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Beyond Skin Deep

A Biomarker Framework for Mushroom-Supported Healthy Ageing

KÄÄPÄ BIOTECH

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Prepared by KÄÄPÄ Biotech Ltd in partnership with MycoStories Ltd, the intelligence platform and network for fungi biotechnology. Scientific review by Heikki Kiheri, Chief Science Officer, KÄÄPÄ Biotech.

REGULATORY NOTE

This document is intended for informational and scientific reference purposes only. Any references to bioactive compounds are based on experimental and published research and do not constitute authorised health claims under EU Regulation (EC) No 1924/2006.

Prepared by KÄÄPÄ Biotech Ltd in partnership with MycoStories.

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Contents

1	Introduction: The Healthy Ageing Claim Crisis	04
2	What Healthy Ageing Actually Means: A Biomarker Framework	07
3	Chaga's Bioactive Profile: What We Know	11
4	Mapping Chaga to the Hallmarks: The Evidence	13
4.1	Oxidative Stress and Genomic Stability	15
4.2	Cellular Senescence and Skin Ageing	16
4.3	Mitochondrial Dysfunction and Stem Cell Exhaustion	18
4.4	Inflammaging and Immunomodulation	20
4.5	Glycation, Dysbiosis, and Metabolic Ageing	22
—	**Bioactive-to-Hallmark Evidence Map**	**24**
5	The Standardisation Imperative	26
6	Where the Evidence Needs to Go	28
7	Conclusion: From Claims to Mechanisms	31
	References	33

HOW TO READ THIS PAPER

Sections 2 to 4 establish the scientific framework and review the supporting evidence. Readers looking for the commercial implications rather than the underlying biology can focus on the key takeaway panels and the Bioactive-to-Hallmark Evidence Map on page 24.



01 Introduction: The Healthy Ageing Claim Crisis

The regulatory environment, the science of ageing, and the commercial vocabulary of healthspan are moving at different speeds. This section sets out the gap between them.

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The market for products promising to extend the healthy years of human life is expanding faster than the science underwriting them. Grand View Research values the global longevity and wellness pharmaceutical market at USD 63.4 billion in 2025, with a projection to USD 67.3 billion in 2026 and continued double-digit growth through the decade.[1] Functional mushroom ingredients sit within one of the most commercially dynamic segments of this category, marketed against an expanding vocabulary of healthspan, resilience, and biological age. The commercial confidence is striking. The evidentiary foundation underneath it is considerably less so.

That gap has now become a regulatory problem. On 30 April 2025, the Court of Justice of the European Union delivered its judgment in Case C-386/23 (Novel Nutriology), ruling that health claims relating to botanical substances cannot be used in commercial communication without prior authorisation, regardless of the European Commission's protracted suspension of its own evaluation process.[2] The judgment clarified that the prohibition under Article 10 of Regulation (EC) No 1924/2006 applies in full, leaving more than 2,000 pending botanical claim applications in regulatory limbo and tightening the practical scope of what European producers can say about their ingredients.[3] The ruling is not the closure of the conversation but its most consequential recent marker. The direction of regulatory travel is firmly toward higher evidentiary thresholds, not lower ones, and the functional mushroom ingredients sector is being pushed, whether or not it is ready, toward mechanism-based substantiation.

This paper takes Chaga (*Inonotus obliquus*) as its working example. Chaga is a useful test case for the argument that follows: it is one of the most commercially prominent functional mushroom ingredients, it carries a broad and chemically complex bioactive profile, and it now sits behind the first acute human data in the category. The framework set out here is general, but it is easier to follow, and easier to hold to an evidentiary standard, when it is traced through a single ingredient.

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1 Grand View Research. Longevity and Wellness Pharmaceutical Market, 2025–2033.

2 CJEU. Case C-386/23, judgment of 30 April 2025. ECLI:EU:C:2025:304.

3 Regulation (EC) No 1924/2006. OJ L 404, 30.12.2006.

IN BRIEF

A growing longevity market is meeting a higher regulatory bar: USD 63.4bn in 2025, while more than 2,000 botanical claim applications remain in regulatory limbo.

At precisely the moment the regulatory framework is becoming more demanding, the scientific framework for what healthy ageing actually means is becoming more rigorous. The López-Otín 2023 Hallmarks of Ageing review,[4] with its companion López-Otín and Kroemer 2021 Hallmarks of Health framework,[5] has crystallised a set of measurable biomarkers that describe both the mechanisms of biological decline and the mechanisms of preserved resilience. As recent work documents,[6] this framework has rapidly become the operating standard across geroscience and adjacent fields, and its biomarker-level language increasingly defines what credible mechanism-based substantiation looks like.

During an interview, Christine Fields of Applied Food Sciences noted that "clinical outcomes for dietary supplements are hard to evaluate because you are always working with healthy subjects, and it is difficult to discern the active from placebo when you do not have the deviations you would see in a disease state. Anti-ageing becomes more mechanistic because you can ask whether you are having an effect that will produce an outcome over time. That is why mechanism of action becomes really important."

The convergence of these forces shapes this paper's argument. The future of credible functional mushroom positioning for healthy ageing lies in moving from outcome claims, such as skin appearance, energy, or longevity, to mechanism mapping against measurable biomarkers, anchored simultaneously in the slowing of biological decline and the preservation of biological resilience and function.

An early illustration of what that language makes possible is a recent acute human proof-of-concept trial of a standardised Chaga extract, examined in detail in Section 4.3: within hours of a single dose, it produced a statistically significant increase in circulating stem cells, a directional signal of the kind that mechanism-based positioning now requires.

REFERENCES

4 López-Otín C, et al. Cell. 2023;186(2):243–278.

5 López-Otín C, Kroemer G. Cell. 2021;184(1):33–63.

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"Anti-ageing becomes more mechanistic because you can ask whether you are having an effect that will produce an outcome over time."

Christine Fields
Applied Food Sciences

02 What Healthy Ageing Actually Means: A Biomarker Framework

The World Health Organization defines healthy ageing as the process of developing and maintaining the functional ability that enables well-being in older age.[27] That definition, spanning sensory, cognitive, and mobility function, is the public-health anchor for the more granular, biological account developed below.

