EDITORIAL
Traditional Medicine Research 2026;11(9):57. https://doi.org/10.53388/TMR20260313001

Natural products, traditional medicine, and aging mechanisms: future directions for healthy aging research

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Author contributions

Lee SH was responsible for conceptualization, funding acquisition, project administration, and supervision. Yang SY, Choi HJ, Lee HK, and Lee SH conducted the literature review and interpretation. Yang SY, Choi HJ, Lee HK, and Lee SH contributed to the writing of the original draft. All authors participated in the review and editing of the manuscript.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This research was partially supported by the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (RS-2023-00278670).

Peer review information

Traditional Medicine Research thanks Fu-Wen Yuan and other anonymous reviewers for their contribution to the peer review of this paper.

Citation

Yang SY, Choi HJ, Lee HK, Lee SH. Natural products, traditional medicine, and aging mechanisms: future directions for healthy aging research. *Tradit Med Res.* 2026;11(9):57. doi: 10.53388/TMR20260313001.

Editorial advisory board: Ki-Hyun Kim.
Executive editor: Na Liu and Xiao-Han Li.
Received: 13 March 2026; **Revised:** 20 April 2026; **Accepted:** 6 May 2026; **Available online:** 11 May 2026.

Abstract

Natural products and traditional herbal formulas have long been central to traditional medicine. They are used clinically, embedded in cultural therapeutic systems, and continue to provide important bioactive leads for healthy aging research. This editorial argues that the field should move beyond broad antioxidant claims toward geroscience-aligned mechanisms that can be linked to outcomes that matter for healthspan. Across this issue, several priorities for traditional medicine research on aging become clear. These include alignment with geroscience mechanisms, phenotype-based validation, more rigorous evaluation of multi-component interventions, and greater attention to quality control and safety in translational work. We highlight how network pharmacology can help evaluate complex, multi-component interventions when paired with phenotype-based validation, and we outline what 'good evidence' looks like for single compounds versus formulas. We also argue that translation depends on more than mechanistic promise alone. Reproducible material identity, safety monitoring, and clinically interpretable endpoints are necessary if these interventions are to be evaluated seriously in human studies.

Keywords: natural products; aging mechanisms; geroscience; network pharmacology; healthspan; translational research

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Highlights

1. Progress in aging research depends on translating traditional medicine concepts into measurable, reproducible, and clinically interpretable interventions.
2. Mechanistic studies of natural products should prioritize functional and clinically meaningful outcomes rather than relying solely on descriptive biomarkers.
3. Standardized material quality and compositional consistency are essential to ensure reliable, reproducible, and comparable research findings.

Natural products occupy a distinctive place in medicine and public health: they are part of cultural heritage, used in everyday care, and rich in bioactive chemistry. Traditional medical systems, including East Asian medicine, Ayurveda, and other long-standing herbal traditions, have long approached aging not as a single disease but as a gradual decline in resilience, recovery, and daily function. This function-centered perspective makes traditional medicine especially relevant to current geroscience, which likewise seeks measurable ways to preserve healthspan rather than merely extend lifespan and increasingly emphasizes resilience, maintenance of function, and clinically meaningful health states [1, 2]. In practice, these concerns are reflected in measures such as sleep quality, appetite, physical comfort, and recovery after stress or illness. Modern aging science provides clearer language for these goals, along with better tools to measure them. This editorial links natural products to key aging mechanisms and highlights a shift in the field. Traditional medicine also offers a practical framework for aging research: classical formula-based approaches and multi-herb prescription logic often begin with patterns of function, recovery, and resilience that align naturally with healthspan-oriented phenotypic results. The central question is not whether natural products influence aging-related pathways, but which lines of evidence should count as credible evidence for healthspan claims and how such evidence should be reported.

