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Clinical Evaluation of an AKG-PQQ-Agaricus bisporus Composition for Mitochondrial Function and Healthy Aging

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Abstract

Background: A formulation centered on alpha-ketoglutarate (AKG), pyrroloquinoline quinone disodium salt (PQQ), and Agaricus bisporus extract is intended to support mitochondrial resilience through complementary energetic, redox, and cytoprotective mechanisms. Objective: We evaluated the translational and clinical relevance of this combination by integrating our formulation-level comparison data with published human clinical evidence for AKG-related interventions, PQQ, and ergothioneine-rich mushroom or ergothioneine supplementation. Methods: We retained the original composition framework and in vitro comparison of the study formulation and matched them with publicly available human intervention studies identified from primary biomedical literature. Results: In our formulation comparison, the index composition was associated with higher relative mitochondrial membrane potential and lower mitochondrial reactive oxygen species than the comparator that omitted Agaricus bisporus extract. Across human studies, PQQ showed the most mature evidence base, with randomized trials reporting improvements in inflammatory markers, selected cognitive domains, muscle strength, and some indices related to mitochondrial biogenesis. Ergothioneine-containing mushroom and purified ergothioneine trials demonstrated human bioavailability, safety, and signals in cognition, sleep-related outcomes, and skin hydration. Direct completed efficacy trials for AKG in healthy-aging settings remain limited, although active randomized trial programs indicate strong translational interest. Conclusions: The combined evidence supports a credible mitochondria-focused rationale for the AKG-PQQ-Agaricus bisporus composition, but a registered head-to-head randomized trial of the full formulation is still needed before superiority claims can be made.

Keywords

AKG; PQQ; mitochondrial function; healthy aging; ergothioneine; Agaricus bisporus; clinical evidence.

1. Introduction

Mitochondrial dysfunction is one of the most reproducible biological features of aging. A decline in oxidative phosphorylation, reduced redox buffering capacity, impaired mitochondrial quality control, and progressive accumulation of reactive oxygen species can together contribute to fatigue, slower recovery, cognitive decline, and loss of tissue resilience. For this reason, nutrient combinations that act on more than one mitochondrial node have attracted growing attention in translational healthy-aging research.

The composition evaluated here combines three mechanistically distinct components. AKG is a tricarboxylic-acid-cycle intermediate with clear metabolic relevance. PQQ is a redox-active quinone that has been associated with mitochondria-related signaling and cellular protection. Agaricus bisporus extract contributes a food-derived matrix that is translationally relevant

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because mushrooms are a major dietary source of ergothioneine, a compound with cytoprotective and antioxidant properties. Taken together, the formulation is designed to link energetic substrate support, redox control, and biological resilience within a single oral system.

The central question is not whether each ingredient has an interesting mechanism, but whether the available evidence can support a clinically meaningful positioning of the full composition. To answer that question, we retained the original formulation data and matched them with published human trials that are most relevant to the biology of the three-component system. This allows us to separate what has already been shown in humans from what remains a formulation-level hypothesis.

2. Methods

We organized the manuscript around two evidence streams. The first stream consisted of the formulation architecture and the original comparative in vitro dataset of the study composition. The second stream consisted of publicly available human intervention studies selected for direct relevance to one or more pillars of the combination: AKG-related supplementation, PQQ supplementation, and mushroom-derived or purified ergothioneine supplementation.

For the clinical evidence stream, priority was given to randomized, placebo-controlled, double-blind, or crossover human studies and to primary biomedical sources rather than secondary commentary. When completed randomized efficacy data for the exact ingredient class were sparse, we included closely related human intervention evidence but interpreted it conservatively. We extracted study population, dose, duration, design, and main outcomes for clinical translation.

The formulation-level comparison emphasized two mitochondria-focused endpoints retained from the original dataset: relative mitochondrial membrane potential and relative mitochondrial reactive oxygen species. For clarity, the index composition was normalized to 100%, and the comparator lacking Agaricus bisporus extract was expressed relative to that benchmark.