Healthy ageing, as the consumer market uses the term, refers to a constellation of visible and felt outcomes: smoother skin, steadier energy, sharper cognition, i.e. fewer of the small daily reminders that the body is declining. As geroscience uses the term, it refers to something more specific and considerably more measurable. Healthy ageing is the maintenance of physiological function across the lifespan, characterised at the molecular and cellular level by the progressive accumulation of damage that drives decline and by the adaptive responses that sustain resilience until, in time, they begin to fail. It is not the absence of disease, nor is it longevity in the simple sense of more years lived. It is the trajectory of biological function across those years, and that trajectory can be described in increasingly precise terms.



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TWO PERSPECTIVES

The consumer market describes healthy ageing through visible and felt outcomes. Geroscience defines it through measurable changes in physiological function over time. This paper follows the second approach.

The contemporary scientific standard for describing what fails in ageing biology is the Hallmarks of Ageing framework, originally proposed by López-Otín and colleagues in 2013[7] and substantially expanded in its 2023 revision.[4] The framework identifies twelve interconnected hallmarks conventionally organised into three categories. The primary hallmarks (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, and disabled macroautophagy) act as the upstream drivers of the process, initiating ageing through the cumulative molecular damage that the cell cannot fully repair. The antagonistic hallmarks (deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence) are double-edged: at low intensity they are protective, through mechanisms such as mitohormesis and senescence-mediated wound healing, but they become harmful when chronic or excessive. The integrative hallmarks (stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis) emerge as systemic consequences once the upstream damage overwhelms homeostatic capacity. The framework's value lies less in any single hallmark than in the explicit mapping of how they interact, and which of them are most amenable to measurement and intervention.

This is half of the picture. The complementary Hallmarks of Health framework, published by López-Otín and Kroemer in 2021,[5] describes what is preserved when biology is functioning rather than what fails when it is not. The framework organises eight hallmarks across three levels: spatial compartmentalisation (the integrity of biological barriers and the containment of local perturbations), maintenance of homeostasis over time (recycling and turnover, the integration of regulatory circuitries, and rhythmic oscillations), and the capacity for adequate responses to stress (homeostatic resilience, hormetic regulation, and repair and regeneration). Where the *Hallmarks of Ageing* describes the trajectory of decline, the *Hallmarks of Health* describes the architecture of resilience.

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4 López-Otín C, et al. Cell. 2023;186(2):243–278.

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Twelve hallmarks of decline.
Eight hallmarks of resilience.
One biology.

FIGURE 1

Two complementary frameworks, one biology: decline and resilience

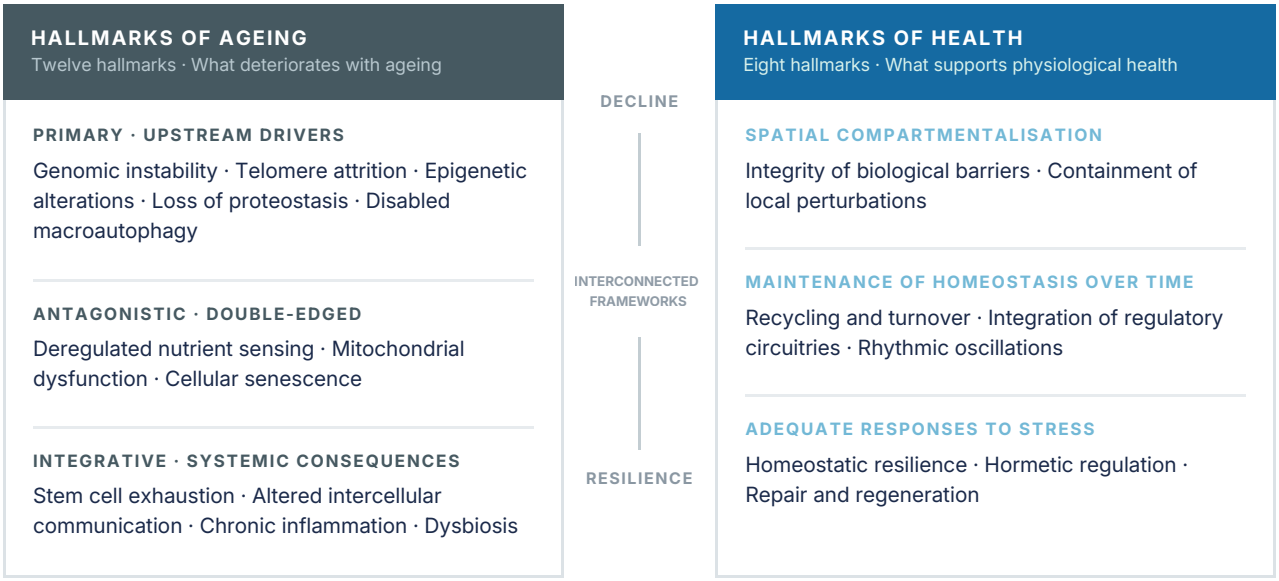


Figure 1. The Hallmarks of Ageing describe interconnected processes that contribute to biological decline, while the Hallmarks of Health describe organisational and adaptive features that help maintain physiological function.
Constructed from López-Otín et al. 2023 (ref 4) and López-Otín and Kroemer 2021 (ref 5).