For many years, ‘anti-aging’ claims in natural products focused on antioxidant capacity. It was easy to measure and easy to explain. The idea sounded simple. If free radicals cause damage, stronger antioxidants should help. Human data have made this shortcut harder to defend. A large analysis of randomized trials found that beta-carotene and vitamins A and E were linked to higher all-cause mortality, while benefits for other antioxidants were unclear [3]. Another controlled study suggested that vitamins C and E can reduce some exercise-related metabolic benefits [4]. These findings do not deny that oxidative damage matters in aging. They show that redox biology is complex. ‘Antioxidant’ alone is not enough as a stand-in for clinically meaningful effects that matter. The most convincing work will connect a natural product to specific aging pathways and then show clear changes in functional or healthspan-related measures.

A more useful frame comes from geroscience. The hallmarks-of-aging framework helps because it turns ‘aging’ into processes we can study, and recent updates have further expanded this framework to include additional interconnected aging processes [5, 6]. These include changes in nutrient sensing, mitochondrial function, cellular senescence, protein quality control, and cell-to-cell signaling [5]. Geroscience also offers the broader point that these processes sit upstream of many chronic diseases and increasingly provide a framework for translational and precision-oriented intervention strategies in aging research [1, 7]. If we can affect shared mechanisms, we may improve healthspan across several conditions, not just one [1]. This is helpful for natural products. Many natural products act on more than one pathway. That is not a problem if the effects map to a small set of key aging mechanisms and lead to real functional benefits.

Across the articles in this collection, that shift is clear. The papers do not rely on broad labels like ‘antioxidant.’ They connect natural products to specific aging processes such as metabolic regulation, mitochondrial energy control, inflammation, senescence-related changes, protein homeostasis, or tissue repair. The more important question is which lines of evidence can credibly support a healthspan claim. This orientation fits traditional medicine research particularly well. In many traditional settings, this logic is expressed not only through individual medicinal materials but also through classical formula-inspired approaches, in which combinations are selected to address coexisting disturbances in energy, recovery, sleep, digestion, or inflammatory burden. In real-world traditional practice, interventions are often selected to improve function-centered complaints (such as fatigue, sleep disturbance, digestive discomfort, pain, and delayed recovery) rather than to modify a single laboratory marker. Here, we focus on clinically interpretable functional measures that can be directly assessed, rather than repeatedly invoking general conceptual labels. These findings are framed in terms of measurable physiological or cellular responses, allowing clearer linkage to experimental validation. Traditional function-centered complaints should not be treated as direct mechanistic categories, but as starting points for defining testable phenotypic and biological hypotheses. Accordingly, traditional theoretical constructs are not presented here as direct equivalents of geroscience mechanisms, and not all traditional formulations should be assumed to align with geroscience principles without explicit experimental validation.

For example, a representative functional pattern characterized by fatigue and delayed recovery can be operationally mapped onto mitochondrial dysfunction, low-grade inflammation, and impaired stress-response signaling, each of which can be linked to measurable indicators such as energy metabolism, inflammatory markers, and recovery kinetics. When such outcomes are mapped onto geroscience mechanisms, traditional medicine can retain its clinical logic while speaking clearly to biomedical readers and meeting modern expectations for mechanistic clarity and reproducibility. Several papers also avoid a common trap. They do not treat one molecular marker as the whole result. Biomarkers are used as support and are interpreted alongside functional changes. Recent reports also suggest that autophagy-linked signaling can be one part of broader stress-response programs. These include redox balance, inflammation control, and metabolic regulation. The best examples connect mechanisms to meaningful changes in skin aging and metabolic dysfunction [8, 9]. More recently, these lines of work have been discussed in the broader context of natural products, artificial intelligence, and the future of human-centered anti-aging pharmacology [10]. Complex interventions raise a different problem: how should they be judged when their effects are distributed across multiple targets? Natural products, especially multi-herb medicines, rarely fit a ‘one compound, one target’ model. Network pharmacology can help because many effective therapies shift network states and act on more than one protein, but recent evaluations in herbal medicine suggest that such predictions are most informative when paired with experimental and phenotype-level validation [11, 12].

