^{2-}), chloride (Cl^-), and other dissolved ions. The relative proportions of these components determine both the hydrochemical classification of the water and its physiological and therapeutic properties (Nasermoaddeli & Kagamimori, 2005; Cheleschi et al., 2020).

Thermal waters are additionally categorized according to temperature and geothermal origin. Beyond their chemical composition, their elevated temperature contributes substantially to therapeutic efficacy by improving hemodynamics, enhancing microcirculation, promoting muscle relaxation, and modulating neuromuscular function. Consequently, thermal therapy combines physicochemical and thermal mechanisms that act synergistically during treatment (Fioravanti et al., 2011; Karagülle & Karagülle, 2022).

Peloids represent complex natural matrices composed of mineral particles, organic matter, and biologically active substances. Their therapeutic properties arise from the combined effects of chemical composition, thermal retention capacity, and mechanical characteristics. Peloid therapy is widely employed in the management of inflammatory disorders, musculoskeletal diseases, degenerative conditions, and rehabilitation programs due to its multifactorial biological effects (Fioravanti et al., 2011; Gálvez et al., 2018).

Therefore, the classification of balneological resources constitutes a fundamental prerequisite for their chemical characterization, mechanistic investigation, clinical standardization, and evidence-based therapeutic application (Cheleschi et al., 2020).

2.2. Chemical Composition of Natural Therapeutic Resources

The biological and clinical potential of natural therapeutic resources is largely determined by their chemical composition, which includes major ions, trace elements, dissolved gases, and biologically active organic compounds. This chemical profile forms the basis for the classification of natural therapeutic resources and largely determines their biological activity and clinical applicability (Cheleschi et al., 2020).

In mineral waters, the dominant ionic composition is primarily represented by calcium (Ca^{2+}), magnesium (Mg^{2+}), sodium (Na^+), bicarbonate (HCO_3^-), sulfate (SO_4^{2-}), and chloride (Cl^-). Variations in the concentration and relative proportions of these ions define both the hydrochemical type of the water and its physiological characteristics. Different ionic profiles are associated with distinct biological responses, influencing electrolyte homeostasis, acid-base balance, metabolic regulation, and cardiovascular function (Gröber et al., 2015; de Baaij et al., 2015; Peacock, 2010).

In addition to major ions, natural waters frequently contain trace elements such as iron (Fe), zinc (Zn), selenium (Se), and iodine (I). Although present at relatively low concentrations, these micronutrients participate in numerous enzymatic, endocrine, immune, and antioxidant processes, thereby contributing to the overall biological activity of mineral waters (Gröber et al., 2015).

Dissolved gases constitute another important component of the chemical profile. Carbon dioxide (CO_2) and hydrogen sulfide (H_2S) are among the most extensively investigated gaseous constituents due to their significant physiological effects. Carbon dioxide promotes vasodilation, improves peripheral circulation, and enhances tissue oxygen delivery, whereas hydrogen sulfide

is currently recognized as an endogenous gaseous signaling molecule (gasotransmitter) involved in vascular regulation, antioxidant defense, and modulation of inflammatory pathways (Kimura, 2020).

The chemical composition of therapeutic muds (peloids) is considerably more complex, consisting of mineral fractions, humic substances, organic compounds, microorganisms, and various bioactive molecules. The interaction of these components contributes to the unique physicochemical properties of peloids and underlies their diverse biological and therapeutic activities (Cheleschi et al., 2020).

Overall, the chemical composition of natural therapeutic resources provides the molecular basis for their biological effects and represents a critical determinant of their clinical efficacy, standardization, and translational application in modern healthcare (Karagülle & Karagülle, 2022).

2.3. Biological Mechanisms of Action

The biological effects of natural therapeutic resources result from complex interactions among their chemical constituents, physical properties, and physiological responses. Rather than acting through a single mechanism, these resources exert multifactorial biological effects involving numerous molecular pathways and organ systems (Cheleschi et al., 2020).

One of the principal mechanisms involves modulation of inflammatory processes. Numerous studies suggest that mineral waters, thermal waters, and peloids influence inflammatory signaling by regulating cytokine production, reducing oxidative stress, and activating endogenous cellular defense mechanisms. These effects contribute to symptom improvement in chronic inflammatory and degenerative disorders and may partially explain the clinical benefits observed in rehabilitation medicine (Fioravanti et al., 2011; Gálvez et al., 2018).

Natural therapeutic resources also participate in the regulation of metabolic processes. Their chemical constituents influence lipid metabolism, glucose homeostasis, electrolyte balance, mitochondrial function, and energy metabolism, suggesting potential applications in the management of metabolic disorders and chronic non-communicable diseases (Gröber et al., 2015; de Baaij et al., 2015).

Furthermore, several natural therapeutic factors affect neuroendocrine regulation, hormonal homeostasis, cardiovascular function, and neuromuscular activity. Thermal stimulation, combined with chemical and mechanical influences, enhances peripheral circulation, improves tissue oxygenation, facilitates muscle relaxation, and modulates autonomic nervous system activity. Collectively, these responses produce a broad physiological adaptation that supports rehabilitation, functional recovery, and preventive healthcare (Cheleschi et al., 2020; Karagülle & Karagülle, 2022).

The therapeutic effects of natural resources therefore arise from the synergistic interaction of chemical, thermal, mechanical, and biological factors rather than from individual components alone. Understanding these integrated mechanisms is essential for establishing evidence-based clinical protocols and for facilitating the translational integration of natural therapeutic resources into modern personalized and integrative medicine (Woolf, 2008; Rubio et al., 2010; Snyderman & Yoediono, 2021).

3. METHODOLOGICAL APPROACH AND TRANSLATIONAL FRAMEWORK
3.1. Study Design and Methodological Approach

Study Design

The present study was designed as a structured narrative review integrating and critically synthesizing evidence from medical chemistry, biochemistry, balneology, translational medicine, integrative medicine, and public health. The primary objective was to develop a comprehensive conceptual framework describing the translational integration of natural therapeutic resources into contemporary healthcare (Woolf, 2008; Rubio et al., 2010).