FIGURE 2

Three tiers of biomarker

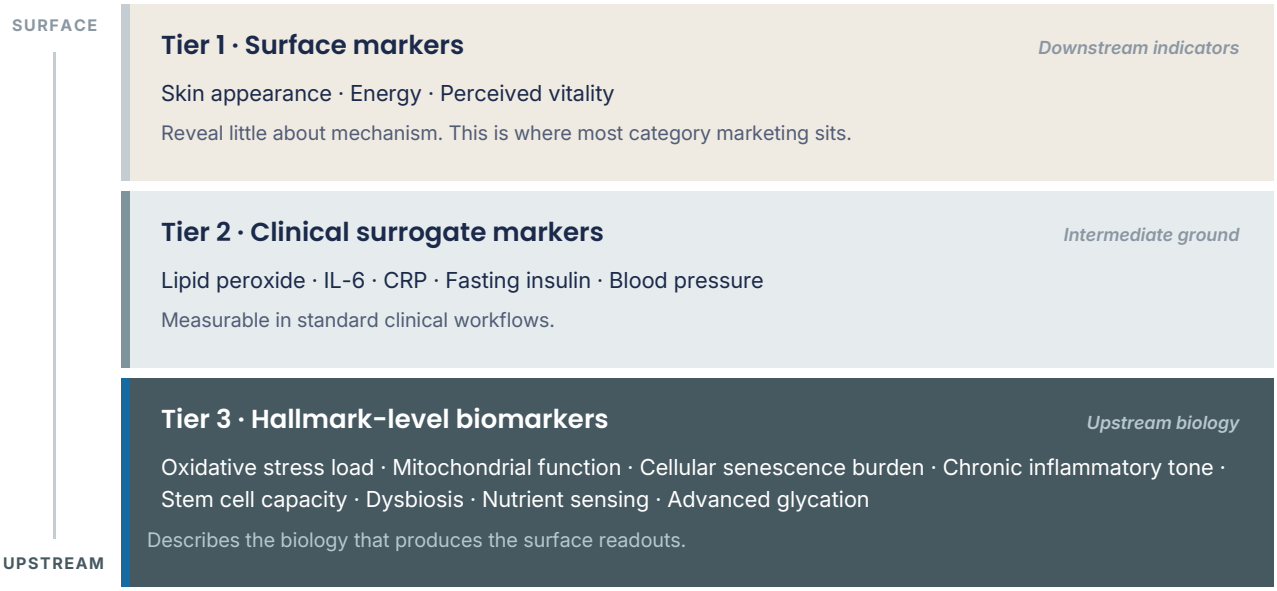


Figure 2. Tier definitions and marker lists as set out in Section 2; clinical surrogate tier per Franceschi et al. 2018 (ref 8).

The dual perspective is the conceptual core of this paper. Healthy ageing is not only about the slowing of biological decline; it is also about the active preservation of biological function. The two frameworks now function as a conceptual scaffold across geroscience and adjacent fields, operating as tightly connected counterparts rather than independent constructs.[6] This dual framing remains conspicuously underused in industry-facing functional ingredient content. That is a notable gap, given its direct relevance to the resilience and adaptive-stress positioning that defines the functional mushroom category.

COMMERCIAL READ

Resilience is already central to functional mushroom positioning. The opportunity now is to connect that promise to measurable biomarkers and mechanism-level evidence.

Within this framework, we distinguish three tiers of biomarker as an organising device for this paper. Surface markers, such as skin appearance, energy, and perceived vitality, are downstream indicators of biological state but reveal little about mechanisms. Hallmark-level biomarkers, including oxidative stress load, mitochondrial function, cellular senescence burden, chronic inflammatory tone, stem cell capacity, dysbiosis, nutrient sensing, and advanced glycation, sit upstream and describe the biology that produces the surface readouts. Clinical surrogate markers, including lipid peroxide, IL-6, CRP, fasting insulin, and blood pressure, occupy the intermediate ground and are measurable in standard clinical workflows. The work of inflammaging research, anchored in the Franceschi 2018 framework,[8] has demonstrated how powerfully these clinical surrogate markers, the intermediate tier between surface readouts and hallmark biology, can carry meaning when interpreted against the hallmark-level biology.

These distinctions structure the rest of this paper. Two parallel questions follow. Which hallmark-level biomarkers of ageing does Chaga (*Inonotus obliquus*) modulate? And which dimensions of biological resilience does Chaga help preserve? The answers to both, drawn from the available evidence, are the subject of Section 4.

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8 Franceschi C, et al. Nature Reviews Endocrinology. 2018;14(10):576–590.

KEY TAKEAWAYS

"Healthy ageing" can now be discussed through measurable changes in the body related to some target biomarkers, not only broad wellness claims. This gives us a clearer and more credible way to explain how Chaga may support healthy ageing and where further evidence is still needed.

03 Chaga's Bioactive Profile: What We Know

Inonotus obliquus is a parasitic fungus that grows primarily on living birch (*Betula*) species across northern boreal forests, producing the dense, charcoal-like sclerotium familiar from Northern European, Russian, and East Asian traditional medicine. Modern interest in Chaga sits considerably downstream of that history, in the analytical chemistry of its bioactive compounds and the mechanisms they engage. As recent comprehensive reviews summarise,[9,10] that chemistry resolves into four principal bioactive classes: polysaccharides, triterpenoids, polyphenols, and melanins.

First, polysaccharides are the most abundant class and the structural family most often associated with Chaga's mechanistic profile. The fraction is dominated by β-glucans, which underpin much of the immunomodulatory and metabolic activity attributed to the fungus, alongside related heteropolysaccharides and melanin-bound polysaccharide complexes. Second, triterpenoids are the second principal class, with the lanostane derivative inotodiol distinguished by its near-exclusive occurrence in *Inonotus obliquus* and its consequent value as an analytical marker. Inotodiol is supported in the triterpenoid fraction by betulinic acid and betulin, both of which Chaga concentrates from its birch host substrate during parasitic growth. Third, the polyphenol fraction, including phenolic acids and stilbenoids, contributes the majority of Chaga's antioxidant capacity in standard *in vitro* assays. Fourth, the melanins, a chemically distinct class, have a dual functional profile, contributing both antioxidant activity and prebiotic effects on the gut microbiota.



Sclerotium, culture and conk pieces. The analytical question is what carries across from one to the next.

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9 Camilleri E, et al. Heliyon. 2024;10(15):e35638.

10 Ern PTY, et al. Mycology. 2024;15(2):144–161.

This compositional breadth is the source of Chaga's appeal as a functional ingredient. It is also the source of its analytical problem. Bioactive content varies substantially between wild-harvested and cultivated material, between sclerotium (conk) and mycelium-based preparations, and between extraction methods. Aqueous, ethanolic, and dual-extraction protocols each yield materially different bioactive fingerprints, with polysaccharides recovered preferentially in water and triterpenoids in ethanol. Without standardised characterisation of the underlying ingredient, cross-study comparison becomes difficult and mechanism-level claims become unmoored from the material that supposedly produces them. Work evaluating inotodiol's toxicity and anti-inflammatory activity in an animal model[11] illustrates the kind of compound-specific characterisation that mechanism-level discussion requires.

The bioactive complexity is real, and it is the precondition for everything that follows. Section 4 maps the evidence on what these classes have been shown to do across the hallmarks of ageing.

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11 Nguyen TMN, et al. Molecules. 2022;27(15):4704.