However, several core methodological challenges remain. The biological activity of a multi-component formula cannot be assumed to reflect true synergy unless additive and non-additive effects are explicitly distinguished under controlled conditions. Establishing causal attribution within mixtures remains inherently difficult, particularly when multiple components converge on overlapping pathways. In addition, without compositional reproducibility, mechanistic interpretation at the formula level remains inherently unstable, limiting both comparability and translational confidence. Network-based analyses should therefore be treated as hypothesis-generating tools rather than substitutes for experimental validation, especially in the context of complex interventions.

Still, network maps can mislead. They can turn into busy diagrams that look impressive but do not prove much. The best safeguard is to return to phenotype. We should ask what changes in a way that matters. Drug discovery experience also supports this. Many first-in-class medicines came from phenotype-driven work, which shows the value of functional measures [12]. The articles here show practical ways to combine networks with phenotypes. Some papers highlight pathway convergence, showing that different compounds or preparations point toward a small set of relevant modules rather than

a long list of unrelated pathways. Others start from functional readouts (metabolic flexibility, inflammatory tone, tissue resilience, and performance-related measures) and then use biomarkers to explain those changes. Across these studies, mechanistic claims are most persuasive when they are paired with phenotypes that remain meaningful across models and study designs. This also makes it easier to compare studies, even when materials, extraction methods, or models differ.

Single compounds remain valuable when the goal is to establish causality, pharmacokinetics, and dose–response relationships with precision. By contrast, traditional multi-herb formulas may be especially relevant when the clinical target is a broader functional state (such as frailty, impaired recovery, or chronic inflammatory burden) that is unlikely to be captured by a single-target model. Instead of separating conceptual discussion from validation, we consider phenotype-level evidence and functional changes together as part of a single evaluative framework. For such formulas, convincing evidence should include reproducible composition, authenticated source materials, chemical fingerprinting, and consistent phenotype-level improvements supported by mechanistic coherence. This makes it easier to judge whether a biologically plausible effect also carries functional relevance. Classical formula-inspired approaches are especially informative when they preserve traditional combination logic while incorporating modern expectations for authentication, batch consistency, and mechanism-linked phenotype validation. Pharmacokinetic considerations are equally important at this stage. Many natural products, particularly polyphenolic compounds, show limited translational potential because poor intestinal absorption, rapid metabolism, and low systemic exposure can prevent mechanistic effects observed in vitro from being reproduced under physiologically achievable in vivo conditions.

Translation is where many otherwise promising interventions falter. Even when a mechanism looks strong and a phenotype improves, progress can stall if the intervention cannot be reproduced or safely delivered, or evaluated within a clear regulatory framework [13]. For natural products, quality is not a minor detail; it defines what the intervention actually is. WHO guidance emphasizes that identity, purity, and control of contaminants and residues are basic requirements for safety and efficacy in herbal medicines [14]. Several papers in this collection show how this changes interpretation: when materials are authenticated, chemically described, and batch-consistent, biological findings become easier to trust and easier to compare. However, these strengths should not obscure persistent limitations in the field. Reproducibility can be undermined by compositional variability, inconsistent authentication, and the tendency to overinterpret mechanistic associations in the absence of phenotype validation. As a result, biological plausibility alone should not be treated as sufficient support for translational claims.

Reporting quality matters too. For complex formulas, clear reporting of composition, preparation, dosing, and rationale is essential for replication and meta-analysis, and CONSORT guidance for Chinese herbal medicine formulas offers a useful template [15]. Safety deserves the same level of attention. Traditional use can guide expectations, but it does not replace modern safety monitoring, especially with concentrated products, long-term use, and older adults who often take multiple medications. Translation improves when interaction risks are considered, adverse events are reported clearly, and benefits are interpreted in functionally meaningful and clinically interpretable settings.

Finally, the choice of evaluation criteria determines whether healthy aging claims are experimentally testable, clinically interpretable, and appropriate for early-stage human evaluation. Geroscience trial discussions emphasize how hard it is to design feasible human studies with outcomes that truly matter [16]. There is growing agreement that function-first assessments (physical performance, frailty-related measures, resilience to stressors, multimorbidity trajectories, and intrinsic capacity) are easier to interpret than molecular shifts alone, especially in older adults [17, 18]. Read together, the papers in this collection point to a clear direction: move beyond antioxidant shortcuts; align claims with core aging mechanisms; support multi-target stories with network-and-phenotype evidence; and bring forward interventions that can be reproduced, evaluated safely, and judged using clinically meaningful measures in early human studies. A practical implication is that claims should remain closely matched to the level of evidence actually available.