Although this study was not conducted as a formal systematic review or meta-analysis, the literature search and selection process followed a structured and transparent methodology inspired by the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). This approach was adopted to enhance methodological transparency, reproducibility, and scientific rigor while allowing conceptual synthesis across multiple scientific disciplines (Page et al., 2021; National Center for Advancing Translational Sciences, 2024).

Literature Search Strategy

A structured literature search was performed using the following international scientific databases:

- PubMed/MEDLINE
- Scopus
- Web of Science Core Collection
- ScienceDirect

Supplementary searches were additionally conducted using Google Scholar to identify potentially relevant publications that were not indexed in the primary databases.

The review preferentially included studies published between January 2020 and March 2026, while seminal publications published before 2020 were also incorporated when they provided fundamental theoretical concepts relevant to balneology, medical chemistry, translational medicine, or integrative medicine.

The search strategy combined Medical Subject Headings (MeSH), controlled vocabulary where applicable, and free-text keywords, including:

- natural therapeutic resources
- mineral water
- thermal water
- balneotherapy
- therapeutic mud
- peloids
- medical chemistry
- translational medicine
- integrative medicine
- rehabilitation
- precision medicine
- chemical characterization
- biological mechanisms

Boolean operators (AND, OR) were applied to optimize database retrieval and ensure comprehensive identification of relevant publications.

Eligibility Criteria

Studies were considered eligible when they fulfilled one or more of the following criteria:

- investigated the chemical composition or physicochemical characteristics of natural therapeutic resources;
- described molecular, biochemical, or physiological mechanisms of therapeutic action;
- evaluated clinical outcomes associated with balneotherapy or other natural therapeutic interventions;
- addressed translational medicine, integrative medicine, rehabilitation, or public health perspectives;
- were published in peer-reviewed international scientific journals.
- Studies were excluded when they:
- lacked sufficient methodological information;
- consisted only of conference abstracts, editorials, or letters without complete scientific data;
- duplicated previously published findings;
- were not directly relevant to the objectives of the present review.

The overall literature identification strategy used in the present review is summarized in Table 1.

Table 1. Summary of the literature search strategy and eligibility criteria applied in the present structured narrative review.

Database	Representative Search Terms	Publication Period	Language	Document Types
PubMed/ MEDLINE	"natural therapeutic resources", "mineral water", "balneotherapy", "translational medicine", "integrative medicine"	2020–2026*	English	Original articles, reviews, clinical studies
Scopus	"natural therapeutic resources" AND "chemical characterization"; "balneotherapy"; "rehabilitation"	2020–2026*	English	Research articles, reviews
Web of Science Core Collection	"natural therapeutic resources"; "translational medicine"; "biological mechanisms"	2020–2026*	English	Research articles, reviews
ScienceDirect	"mineral water", "thermal water", "peloids", "medical chemistry"	2020–2026*	English	Research articles, reviews
Google Scholar†	Supplementary searches using combinations of the above keywords	2020–2026*	English	Additional peer-reviewed literature

** Landmark publications published before 2020 were additionally included when considered fundamental to the theoretical background of balneology, translational medicine, or integrative medicine.*

† Google Scholar was used only as a supplementary source to identify additional peer-reviewed publications not retrieved through the primary databases.

Note. The literature search was conducted using predefined keywords and database-specific search strategies. Retrieved publications were screened according to predefined eligibility criteria and subsequently synthesized using a thematic analytical approach. As the present study represents a structured narrative review, the search strategy was designed to maximize comprehensiveness rather than perform a formal systematic review or meta-analysis.

Literature Selection and Data Synthesis

Retrieved publications were systematically screened according to the predefined eligibility criteria through title, abstract, and full-text evaluation. Priority was given to recent high-quality publications presenting mechanistic, translational, or clinical evidence related to natural therapeutic resources.

The selected literature was synthesized using a thematic analytical approach based on five predefined domains:

- chemical characterization;
- molecular and biological mechanisms;
- clinical evidence;
- translational implementation;
- public health integration.

Rather than quantitatively pooling results, the objective of the analysis was to integrate evidence from diverse scientific disciplines into a coherent conceptual framework. The thematic synthesis provided the scientific foundation for the development of the proposed Translational-Integrated Framework for Natural Therapeutic Resources, systematically linking chemical characterization, mechanistic evidence, clinical applications, and public health implementation (Woolf, 2008; Rubio et al., 2010).

The literature search was designed to ensure comprehensive coverage of current scientific evidence relevant to the objectives of the present conceptual review. The search strategy was developed collaboratively by the authors and refined iteratively to maximize sensitivity and relevance.

3.2. Translational Medicine Framework

One of the central contributions of the present review is the development of a Translational Medicine Framework illustrating the sequential progression of scientific knowledge from fundamental chemical characterization to evidence-based clinical implementation. The framework follows the classical bench-to-bedside paradigm while incorporating additional public health and integrative medicine dimensions specifically relevant to natural therapeutic resources (Woolf, 2008; Rubio et al., 2010; National Center for Advancing Translational Sciences, 2024).

The proposed translational pathway consists of four interconnected levels:

Chemical Level

Comprehensive characterization of natural therapeutic resources through hydrochemical profiling, including the identification of major ions, trace elements, bioactive metabolites, dissolved gases, organic constituents, and other bioactive compounds responsible for their physicochemical properties.

Biological Level

Investigation of molecular, cellular, and physiological mechanisms underlying therapeutic activity, including inflammatory modulation, oxidative stress regulation, metabolic adaptation, neuroendocrine responses, vascular function, and tissue regeneration.

Clinical Level

Translation of mechanistic evidence into clinical practice through therapeutic validation, optimization of treatment protocols, individualized dosing strategies, rehabilitation medicine, disease prevention, and evidence-based clinical applications.