FIGURE 3

From bioactive class to hallmark territory

BIOACTIVE CLASS	WHAT THE LITERATURE ATTRIBUTES TO IT	HALLMARK TERRITORY IN SECTION 4
Polysaccharides β-glucans, heteropolysaccharides, melanin-bound complexes	Most abundant class; underpins much of the immunomodulatory and metabolic activity attributed to the fungus	Cellular senescence (4.2) · Inflammaging (4.4) · Nutrient sensing, dysbiosis and glycation (4.5)
Triterpenoids Inotodiol, betulinic acid, betulin	Inotodiol near-exclusive to *Inonotus obliquus*, hence its value as an analytical marker	Inflammaging (4.4), through selective mast cell and microglial mechanisms
Polyphenols Phenolic acids, stilbenoids	Majority of Chaga's antioxidant capacity in standard *in vitro* assays	Oxidative stress and genomic stability (4.1)
Melanins Chemically distinct class	Dual profile: antioxidant activity and prebiotic effects on the gut microbiota	Oxidative stress (4.1) · Dysbiosis (4.5)

Figure 3. Bioactive classes and compounds are based on refs 9 and 10; reported biological activities and hallmark mapping reflect the evidence reviewed in Sections 3 and 4. Colour indicates the highest level of evidence identified for each bioactive class: blue for human clinical evidence and grey for preclinical evidence.

KEY TAKEAWAYS

Chaga's activity comes from four bioactive classes, of which inotodiol is near-unique to Chaga, which makes it a natural standardisation marker. The commercial point is simple: what can be measured can be standardised, and what can be standardised can be sold with confidence.



04 Mapping Chaga to the Hallmarks: The Evidence

The mapping is intended as an intervention menu rather than a catalogue of associations: for each hallmark, the operative question is which Chaga bioactive class acts on it, and how directly.

IN THIS SECTION

4.1	Oxidative Stress and Genomic Stability
4.2	Cellular Senescence and Skin Ageing
4.3	Mitochondrial Dysfunction and Stem Cell Exhaustion
4.4	Inflammaging and Immunomodulation
4.5	Glycation, Dysbiosis, and Metabolic Ageing
—	**Bioactive-to-Hallmark Evidence Map**

This section maps the available evidence on Chaga's bioactive effects against the Hallmarks of Ageing framework, organising the discussion around the hallmarks where the literature is most concentrated rather than attempting an exhaustive sweep of all twelve. Two hallmarks, epigenetic alterations and telomere attrition, fall outside the current Chaga evidence base entirely and are taken up in Section 6 as priorities for human research. A third, disabled macroautophagy, is engaged indirectly through the autophagy and mitophagy mechanisms discussed below but has not been measured directly in humans, where autophagic flux is the obvious next endpoint. The map is summarised in a structured table at the close of the section, presented as the paper's central reference for product development and scientific affairs use. Where the Hallmarks of Ageing evidence aligns cleanly with constructs in the complementary Hallmarks of Health framework, particularly homeostatic resilience, hormetic regulation, and repair and regeneration, those connections are flagged within the relevant sub-sections.

COVERAGE AT A GLANCE

Nine of the twelve hallmarks are represented in the current Chaga evidence base. Two remain unsupported, and one is engaged indirectly. Figure 4 shows the full picture.

FIGURE 4

Chaga evidence across the twelve hallmarks of ageing

HALLMARK	CATEGORY	CHAGA EVIDENCE	WHERE
Genomic instability	Primary	Human clinical and preclinical	4.1
Telomere attrition	Primary	No evidence: Section 6 priority	6
Epigenetic alterations	Primary	No evidence: Section 6 priority	6
Loss of proteostasis	Primary	Preclinical, *in vitro*	Map
Disabled macroautophagy	Primary	Indirect, via autophagy and mitophagy	4.2, 4.3
Deregulated nutrient sensing	Antagonistic	Preclinical, *in vivo*	4.5
Mitochondrial dysfunction	Antagonistic	**Human clinical, acute**	4.3
Cellular senescence	Antagonistic	Preclinical, *in vitro* and *in vivo*	4.2
Stem cell exhaustion	Integrative	**Human clinical, acute**	4.3
Altered intercellular communication	Integrative	Not addressed in this review	—
Chronic inflammation	Integrative	Preclinical, *in vivo*	4.4
Dysbiosis	Integrative	Preclinical, *in vitro* and *in vivo*	4.5

Human clinical and preclinical
Preclinical, *in vitro*
No direct evidence identified or not addressed in this review
Preclinical, *in vivo*
Indirect evidence

Figure 4. Hallmark set and categories per López-Otín et al. 2023 (ref 4). Evidence status as assessed in Sections 4.1 to 4.5 and the Evidence Map; gaps as identified in Section 6.

4.1 Oxidative Stress and Genomic Stability

Oxidative stress is the most upstream of the ageing-related biological processes, and the one with the broadest downstream consequences. Free radical accumulation drives macromolecular damage to lipids, proteins, and DNA; the antioxidant response systems that contain this damage decline in capacity with age; and the resulting oxidative burden contributes mechanistically to most other hallmarks in the framework, from mitochondrial dysfunction to cellular senescence to chronic inflammation. It is also the hallmark for which the Chaga evidence base is deepest.

The direct human evidence begins with a randomised controlled trial conducted by Yonei and colleagues in 2007, in which 60 healthy adults were administered Chaga extract at either 5 ml or 15 ml per day over 8 weeks, and observed a significant 7.89 percent reduction in serum lipid peroxide in the 5 ml group, accompanied by significant reductions in systolic and diastolic blood pressure.[12] The result is mechanistically coherent but the dose-response was equivocal, with the higher dose producing non-superior effects on the primary endpoint, and the study has not been replicated at scale. The preclinical evidence is more consistent. In a scopolamine-induced mouse model of cognitive dysfunction and brain oxidative stress, a Chaga methanolic extract reduced brain malondialdehyde and restored brain glutathione and superoxide dismutase levels, oxidative stress and antioxidant-defence markers.[13] In human skin fibroblasts, a Chaga water extract reduced both intracellular reactive oxygen species and damage to cellular lipids under induced oxidative stress.[14] A comprehensive review summarises supporting *in vitro* and *in vivo* evidence across multiple extract types.[9]



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12 Yonei Y, et al. Anti-Aging Medicine. 2007;4(1):1–10.

13 Giridharan VV, et al. Food & Function. 2011;2:320.

14 Yun JS, et al. Molecules and Cells. 2011;31(5):423–430.

The defensible reading of this body of work is that Chaga modulates oxidative stress through mechanistically credible pathways in cells, in animal models, and at least once in a controlled human study. That this oxidative modulation translates into measurable healthspan outcomes in humans has not yet been adequately tested. Within the Hallmarks of Health framework, this category of evidence sits most closely with the constructs of homeostatic resilience and hormetic regulation, where the relevant question is not whether oxidative stress is reduced but whether the system's adaptive capacity to manage it is preserved.