These papers are most informative when read together, because they converge on a common problem: linking mechanistic claims to biological and clinical effects that remain interpretable in translational settings. Some papers connect function-centered thinking with mechanism-based framing. Others connect chemistry with biology by showing that material characterization is the starting point for credible inference. Still others connect preclinical work with clinical realism by discussing dose forms, exposure, comparators, and assessment strategies suitable for early human studies. This is particularly important when experimental activity is reported at concentrations that may not be realistically achieved in vivo. In such cases, exposure-informed interpretation, formulation strategies, and clinically interpretable indicators become essential for judging translational relevance.

Taken together, these studies make it easier to connect pathway-level findings with plausible improvements in human function. Figure 1 summarizes this framework. Several well-studied

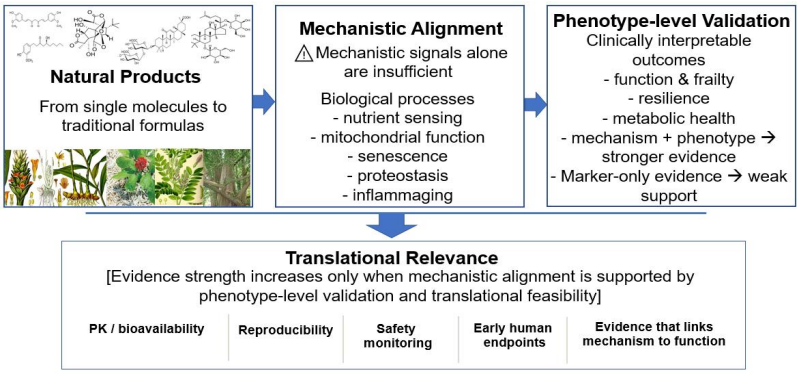

Figure 1 Evaluative framework for linking natural products to geroscience and clinically interpretable outcomes.
Natural products and traditional herbal interventions (including representative single compounds such as quercetin, trans-resveratrol, and ginsenoside Rg1, as well as multi-herb formulations used in traditional practice) are aligned with geroscience mechanisms (mechanistic alignment) and evaluated through clinically interpretable outcomes (phenotypic coherence and translational relevance). The framework distinguishes multiple layers of evidence, including mechanistic plausibility, phenotype-level validation, and function-centered outcomes. These layers are organized to reflect an evaluative hierarchy, linking biological mechanisms to phenotypic coherence and ultimately to clinically interpretable endpoints. This structure is intended to guide interpretation and assessment of evidence, rather than merely restate the conceptual premise of the manuscript.

natural products help make this point more concrete. Ginsenosides are often discussed in relation to mitochondrial function and senescence, resveratrol to NAD^+-linked metabolism, and quercetin to senolytic and anti-inflammatory effects. These examples show how defined compounds can be tied to measurable biological outcomes. Overall, the articles in this issue point to a more rigorous path for traditional medicine research on aging: not simply to restate familiar concepts in modern language, but to translate them into reproducible interventions, mechanism-linked phenotypes, and clinically interpretable outcomes. This shift does not require abandoning the complexity of traditional interventions. Rather, it requires studying that complexity with clearer definitions, stronger material control, and outcomes that remain meaningful across experimental and clinical contexts. Moving toward clinical application will require clearer intervention designs and better-defined materials, along with measures that reflect real functional changes, such as physical performance, metabolic status, and inflammation. Greater consistency and standardization of herbal formulations will be important to improve reproducibility between studies. This also means recognizing that mechanistic promise does not guarantee clinical relevance. Claims that extend beyond the level of evidence available risk weakening, rather than strengthening, the translational credibility of the field. Future work should move beyond descriptive antioxidant narratives toward experimentally constrained and functionally meaningful models of healthy aging.

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