Public Health Level

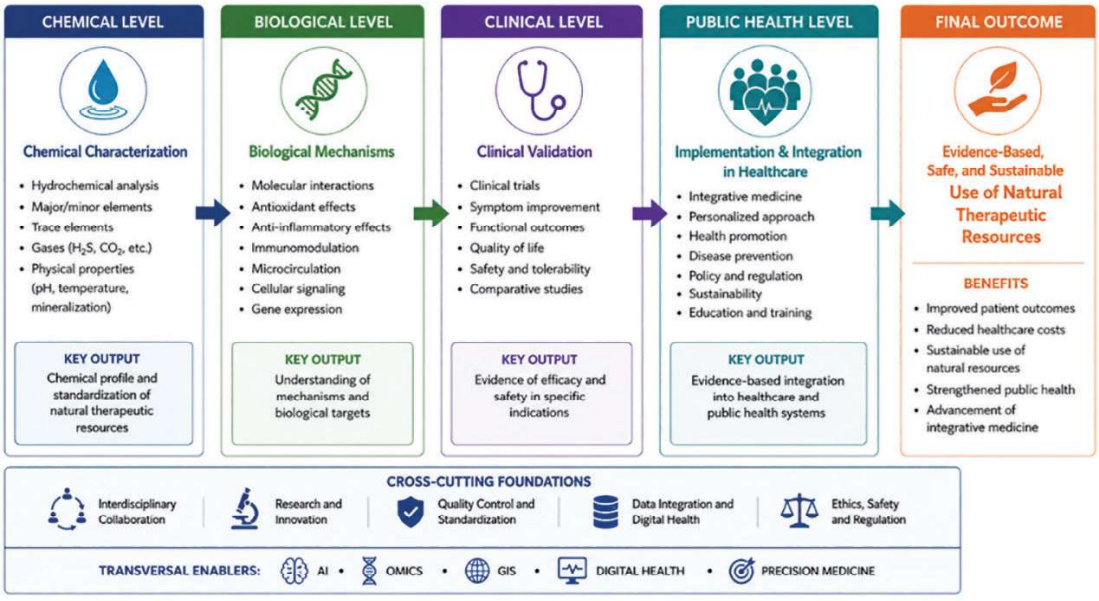
Integration of scientifically validated natural therapeutic resources into healthcare systems as preventive, complementary, and rehabilitation interventions, contributing to population health, health promotion, healthy ageing, and personalized healthcare strategies (World Health Organization, 2013; Snyderman & Yoediono, 2021).

The proposed framework establishes a continuous translational pathway linking laboratory discoveries with clinical implementation and public health practice. By integrating chemical characterization, mechanistic validation, clinical evidence, and healthcare implementation within a single conceptual structure, the model provides a systematic basis for the evidence-based utilization of natural therapeutic resources (Woolf, 2008; National Center for Advancing Translational Sciences, 2024).

The overall Translational-Integrated Framework is presented schematically in Figure 1.

Figure 1. Translational-Integrated Framework for Natural Therapeutic Resources.

Proposed conceptual framework illustrating the translational continuum from the chemical characterization of natural therapeutic resources to their evidence-based clinical and public health implementation. The framework integrates four interconnected domains—Chemical, Biological, Clinical, and Public Health—demonstrating how physicochemical profiling, molecular mechanisms, clinical validation, and healthcare implementation contribute to the standardized and personalized use of natural therapeutic resources.



Source: *Authors' conceptual framework based on the reviewed literature.*

3.3. Integrated Analytical Approach

The present study employs an integrated analytical approach that combines evidence from multiple scientific disciplines into a unified conceptual framework. This methodology enables natural therapeutic resources to be evaluated not only according to their individual chemical constituents but also through the synergistic interactions among their chemical, biological, physical, and clinical characteristics (Cheleschi et al., 2020; Karagülle & Karagülle, 2022).

The integrated analysis incorporates several complementary components:

- correlation between chemical profiles and biological mechanisms of action;
- comparative evaluation of clinical outcomes associated with different categories of natural therapeutic resources;
- assessment of interactions between conventional medical therapies and natural therapeutic interventions;
- identification of current knowledge gaps and translational barriers limiting evidence-based clinical implementation.

Considering the inherently complex nature of natural therapeutic resources, where multiple physicochemical factors simultaneously contribute to biological responses, an interdisciplinary analytical perspective is essential. Such an approach facilitates a more comprehensive understanding of therapeutic mechanisms and supports the development of standardized clinical protocols based on robust scientific evidence.

Furthermore, the integrated analytical strategy provides the methodological foundation for the proposed Translational-Integrated Framework, enabling systematic integration of chemical characterization, mechanistic evidence, clinical validation, personalized medicine, and public health implementation. By bridging traditionally separate scientific disciplines, the framework strengthens the evidence base supporting the incorporation of natural therapeutic resources into modern translational and integrative medicine (Woolf, 2008; Rubio et al., 2010; Snyderman & Yoediono, 2021).

4. RESULTS AND ANALYSIS

4.1. Chemical Profile and Biological Effects

The chemical composition of natural therapeutic resources represents one of the principal determinants of their biological activity. The concentration and interaction of major ions, trace elements, dissolved gases, and bioactive organic compounds collectively influence a wide range of physiological responses at both the cellular and systemic levels (Cheleschi et al., 2020; Fioravanti et al., 2011).

Magnesium-rich (Mg^{2+}) mineral waters are associated with stabilization of the nervous system, reduction of muscle spasms, and stress-relieving effects. These biological activities can be attributed to magnesium's role as a cofactor in more than 300 enzymatic reactions. Magnesium participates in ATP-dependent biochemical processes, neuromuscular transmission, calcium channel regulation, and modulation of N-methyl-D-aspartate (NMDA) receptors, thereby contributing to neuronal stability and muscle function (Gröber et al., 2015; de Baaij et al., 2015).

Calcium-containing (Ca^{2+}) mineral waters play a fundamental role in bone metabolism and intracellular signaling. Calcium is essential for skeletal mineralization, muscle contraction, neurotransmitter release, and numerous intracellular signaling pathways. Consequently, calcium-rich waters may contribute to the maintenance of bone homeostasis and the regulation of osteometabolic processes (Peacock, 2010).