The question is not simply whether oxidative stress is reduced, but whether the body's adaptive capacity to manage it is preserved.

KEY TAKEAWAYS · 4.1

Chaga has been studied most for its antioxidant potential. In a human study, it reduced markers of oxidative damage (lipid peroxide), which occurs when harmful molecules damage cells and tissues. The study also reported a reduction in blood pressure. These outcomes are consistent with findings from cell and animal studies, which provide further evidence of Chaga's antioxidant potential.

4.2 Cellular Senescence and Skin Ageing

Cellular senescence is the hallmark on which the paper's title rests, and the one where the mechanistic case for treating skin ageing as a window onto systemic biology is most directly made. Senescent cells accumulate with age across tissues, exit the cell cycle, and acquire a secretory phenotype that releases inflammatory cytokines, matrix-degrading enzymes, and growth factors into surrounding tissue. The result is a low-grade inflammatory and proteolytic environment that drives both visible skin ageing and systemic inflammaging. Critically, this relationship is causal rather than correlative. Victorelli and colleagues (2019) demonstrated in 3D human-skin culture that senescent melanocytes drive surrounding skin ageing through paracrine telomere dysfunction, and that pharmacological elimination of those senescent cells restored keratinocyte proliferation and epidermal thickness.[15] Skin ageing is not a separate cosmetic biology layered over systemic ageing; it is the same biology, visible at the surface.

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15 Victorelli S, et al. The EMBO Journal. 2019;38(23):e101982.

Three Chaga-specific studies form the mechanistic spine of the evidence base. A Chaga water extract suppressed premature senescence in human skin fibroblasts under oxidative stress and reduced extracellular matrix degrading enzymes, MMP-1 and MMP-9. This was translated *in vivo* in hairless mice receiving topical Chaga extract as suppression of UV-induced skin thickening and wrinkle formation.[14] In UVB-stressed keratinocytes, Chaga polysaccharides showed anti-photoageing effects through suppressing the canonical senescence and apoptosis biomarkers p16, p21, and p53, through modulating autophagy, improving antioxidant defence and preventing ROS generation.[16] Further work, *in vitro* and *in vivo*, showed that Chaga polysaccharides prevent UVB-induced photodamage via the Sirt3-activated Foxo3a/PINK1-Parkin mitophagy pathway, connecting senescence biology to this central pathway in mitochondrial quality control.[17]

The senescence process causally drives skin ageing, and the Chaga evidence shows that the bioactives modulate the exact biomarkers and pathways on which that process depends. The mechanisms that drive skin photoageing are continuous with those that drive systemic decline, and the bioactive class that addresses the visible readout is also the class that engages the underlying mechanism. Surface treatments address symptoms. Internal interventions address mechanisms.

Within the Hallmarks of Health framework, this maps onto the construct of repair and regeneration, with the mitophagy mechanism[17] additionally aligning with recycling and turnover. Chaga both slows the senescence-driven hallmark of ageing and supports the repair-and-regeneration architecture of biological resilience.

The honest limitation is that all three Chaga-specific studies are *in vitro* or in animal models. No human randomised controlled trial has yet measured senescence biomarkers in response to Chaga supplementation. A trial that did so, ideally measuring p16 and p21 alongside senescence-associated secretory phenotype (SASP) cytokines in a powered adult population, would constitute the highest-value next study the field could undertake.

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KEY BIOMARKERS AND PATHWAYS

p16 · p21 · p53
MMP-1 · MMP-9
ROS
Sirt3 / Foxo3a / PINK1-Parkin

KEY TAKEAWAYS · 4.2

Some of the same biological processes involved in visible skin ageing also contribute to systemic ageing. Early cell and animal research suggests that Chaga may help protect against these processes, and human clinical evidence is warranted.

4.3 Mitochondrial Dysfunction and Stem Cell Exhaustion

Mitochondrial dysfunction and stem cell exhaustion are the two hallmarks that together constitute the regenerative engine of ageing biology. Mitochondrial decline drives age-related energy deficit, increased reactive oxygen species production, and impaired capacity to respond to metabolic and oxidative stress, with consequences that propagate across most other hallmarks. Stem cell exhaustion limits the regenerative reserves that tissues draw on to repair accumulated damage. Where the senescence biology of Section 4.2 describes how tissues deteriorate, this pair describes the machinery on which their restoration depends, and it is the territory in which Chaga's evidence speaks most directly to active resilience rather than the mere slowing of decline.



Strain work at KÄÄPÄ. Defined material is the precondition for the human data that follows.

The Chaga evidence here is anchored by a recent acute human proof-of-concept study. Jensen and colleagues (2026) administered KÄÄPÄ Biotech's ***NordRelease®*** organic Chaga extract powder, supplied through KÄÄPÄ Biotech's strategic North American partner Applied Food Sciences (AFS), in a randomised, double-blind, placebo-controlled crossover enrolling four healthy adults.[18] The tested material was an extract of pure Chaga sclerotium, named MycoThrive Chaga in the source study. Blood was sampled at baseline and at one, two, and three hours after a single dose, with each participant's circadian variation captured on the placebo visit and subtracted from the active condition. Chaga intake produced a 36 percent average increase in circulating endothelial stem cells against placebo, reaching statistical significance at two hours, alongside a significant rise in circulating pluripotential stem cells at one hour. It also supported higher mitochondrial volumes in lymphocytes under *ex vivo* oxidative stress at two and three hours, and modulated mitochondrial membrane potential under oxidative and inflammatory stress. The Sirt3-activated Foxo3a/PINK1-Parkin mitophagy pathway mentioned above might be the plausible quality-control mechanism underpinning these functional effects.[17]

What distinguishes this profile is its speed. The functional shifts appear within one to three hours of a single dose, a time-course that, as Christine Fields notes, is uncommon among botanicals and even among many drugs. The pattern is better read as adaptive than as simply suppressive. In her account, Chaga “acts as a dynamic shield with a biphasic response to inflammatory stress”, so that the relevant story “is not just its mitochondrial modulation, it is adaptive cellular resilience.” That biphasic, context-dependent behaviour maps directly onto the hormetic regulation construct in the Hallmarks of Health framework, where the measure of health is not the elimination of stress but the calibration of the response to it.

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17 Lin P, et al. Food Science and Human Wellness. 2025;14:9250216.

18 Jensen GS, et al. Functional Food Science. 2026;6(1):27–50.

“acts as a dynamic shield with a biphasic response to inflammatory stress”

“is not just its mitochondrial modulation, it is adaptive cellular resilience.”

Christine Fields
Applied Food Sciences

While the study was designed as a proof-of-concept trial with a small n=4 and not powered for definitive efficacy conclusions, the observed biological responses provide valuable early evidence supporting further clinical investigation. Where Chaga's signal is the clearest is in the acute mobilisation of regenerative cells into the blood circulation, the process Fields describes as homing, an anti-ageing action on damaged tissue and repair. Within the Hallmarks of Health framework, mitochondrial resilience aligns with homeostatic resilience, mitophagy with recycling and turnover, and stem cell mobilisation with repair and regeneration. This is the hallmark territory in which Chaga's potential to support active resilience would be most directly demonstrated, and the gap between proof-of-concept and powered evidence is the gap the next phase of research has the opportunity to close.

HUMAN PROOF-OF-CONCEPT

+36%

Average increase in circulating endothelial stem cells versus placebo following a single dose, reaching statistical significance at two hours. Jensen et al., 2026

KEY TAKEAWAYS · 4.3

A single dose of ***NordRelease®*** Chaga produced measurable effects within one to three hours, most clearly rapid mobilisation of regenerative stem cells and support for mitochondrial resilience under stress. Christine Fields of Applied Food Sciences (AFS) describes this as a “dynamic shield”, an adaptive response rather than simple suppression. This is the flagship human proof-of-concept.

4.4 Inflammaging and Immunomodulation

Chronic low-grade inflammation, captured in the geroscience literature as inflammaging, is the connecting thread between most other hallmarks. It drives cellular senescence, contributes to mitochondrial damage, and shapes the tissue environment in which other ageing processes either accelerate or are contained. The framework established by Franceschi and colleagues (2018) identifies IL-6, CRP, and TNF-α as the canonical inflammaging biomarkers.[8] It is worth reading the immunomodulation literature in this light: the immune signals long measured for Chaga are in large part a downstream readout of the regenerative activity described in Section 4.3, the homing, stem cell mobilisation, and mitochondrial repair that follow a challenge, rather than a separate property of the fungus.

REFERENCES

8 Franceschi C, et al. Nature Reviews Endocrinology. 2018;14(10):576–590.

The Chaga evidence spans multiple bioactive classes engaging the hallmark through distinct mechanisms. Chaga polysaccharides modulated a limited panel of inflammatory cytokines alongside glycaemic improvement in streptozotocin-diabetic mouse model, consistent with a polysaccharide contribution to cytokine regulation.[19] Inotodiol selectively suppressed mast cell function in a food allergy mouse model, demonstrating a triterpenoid-specific mechanism distinct from the crude Chaga extract that affected multiple immune responses.[20] In an Alzheimer's mouse model, an inotodiol-enriched ethanol extract of Chaga (INO10) attenuated neuroinflammation, and showed anti-inflammatory effect in LPS-stimulated microglial cells through suppressing IL-1β, IL-6, and TNF-α; it is worth noting that this was a disease-specific neuroinflammation model, and the mechanism it points to may extend to other immunomodulatory functions.[21] A peer-reviewed study reported that an orally administered aqueous Chaga extract ameliorated acute DSS-induced colitis in mice and has anti-inflammatory effect, suppressing histological damage and reducing pro-inflammatory signalling.[22]

Distinct Chaga bioactive classes engage inflammaging through distinct mechanisms: polysaccharides drive broad cytokine modulation, while triterpenoids drive selective cell-specific mechanisms. The inflammaging-specific evidence remains preclinical: the role of Chaga in immunomodulation and its longer-term effects on low-grade inflammation still need to be established in humans, and warrant dedicated clinical investigation. Ideally, future *in vivo* work would measure senescence-associated markers alongside inflammatory markers as parallel readouts. Within the Hallmarks of Health framework, this evidence maps onto containment of local perturbations and homeostatic resilience, the two constructs concerned with keeping inflammatory responses spatially bounded and temporally appropriate.

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INFLAMMAGING MARKERS

IL-6 · CRP · TNF-α

Canonical markers used in the Franceschi et al. 2018 inflammaging framework.

Different bioactive classes act through different mechanisms, creating opportunities for more targeted formulation strategies.

KEY TAKEAWAYS · 4.4

Inflammaging is the persistent, low-level inflammation that tends to increase with age and can contribute to age-related decline. Early research suggests that different compounds in Chaga may help regulate this process in different ways. Triterpenoids appear to target specific inflammatory pathways, while polysaccharides may have a broader effect on the immune response. These findings are still preclinical and await human confirmation.

4.5 Glycation, Dysbiosis, and Metabolic Ageing

Three further hallmarks warrant inclusion despite their evidence base being the least developed within the Chaga literature. Advanced glycation, gut microbiome dysbiosis, and deregulated nutrient sensing are each biologically important for healthy ageing, and each is supported by mechanistically credible but preliminary work that points to where the next decade of Chaga research will need to concentrate.

On advanced glycation, a Chaga polysaccharide has been shown to protect skin fibroblasts against methylglyoxal-induced glycation, which is the clearest bridge in the current Chaga literature between advanced glycation end products (AGE) -formation mechanisms and skin-ageing readouts.[23] On dysbiosis, Chaga polysaccharide altered gut microbiota composition and diversity towards a healthier profile in a chronic pancreatitis mouse model,[24] with additional support for the prebiotic and bifidogenic activity of Chaga-derived melanins.[25] Moreover, Chaga polysaccharide reduced fasting plasma glucose and improved glycometabolism in a STZ-diabetic mouse model,[19] and metabolomic profiling identified differential metabolites including aromatic amino acids and arachidonic acid which could serve as additional mechanistic regulation points in relation to glucose homeostasis.[26]

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The evidence is suggestive rather than established. The species, the disease models, and the dose-response gaps are real limitations, and translation from disease-model preclinical work to healthy ageing in humans remains difficult, as the broader literature on preclinical-to-clinical translation makes clear; more studies in healthy individuals are needed. This is the hallmark territory in which Chaga research has the most to gain from rigorous human investigation.

KEY TAKEAWAYS · 4.5

Preliminary evidence links Chaga to reduced glycation, a healthier gut microbiota, and better glucose metabolism, three mechanisms increasingly tied to healthy ageing. These are early, mostly in vivo signals, and are best framed as directions for future research rather than claims.



Bioactive-to-Hallmark Evidence Map

The evidence presented across the five sub-sections above is summarised below. This table is the central structural reference of the paper and the basis on which the following standardisation argument rests. A strength-of-evidence column has been added to make the evidence hierarchy explicit for industry readers.