Sodium (Na^{+}) and chloride (Cl^{-}) ions are essential regulators of osmotic balance, extracellu-

lar fluid volume, and electrolyte homeostasis. Their physiological functions provide the rationale for the therapeutic application of sodium-rich mineral waters in selected metabolic and hydroelectrolytic disorders (Nasermoaddeli & Kagamimori, 2005).

Dissolved gases also exert important biological effects. Carbon dioxide (CO_2)-rich mineral waters improve peripheral blood circulation, enhance microvascular perfusion, and promote vasodilation through local pH alterations and endothelial responses. These mechanisms contribute to improved tissue oxygenation and cardiovascular function (Fioravanti et al., 2011).

Hydrogen sulfide (H_2S) has emerged as one of the most extensively investigated gaseous signaling molecules (gasotransmitters) in modern physiology. It participates in vascular regulation, modulation of inflammatory responses, and protection against oxidative stress. Its biological activity has been associated with regulation of the NF-κB signaling pathway, enhancement of endogenous antioxidant defenses, and suppression of pro-inflammatory cytokine production (Kimura, 2020).

In therapeutic muds (peloids), clinical efficacy results from the synergistic interaction between thermal and chemical factors. Their mineral, organic, and biologically active components have been associated with induction of heat shock proteins, downregulation of pro-inflammatory cytokines, modulation of pain pathways, and stimulation of tissue repair and regeneration (Gálvez et al., 2018; Cheleschi et al., 2020).

Collectively, these findings demonstrate that the chemical profile of natural therapeutic resources constitutes the molecular basis of their biological and clinical effects. Consequently, comprehensive chemical characterization represents a prerequisite for their evidence-based translational implementation and clinical standardization (Karagülle & Karagülle, 2022). The principal chemical constituents, proposed biological mechanisms, and potential clinical relevance of natural therapeutic resources are summarized in **Table 2**.

Table 2. Major Chemical Constituents of Natural Therapeutic Resources, Their Biological Mechanisms, Clinical Relevance, Level of Evidence, and Representative References

Chemical Component / Factor	Primary Biological Mechanisms	Potential Clinical Relevance	Level of Evidence*	Representative References
Magnesium (Mg^{2+})	ATP-dependent enzymatic activity; NMDA receptor modulation; neuromuscular regulation	Stress reduction; muscle relaxation; neuromuscular stabilization	Moderate–High	de Baaij et al., 2015; Gröber et al., 2015; Costello et al., 2016
Calcium (Ca^{2+})	Intracellular signaling; bone metabolism; neurotransmitter release	Bone health support; osteometabolic regulation	High	Peacock, 2010; Ross et al., 2011
Sodium (Na^{+})/ Chloride (Cl^{-})	Osmotic balance; extracellular fluid regulation	Electrolyte homeostasis; metabolic support	Moderate	Verbalis et al., 2013

Bicarbonate (HCO_3^-)	Acid–base buffering; modulation of gastric secretion	Gastrointestinal functional support	Moderate	
Sulfate (SO_4^{2-})	Detoxification pathways; digestive stimulation	Hepatobiliary and digestive support	Low–Moderate	Nasermoaddeli & Kagamimori, 2005
Carbon Dioxide (CO_2)	Vasodilation; enhancement of microcirculation	Cardiovascular rehabilitation; peripheral circulation improvement	Moderate–High	Forestier et al., 2014
Hydrogen Sulfide (H_2S)	NF-κB modulation; antioxidant signaling; anti-inflammatory effects	Anti-inflammatory therapy; vascular protection	Moderate	Wang, 2012; Kimura, 2020; Szabó, 2017
Trace Elements (Zn, Se, Fe, I)	Enzymatic cofactor activity; endocrine and immune regulation	Endocrine support; immune modulation	High	Prasad, 2013
Peloid Mineral Fraction	Thermal retention; mineral transfer; enhancement of local circulation	Pain reduction; musculoskeletal rehabilitation	Moderate	Fioravanti et al., 2011
Peloid Organic Fraction	Cytokine modulation; heat shock protein induction	Anti-inflammatory effects; tissue regeneration	Moderate	Gálvez et al., 2018

Evidence levels were qualitatively assigned based on the consistency, methodological quality, and overall strength of currently available mechanistic, preclinical, translational, and clinical evidence. The proposed classification is intended solely for conceptual comparison and does not represent a formal evidence grading system (e.g., GRADE).

4.2. From Biological Mechanisms to Clinical Applications

The biological mechanisms underlying the activity of natural therapeutic resources are directly reflected in their clinical applications. These resources are widely incorporated into rehabilitation medicine, particularly in the management of chronic diseases and functional disorders (Karagülle & Karagülle, 2022).

Mineral waters have demonstrated therapeutic value in the management of functional gastrointestinal disorders, metabolic syndrome, and selected endocrine conditions. Similarly, thermal waters and therapeutic muds are extensively applied in the treatment of musculoskeletal diseases, including osteoarthritis and inflammatory arthropathies, where their thermal, chemical, and mechanical effects act synergistically to reduce pain, improve mobility, and enhance functional recovery (Fioravanti et al., 2011; Cheleschi et al., 2020).

Natural therapeutic resources also play an increasingly important role in preventive medicine. Their application has been associated with stress reduction, immune support, improvement

of general well-being, and promotion of healthy aging. These preventive effects are particularly relevant within contemporary healthcare systems that increasingly emphasize disease prevention, health promotion, and patient-centered care (World Health Organization, 2013; Snyderman & Yoediono, 2021).

Current scientific evidence indicates that the strongest clinical support exists for the use of natural therapeutic resources in musculoskeletal rehabilitation, chronic pain management, and functional metabolic disorders. Nevertheless, growing interest has also emerged regarding their preventive and wellness-oriented applications. Despite these promising findings, further standardized, high-quality clinical trials are required to strengthen the evidence base supporting their broader implementation in evidence-based medicine (Karagülle & Karagülle, 2022).

4.3. Translational Links and Current Gaps

Despite substantial progress in understanding the chemistry and biology of natural therapeutic resources, their translation into standardized clinical practice remains incomplete. One of the major challenges is the lack of standardized classification and characterization systems, which complicates comparisons among studies and limits the development of universally accepted clinical recommendations (Cheleschi et al., 2020).