Bioactive-to-Hallmark Evidence Map

1 of 2

HALLMARK OF AGEING	CHAGA BIOACTIVE CLASS	MECHANISM	BEST EVIDENCE	STRENGTH OF EVIDENCE
Mitochondrial dysfunction	Whole extract, inotodiol-standardised	Restoration of mitochondrial volume and membrane potential under stress; mitophagy regulation	Jensen 2026; Lin 2025	**Human clinical (acute, proof-of-concept) + preclinical**
Stem cell exhaustion	Whole extract, inotodiol-standardised	Acute mobilisation of endothelial progenitor cells	Jensen 2026	**Human clinical (acute, proof-of-concept)**
Oxidative stress and genomic stability	Polysaccharides, phenolics, melanins	ROS scavenging; lipid peroxidation reduction; SOD and GSH restoration	Yonei 2007; Giridharan 2011; Yun 2011	**Human clinical + preclinical**
Cellular senescence	Polysaccharides	Suppression of p16, p21, p53 in stressed fibroblasts and keratinocytes; MMP-1 and MMP-9 reduction	Yun 2011; Lin 2023	**Preclinical (*in vitro* and *in vivo*)**
Dysbiosis	Polysaccharides, melanins	Gut microbiota modulation; bifidogenic effects	Hu 2017; Burmasova 2019	**Preclinical (*in vitro* and *in vivo*)**

EVIDENCE TIERS

Human clinical denotes the acute proof-of-concept trial in healthy adults; preclinical denotes non-human evidence and spans both in vitro and in vivo (animal) studies.

Human clinical Preclinical, *in vivo* Preclinical, *in vitro*

Table continues overleaf

Bioactive-to-Hallmark Evidence Map

2 of 2, continued

HALLMARK OF AGEING	CHAGA BIOACTIVE CLASS	MECHANISM	BEST EVIDENCE	STRENGTH OF EVIDENCE
Chronic inflammation (inflammaging)	Inotodiol, betulinic acid, β-glucans	Suppression of TNF-α, IL-6, IL-1β; selective mast cell inhibition	Ban 2025; Nguyen 2020 and 2022	**Preclinical (*in vivo*)**
Deregulated nutrient sensing	Polysaccharides	Glycaemic control; α-amylase and α-glucosidase inhibition	Wang 2017; Xu 2021	**Preclinical (*in vivo*)**
Loss of proteostasis	Whole extract	Nrf2/HO-1 activation; oxidative stress, inflammation and autophagy regulation	Lin 2023	**Preclinical (*in vitro*)**
Advanced glycation (AGEs)	Polysaccharides	Methylglyoxal-induced glycation inhibition in fibroblasts	Chen 2024	**Preclinical (*in vitro*)**

READING THE MAP

Rows are ordered by strength of evidence, with human clinical evidence first. The accent colour indicates the evidence tier: blue for human clinical evidence, grey for preclinical in vivo evidence, and pale grey for in vitro evidence. Two hallmarks, telomere attrition and epigenetic alterations, are absent because no Chaga evidence exists for them; they are taken up in Section 6.



05 The Standardisation Imperative

Every mechanism mapped in Section 4 sits behind a question that the evidence cannot answer on its own: what was in the material actually tested? Chaga harvested from a Finnish birch forest is not chemically identical to Chaga harvested in Siberia, cultivated Chaga is not chemically identical to wild-harvested material, sclerotium preparations differ materially from mycelium biomass, and the extraction method (aqueous, ethanolic, or dual-extraction) determines which bioactive classes are recovered in what proportions.[9] The practical consequence is that two studies reporting on "Chaga" may be reporting on materials whose bioactive fingerprints differ significantly, in composition as well as concentration.

This is the analytical foundation problem underneath the entire functional mushroom category, and it begins before biology enters the picture. As Christine Fields of Applied Food Sciences puts it: "Nobody has done an analysis on the composition of matter of what they are studying. When you say Chaga is good for this, or Lion's Mane is good for that, no one has identified what that Lion's Mane actually is, the active level of triterpenoids, the level of β-glucans." The difficulty is compounded by the immaturity of the assays themselves: β-glucans from yeast are structurally close to those from mushrooms yet do not share their clinical behaviour, and standard measurement kits do not cleanly distinguish the two.



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9 Camilleri E, et al. Heliyon. 2024;10(15):e35638.

"Nobody has done an analysis on the composition of matter of what they are studying. When you say Chaga is good for this, or Lion's Mane is good for that, no one has identified what that Lion's Mane actually is."

Christine Fields
Applied Food Sciences

Without standardised characterisation of the underlying ingredient, cross-study comparison becomes unreliable, dose-response relationships cannot be established, and biomarker-level claims cannot be substantiated regardless of the quality of the underlying biology. Work evaluating inotodiol's toxicity and anti-inflammatory efficacy in an animal model[11] illustrates the kind of compound-specific safety characterisation that a deliberate analytical foundation requires. What becomes measurable when that foundation is in place is shown by a recent proof-of-concept trial of KÄÄPÄ's ***NordRelease®*** organic Chaga extract and tested through KÄÄPÄ's US distribution partner Applied Food Sciences.[18] With the material specified, the biology became legible: statistically significant acute mobilisation of circulating stem cells and modulation of mitochondrial function under oxidative stress, observed in healthy adults within hours of a single dose.

This need was set out in KÄÄPÄ's earlier white paper, *Measuring What Matters*, which called for species-specific standards that align bioactive characterisation with the benefits consumers are seeking.

KÄÄPÄ Biotech is among the few producers responding to this requirement at the level the evidence now demands. The company's vertically integrated forest cultivation network in Finland provides supply consistency upstream of the extraction process; its finished extracts are standardised to defined inotodiol and β-glucan content ranges; and its ***NordRelease®*** extraction methodology has been developed to preserve the full bioactive profile within EU regulatory constraints on solvent residues and process integrity. The analytical work underlying these specifications, led by Chief Science Officer Heikki Kiheri and his team, is what allows mechanism-level claims to be tied to a defined material rather than to the species in the abstract.

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WHAT STANDARDISATION ENABLES

- Comparable studies
- Reliable dose-response assessment
- More defensible biomarker-level claims
- Evidence tied to a defined material, not the species in the abstract

KEY TAKEAWAYS · 5

Not all Chaga extracts are the same. Their composition can vary depending on the raw material and extraction process. ***NordRelease®*** Chaga is standardised to a defined level of inotodiol content, which is what allowed the human results to be tied to a specific, traceable ingredient.

The wider point is structural. The biology mapped in the previous section is of no use to a research programme, a regulator, or a buyer if the material that produced it cannot be specified. The producers that solve the standardisation problem are the producers that can credibly enter the biomarker-level evidence conversation, and the producers that can do so under EU regulatory constraints are the producers most likely to define what credible mechanism-based substantiation looks like in the European functional ingredient market.

SECTION 5, CONTINUED

06 Where the Evidence Needs to Go

The evidence base for Chaga and healthy ageing is broader than its critics suggest and shallower than its advocates claim. The honest position is the one Christine Fields shares: the cellular senescence, advanced glycation, and dysbiosis signals "are all there in the evidence, but it relies on animal models and *in vivo* data rather than human clinical evidence." Three specific gaps define where credible research investment would have the highest return over the next decade.

The first is powered human trials measuring multiple hallmark-level biomarkers in parallel. The studies reviewed in Section 4 typically measure one or two endpoints in isolation. Geroscience has moved decisively toward multi-omics and multi-biomarker panel designs,[4] because ageing biology is integrative rather than sequential, and the panel now has well-validated components: DNA methylation and epigenetic-clock measures for epigenetic alterations, autophagic flux read as the LC3-I to LC3-II ratio in blood cells, and the senescence markers p16, p21, and the SASP cytokine signature.

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4 López-Otín C, et al. Cell. 2023;186(2):243–278.

"They are all there in the evidence, but it relies on animal models and in vivo data rather than human clinical evidence."

Christine Fields
Applied Food Sciences

A practical sequence follows. *In vitro* work can extend the existing cell-based evidence to the SASP panel and to autophagic flux. An acute clinical study can repeat the proof-of-concept design in a target ageing population, adding oxidative-stress markers and, where signals are hard to resolve in healthy volunteers, a controlled stressor such as an exercise challenge to elicit a measurable response. A long-term study, of eight to twelve weeks in an older cohort, can then track mitochondrial resilience, oxidative stress, and cytokine profiles alongside functional ability and well-being (spanning cognition, mobility, and quality of life). A programme of this shape would generate evidence of a different order to anything currently available, and would directly reach the epigenetic and telomere hallmarks the current Chaga literature does not yet touch.

The second gap is standardised extract characterisation enabling direct cross-study comparison. The bioactive variability between Chaga preparations is large enough to render cross-study synthesis unreliable.[9] Without standardised reporting of β-glucan content, inotodiol concentration, extraction method, and substrate provenance, meta-analysis remains structurally impossible regardless of how many individual studies accumulate.

The third gap is mechanism differentiation by bioactive class within the whole-Chaga matrix. The polysaccharide, triterpenoid, and melanin fractions engage distinct biological pathways: metabolic and immunomodulatory effects, senescence and selective modulation of cellular activity, and prebiotic and antioxidant activity, respectively. Until formulation can target specific outcomes by bioactive class, health positioning will remain generic and evidence will remain difficult to interpret.



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THREE EVIDENCE GAPS

01 Powered human trials measuring multiple biomarkers in parallel

02 Standardised extract characterisation to enable cross-study comparison

03 Clearer differentiation of mechanisms by bioactive class

Addressing all three gaps requires a dual measurement framework: trials that simultaneously track the slowing of biological decline against the Hallmarks of Ageing and the preservation of biological resilience against the Hallmarks of Health. The producers best positioned to lead this work are those whose standardisation infrastructure already meets the analytical prerequisites the research demands. The credibility of the functional mushroom category in the next decade will be defined largely by those who choose to make that investment.

Track decline and resilience in the same trial, or the framework is only half used.



KEY TAKEAWAYS · 6

The research priorities are powered human trials measuring several biomarkers at once, standardised extract characterisation, and separating effects by bioactive class. Producers with the standardisation infrastructure to lead that work will set the terms of the category.

07 Conclusion: From Claims to Mechanisms

The April 2025 CJEU ruling that closed the botanical claims workaround[2] was widely read as a constraint on the functional mushroom category. It is more accurately read as a selection pressure. The producers that treated health positioning as a vocabulary problem will find the new environment difficult. The producers that have been building the evidentiary infrastructure underneath their positioning will find it clarifying.

The convergence of the Hallmarks of Ageing and Hallmarks of Health frameworks gives the sector something it has not previously had: a defensible scientific language that describes both the slowing of biological decline and the active preservation of biological resilience. That dual perspective is not yet widely used in functional mushroom industry content. It is, for precisely that reason, one of the most significant differentiators available to producers willing to adopt it seriously.

There is a biological through-line beneath the regulatory one. The three hallmarks at the centre of the paper's resilience hypothesis, chronic inflammation, mitochondrial dysfunction, and stem cell exhaustion, are not independent targets but part of an interlinked system, and the most promising hypothesis the next decade of research can test is that addressing them in tandem, rather than one at a time, is what produces a durable effect on healthy ageing. A strategy built around well-characterised fungi is one credible way to act on all three at once. That is a hypothesis rather than a settled claim, but it is the right organising idea for the research the category now needs.

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IN CLOSING

The producers that invest in standardised ingredients, biomarker-level human research, and credible academic partnerships will define what the functional mushroom ingredients category means to buyers, regulators, and consumers over the next decade. Science is available. The framework is in place. The question is who chooses to speak that language, and who can demonstrate they have earned the right to do so. KÄÄPÄ Biotech's investment in ***NordRelease®*** standardisation and the research programme built on it represents one answer to that question.

THE THREE-PART HYPOTHESIS

Chronic inflammation

Preclinical *in vivo*. Polysaccharides broadly, triterpenoids selectively. Section 4.4.

Mitochondrial dysfunction

Acute human proof-of-concept. Volume and membrane potential under stress. Section 4.3.

Stem cell exhaustion

Acute human proof-of-concept. +36 percent circulating endothelial stem cells. Section 4.3.

Not independent targets but a single interlinked system. The hypothesis the next decade can test is whether addressing them in tandem produces a durable effect on healthy ageing.

REGULATORY NOTE

This document is intended for informational and scientific reference purposes only. Any references to bioactive compounds are based on experimental and published research and do not constitute authorised health claims under EU Regulation (EC) No 1924/2006.

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Beyond Skin Deep

A Biomarker Framework for Mushroom-Supported Healthy Ageing

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