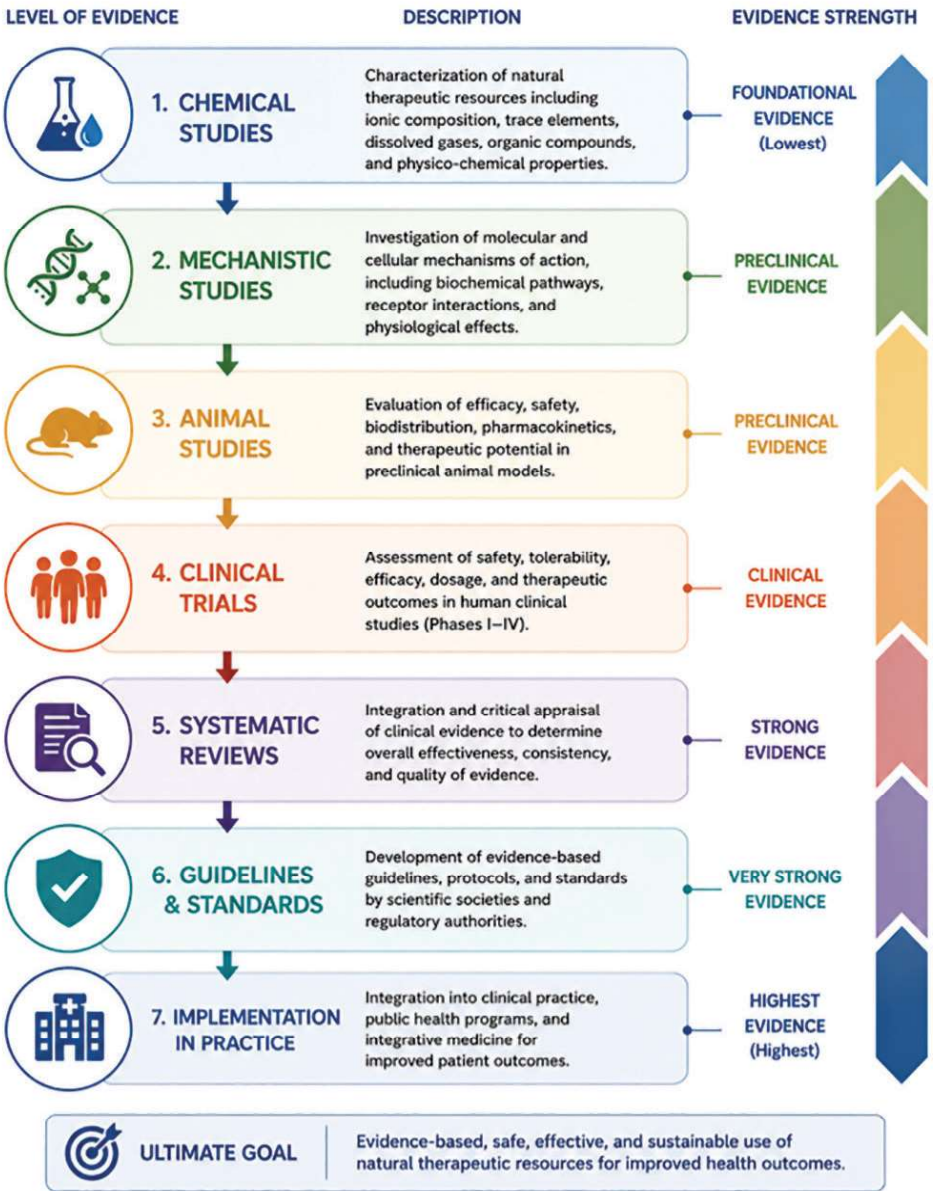
Another important limitation concerns therapeutic dosing. The biological and clinical effects of natural therapeutic resources depend not only on their chemical composition but also on treatment duration, administration protocols, exposure conditions, and individual patient characteristics. Considerable heterogeneity among existing clinical studies further complicates the interpretation of available evidence (Karagülle & Karagülle, 2022).

A significant translational barrier also exists between basic scientific research and clinical implementation. Although numerous chemical and biochemical investigations have identified molecular mechanisms underlying the biological activity of natural therapeutic resources, these findings are only rarely translated into standardized clinical protocols or evidence-based therapeutic guidelines. Conversely, clinical observations are frequently disconnected from detailed mechanistic investigations, limiting the development of scientifically validated therapeutic strategies (Woolf, 2008; Rubio et al., 2010).

Collectively, these limitations highlight the urgent need for standardized translational frameworks capable of integrating chemical characterization, mechanistic validation, clinical evidence, and healthcare implementation. Addressing these translational gaps will be essential for establishing natural therapeutic resources as evidence-based components of modern integrative and personalized medicine (Topol, 2019; Snyderman & Yoediono, 2021).

Figure 2. Evidence Landscape for the Clinical Translation of Natural Therapeutic Resources.

Conceptual illustration of the evidence continuum supporting the translational integration of natural therapeutic resources into modern healthcare. The framework depicts the sequential progression from hydrochemical characterization and mechanistic investigations through preclinical validation, clinical research, systematic evidence synthesis, and guideline development to evidence-based clinical implementation. The model emphasizes that successful translation from bench to bedside requires standardized chemical characterization, high-quality mechanistic and clinical evidence, multidisciplinary collaboration, and personalized therapeutic strategies to achieve safe, effective, and sustainable integration into healthcare systems.



The figure was developed by the authors based on the conceptual synthesis of the reviewed literature.

5. INTEGRATIVE MEDICINE MODEL

5.1. Concept of Integrative Medicine and the Proposed Translational-Integrated Framework

Modern healthcare is increasingly founded on a patient-centered paradigm that integrates disease treatment, prevention, rehabilitation, and the promotion of long-term health and well-being. Within this context, integrative medicine represents an evidence-informed approach that combines conventional medical practice with scientifically validated complementary therapeutic interventions to address the individual needs of patients through personalized and holistic care (World Health Organization, 2013; Snyderman & Yoediono, 2021).

The effective incorporation of natural therapeutic resources into contemporary healthcare requires a translational framework capable of systematically linking chemical characterization, biological mechanisms, clinical evidence, and healthcare implementation. Although substantial

progress has been achieved in understanding the chemistry and biological activity of natural therapeutic resources, the translation of this knowledge into standardized clinical practice remains fragmented (Woolf, 2008; Rubio et al., 2010).

To address this challenge, the present study proposes a novel Translational-Integrated Framework for Natural Therapeutic Resources, designed to bridge fundamental research with evidence-based clinical implementation (National Center for Advancing Translational Sciences, 2024). The proposed model consists of four interconnected levels:

1. Chemical Level – comprehensive characterization of natural therapeutic resources through analysis of their ionic composition, trace element profile, dissolved gases, and bioactive constituents.

2. Biological Level – investigation of molecular, cellular, and physiological mechanisms responsible for therapeutic activity, including inflammatory modulation, metabolic regulation, oxidative stress responses, vascular function, and neuroendocrine signaling.

3. Clinical Level – translation of mechanistic evidence into clinical practice through therapeutic validation, optimization of treatment protocols, individualized dosing strategies, and development of standardized clinical guidelines.

4. Public Health Level – implementation of scientifically validated natural therapeutic resources into preventive medicine, rehabilitation programs, personalized healthcare, and sustainable public health strategies (World Health Organization, 2013).

Unlike conventional reductionist approaches that evaluate isolated chemical constituents, the proposed framework is based on the concept that the therapeutic efficacy of natural therapeutic resources arises from the synergistic interaction of their chemical, physical, and biological properties. Consequently, their evaluation should integrate biomedical, biochemical, environmental, and biopsychosocial perspectives within a unified translational model (Cheleschi et al., 2020; Karagülle & Karagülle, 2022).

By establishing systematic links between laboratory discoveries and clinical implementation, this framework provides a conceptual foundation for the scientific standardization and evidence-based integration of natural therapeutic resources into modern healthcare systems (Woolf, 2008; Rubio et al., 2010).

5.2. Practical and Regional Significance of the Proposed Model

The proposed Translational-Integrated Framework provides a comprehensive conceptual basis for the scientific validation, standardization, and clinical implementation of natural therapeutic resources (Karagülle & Karagülle, 2022). Its application has the potential to strengthen both research methodologies and evidence-based healthcare practices by facilitating:

- systematic chemical and biological characterization of natural therapeutic resources;
- development of standardized, evidence-based clinical protocols;
- promotion of interdisciplinary collaboration among chemists, biochemists, clinicians, environmental scientists, and public health specialists;
- advancement of personalized, preventive, and rehabilitation-oriented therapeutic strategies;
- integration of natural therapeutic resources into modern healthcare systems through evidence-based translational medicine.

Beyond its scientific value, the proposed framework has particular relevance for regions possessing abundant balneological resources. Countries rich in mineral waters, thermal springs, therapeutic muds, and other natural therapeutic factors have unique opportunities to translate

their natural assets into evidence-based healthcare innovations, sustainable medical tourism, and regional health development (World Health Organization, 2013).

This perspective is especially relevant to the Caucasus region, where exceptional geological diversity has resulted in a remarkable concentration of natural therapeutic resources. The systematic implementation of the proposed framework may support not only scientific research and clinical innovation but also public health promotion, regional economic development, and the sustainable utilization of natural therapeutic resources.

Ultimately, the proposed model provides a platform for future interdisciplinary research aimed at establishing internationally harmonized standards for the characterization, clinical evaluation, and translational implementation of natural therapeutic resources within the framework of personalized and integrative medicine (Topol, 2019; Snyderman & Yoediono, 2021).

6. DISCUSSION

The findings presented in this review demonstrate that natural therapeutic resources possess considerable potential for application in modern healthcare. However, their effective integration into evidence-based clinical practice remains constrained by several scientific and practical challenges. The remarkable diversity of their chemical composition and biological activity simultaneously provides broad therapeutic opportunities while creating significant difficulties in terms of standardization, therapeutic dosing, reproducibility, and optimization of clinical implementation (Cheleschi et al., 2020; Karagülle & Karagülle, 2022).

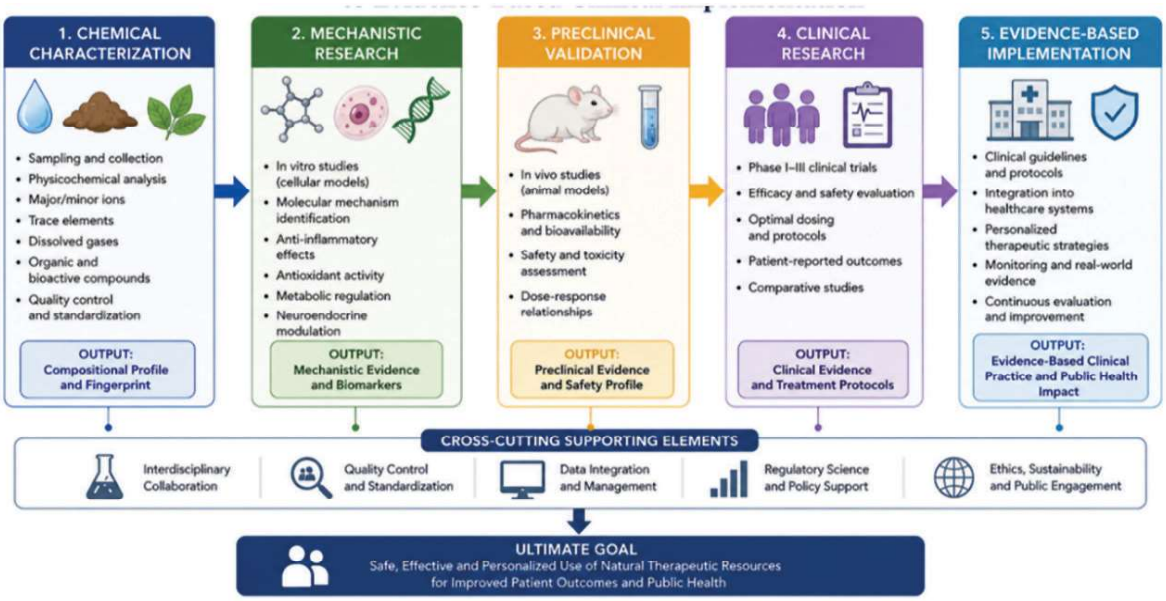
One of the principal limitations is the intrinsic heterogeneity of natural therapeutic resources, which results from differences in geological origin, hydrochemical conditions, environmental factors, and local ecological characteristics. This variability complicates the establishment of standardized quality criteria, limits the comparability of clinical studies, and hinders the development of universally accepted therapeutic recommendations. Consequently, the existing body of evidence often remains insufficient for the formulation of high-level evidence-based clinical guidelines (Karagülle & Karagülle, 2022).

From the perspective of translational medicine, one of the major barriers is the incomplete linkage between molecular mechanisms and clinical outcomes. Although numerous chemical and biochemical investigations have significantly improved our understanding of the mechanisms underlying the biological activity of natural therapeutic resources, these discoveries are only rarely translated into standardized therapeutic protocols or clinical decision-making algorithms. This observation indicates that an integrated translational pipeline, capable of systematically connecting chemical characterization, mechanistic validation, and evidence-based clinical implementation, has not yet been fully established (Woolf, 2008; Rubio et al., 2010).

The current evidence landscape underpinning the translational implementation of natural therapeutic resources is summarized in Figure 3.

Figure 3. Evidence Landscape for the Clinical Translation of Natural Therapeutic Resources.

Hierarchical representation of the current evidence continuum supporting the clinical implementation of natural therapeutic resources. The framework illustrates the progression from fundamental chemical studies through mechanistic and preclinical investigations, clinical trials, systematic reviews, clinical guidelines, and evidence-based healthcare implementation. The figure highlights the increasing strength of scientific evidence required for successful translational integration and emphasizes existing knowledge gaps that should be addressed through future multidisciplinary research.



The figure was developed by the authors based on the conceptual synthesis of the reviewed literature.

Bridging these translational gaps requires stronger interdisciplinary collaboration among chemists, biochemists, clinicians, balneologists, environmental scientists, and public health experts. Only through such multidisciplinary cooperation can natural therapeutic resources be systematically characterized, scientifically validated, and effectively incorporated into evidence-based healthcare (Woolf, 2008).

Within the framework of integrative medicine, natural therapeutic resources appear particularly promising for the advancement of personalized medicine (Topol, 2019; Snyderman & Yoediono, 2021). Future therapeutic strategies may allow the selection of specific balneological interventions according to individual metabolic, endocrine, inflammatory, and functional profiles. Such precision-based approaches could substantially improve treatment efficacy while enhancing patient-centered care and therapeutic individualization.

Particular attention should be directed toward regions characterized by exceptional diversity and abundance of natural therapeutic resources, including the Caucasus region and Georgia. Owing to their unique geological, hydrochemical, and bioclimatic characteristics, these regions represent valuable natural laboratories for translational balneological research. Nevertheless, realizing this scientific and clinical potential requires the integration of advanced analytical and digital technologies, including high-resolution chemical profiling, molecular biochemical analyses, geographic information systems (GIS), artificial intelligence (AI), spatial modeling, and multi-omics approaches (Topol, 2019).

The Translational-Integrated Framework proposed in the present study may therefore be considered a promising conceptual model that systematically connects the chemical, biological, clinical, and public health dimensions of natural therapeutic resources. Beyond addressing current translational gaps, the framework provides a scientific basis for the development of standardized clinical protocols, personalized therapeutic strategies, and future interdisciplinary research (Rubio et al., 2010; National Center for Advancing Translational Sciences, 2024).

The principal challenges, scientific implications, and future research priorities are summarized in Table 3.

Table 3. Current Challenges, Scientific Implications, and Future Directions for the Translational Integration of Natural Therapeutic Resources

Current Challenges	Scientific / Practical Implications	Future Directions / Proposed Solutions
Resource heterogeneity	Variable chemical composition limits reproducibility and comparability across studies	Development of standardized classification systems, harmonized chemical profiling, and international reference databases
Lack of compositional standardization	Difficulty establishing therapeutic dosing and clinical protocols	Standardized analytical protocols, ISO-based quality control, and certified reference materials
Insufficient mechanistic evidence	Weak linkage between chemical composition and biological effects	Advanced in vitro/in vivo studies, molecular pathway analysis, multi-omics integration (genomics, proteomics, metabolomics)
Limited high-quality clinical trials	Reduced evidence base for clinical guidelines	Large-scale multicenter randomized controlled trials (RCTs), long-term follow-up studies, and international clinical registries
Fragmented translational pipeline	Inefficient transfer of laboratory findings into clinical practice	Integrated translational research frameworks linking chemistry, biology, clinical medicine, and public health
Weak interdisciplinary collaboration	Limited communication among chemists, clinicians, balneologists, and environmental scientists	Multidisciplinary research consortia, international collaborative networks, and shared data platforms
Lack of personalized treatment algorithms	Uniform treatment protocols may reduce therapeutic effectiveness	Precision balneology, biomarker-guided therapy, and patient-specific treatment algorithms
Underutilization of digital technologies	Missed opportunities for prediction, monitoring, and clinical decision support	AI-assisted chemical profiling, GIS-based spatial analysis, machine learning, digital health platforms, and digital twins
Regulatory and policy gaps	Limited incorporation into national healthcare systems	Development of evidence-based regulatory frameworks, international clinical guidelines, and health policy integration
Limited biomarker validation	Limited ability to predict individual therapeutic response, monitor treatment efficacy, and optimize patient selection	Biomarker-guided precision balneology, validation of predictive biomarkers, integration with multi-omics profiling, and personalized therapeutic decision-making
Current Challenges	Scientific / Practical Implications	Future Directions / Proposed Solutions

Future translational research should also focus on validating predictive biomarkers that may facilitate patient stratification and precision balneology.

Future Perspectives. Future research should focus on the integration of artificial intelligence, multi-omics technologies, biomarker-guided therapeutic strategies, precision balneology, and digital twin models into the investigation and clinical implementation of natural therapeutic resources. These emerging technologies have the potential to improve chemical characterization, predict therapeutic responses, optimize personalized treatment protocols, and strengthen evidence-based decision-making in translational and integrative medicine (Topol, 2019).

The principal strength of the present review lies in the integration of medical chemistry, balneology, translational medicine, integrative medicine, and public health within a single conceptual framework. Unlike conventional narrative reviews focusing primarily on clinical outcomes, the proposed model systematically links chemical characterization with biological mechanisms and evidence-based implementation, thereby providing a multidisciplinary perspective for future research and healthcare policy.

6.1. Limitations of the Current Evidence Base

Despite the comprehensive analysis presented in this review, several limitations of the current evidence base should be acknowledged. Considerable heterogeneity exists not only in the chemical composition of natural therapeutic resources but also in study design, analytical methodologies, and clinical protocols, making direct comparisons among studies challenging and limiting the formulation of universally applicable clinical recommendations (Karagülle & Karagülle, 2022).

Furthermore, many published clinical investigations involve relatively small sample sizes, insufficient methodological standardization, heterogeneous therapeutic interventions, and variable outcome measures, thereby restricting the generalizability of their findings. Likewise, numerous mechanistic hypotheses proposed in experimental studies still require rigorous validation through well-designed laboratory investigations and high-quality clinical trials (Cheleschi et al., 2020).

Accordingly, the Translational-Integrated Framework proposed in the present study should be regarded as a **conceptual model** rather than a definitive clinical guideline. Its further refinement and validation will require multicenter, standardized, and evidence-based investigations integrating chemical, molecular, clinical, and public health research (Woolf, 2008).

Another limitation is that the proposed framework has not yet undergone prospective clinical validation and should therefore be considered a conceptual model requiring future empirical testing.

7. CONCLUSIONS

Natural therapeutic resources represent an important and multifaceted component of modern healthcare whose therapeutic potential is fundamentally determined by their unique chemical composition and diverse biological activities. The present review demonstrates that their effective and safe implementation requires the integrated evaluation of chemical, biological, clinical, and public health evidence within a unified translational framework (Woolf, 2008; Karagülle & Karagülle, 2022).

This study proposes a novel Translational-Integrated Framework that provides a systematic scientific basis for the characterization, standardization, validation, and evidence-based integration of natural therapeutic resources into contemporary healthcare systems. By establishing a continuous pathway from chemical profiling through mechanistic validation and clinical application to public health implementation, the framework addresses critical gaps between funda-

mental research and clinical practice (Rubio et al., 2010).

The proposed approach is particularly relevant for regions rich in balneological resources, including the Caucasus region, where natural therapeutic factors represent valuable scientific, medical, and socioeconomic assets. Their sustainable utilization requires interdisciplinary collaboration, standardized analytical methodologies, and evidence-based clinical validation (World Health Organization, 2013).

Future research should prioritize large-scale standardized clinical trials, further mechanistic validation, and the integration of advanced analytical, digital, and personalized medicine technologies, including artificial intelligence, GIS-based spatial analysis, multi-omics platforms, and digital health tools to strengthen the translational implementation of natural therapeutic resources in evidence-based healthcare (Topol, 2019).

The proposed framework may serve as a reference model for future translational research, international standardization, and evidence-based implementation of natural therapeutic resources within precision and integrative medicine. Beyond its conceptual contribution, the proposed framework may facilitate future international standardization efforts, interdisciplinary collaboration, and the development of evidence-based clinical guidelines for the safe and personalized implementation of natural therapeutic resources.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Literature Search Strategy Used in the Present Review

This supplementary table summarizes the literature search strategy applied in the present structured narrative review. The search was designed to ensure comprehensive identification of peer-reviewed evidence relevant to natural therapeutic resources, medical chemistry, balneology, translational medicine, integrative medicine, and public health.

Database	Search Terms (examples)	Publication Years	Language	Document Type
PubMed/MEDLINE	"natural therapeutic resources" AND balneotherapy; "mineral water"; "thermal water"; "peloids"; "translational medicine"; "integrative medicine"; "medical chemistry"	2020–2026*	English	Original research articles, systematic reviews, narrative reviews, clinical trials
Scopus	"balneotherapy"; "spa therapy"; "mineral water therapy"; "chemical characterization"; "rehabilitation"; "precision medicine"	2020–2026*	English	Peer-reviewed journal articles and reviews
Web of Science Core Collection	"natural therapeutic resources"; "balneology"; "translational medicine"; "integrative medicine"; "clinical implementation"	2020–2026*	English	Original articles and review papers
ScienceDirect	"thermal waters"; "peloids"; "hydrogen sulfide"; "medical chemistry"; "rehabilitation"; "public health"	2020–2026*	English	Research articles and review articles
Google Scholar	Supplementary searches using combinations of the above keywords to identify additional publications, books, guidelines, and institutional reports	2020–2026*	English	Articles, books, reports, policy documents

Search Strategy

The search strategy combined Medical Subject Headings (MeSH), database-specific indexing terms, and free-text keywords. Boolean operators (**AND**, **OR**) were applied to optimize search sensitivity and specificity. Reference lists of highly relevant review articles were additionally screened to identify eligible publications that were not retrieved during the primary database searches.

Eligibility Criteria

Studies were considered eligible if they:

- investigated the chemical composition of natural therapeutic resources;
- described molecular or biological mechanisms of therapeutic action;
- evaluated clinical outcomes associated with balneotherapy or natural therapeutic resources;
- addressed translational medicine or integrative medicine approaches;
- were published in peer-reviewed international journals.

Studies were excluded if they:

- lacked sufficient methodological information;
- were conference abstracts without full-text publication;
- duplicated previously published data;
- were not directly relevant to the objectives of the present review.

Note

The literature search primarily included publications published between January 2020 and March 2026. Earlier landmark publications were additionally incorporated when considered essential for understanding the historical development of balneology, medical chemistry, translational medicine, or integrative medicine.