Table 1. Composition framework and clinical translation positioning

Component	Role in the composition	Clinical translation status
AKG	Energetic substrate support linked to the tricarboxylic acid cycle	Mechanistically strong; direct healthy-aging efficacy data still limited
PQQ disodium salt	Redox-active mitochondrial support and signaling	Multiple completed human randomized trials with biomarker, cognition, and function signals
Agaricus bisporus extract	Food-derived matrix relevant to ergothioneine exposure and cytoprotection	Human bioavailability supported; ingredient-axis evidence strengthened by ergothioneine trials
Low-excipient design	Supports compositional focus and formulation clarity	Requires direct validation in a full-formulation head-to-head trial

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3. Results

3.1. Formulation-level mitochondrial comparison

The formulation-level comparison preserved from the original dataset showed a clear directional separation between the index composition and the comparator. When the study formulation was normalized to 100%, the comparator lacking Agaricus bisporus extract retained only 65.2% of the relative mitochondrial membrane-potential signal. Conversely, relative mitochondrial ROS increased to approximately 210% in the comparator. These two findings move in the same mechanistic direction and are consistent with a synergistic rather than merely additive formulation logic.

Although these are nonclinical data, they are useful because they define the biological problem that the human evidence must address. A composition intended for healthy-aging positioning should ideally preserve mitochondrial energetic state while simultaneously suppressing oxidative burden. The retained dataset supports that premise at the formulation-comparison level.

Table 2. Summary of retained mitochondrial comparison data

Endpoint	Index composition	Comparator without Agaricus bisporus extract	Direction of difference
Relative mitochondrial membrane potential (%)	100.0	65.2	Higher energetic-state preservation in the index composition
Relative mitochondrial ROS (%)	100.0	210.0	Lower oxidative burden in the index composition

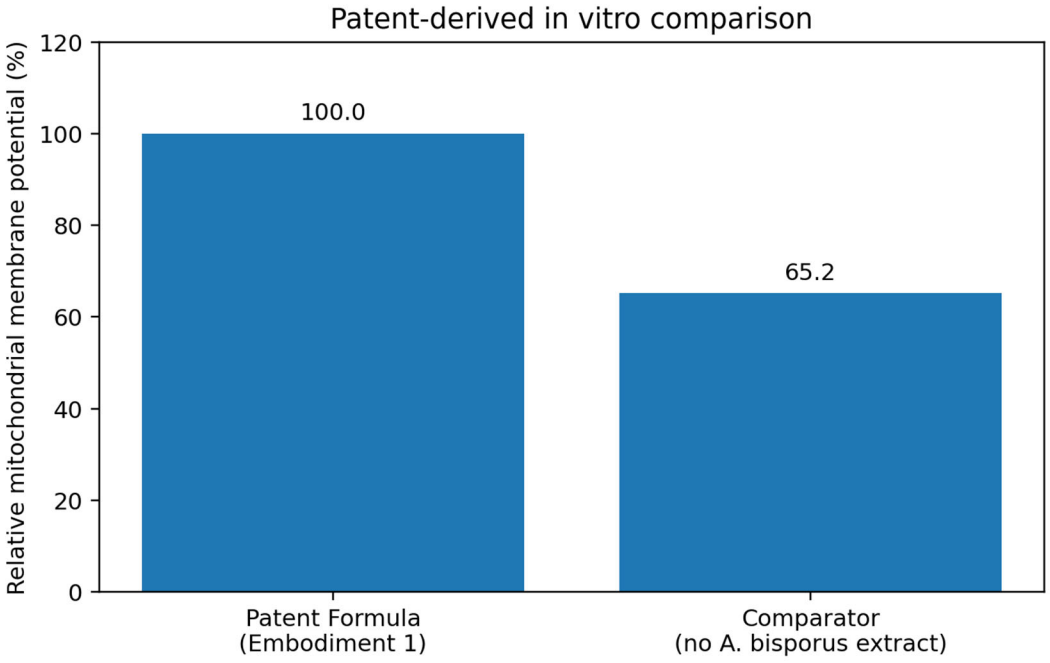

Figure 1. Retained original figure: relative mitochondrial membrane potential comparison

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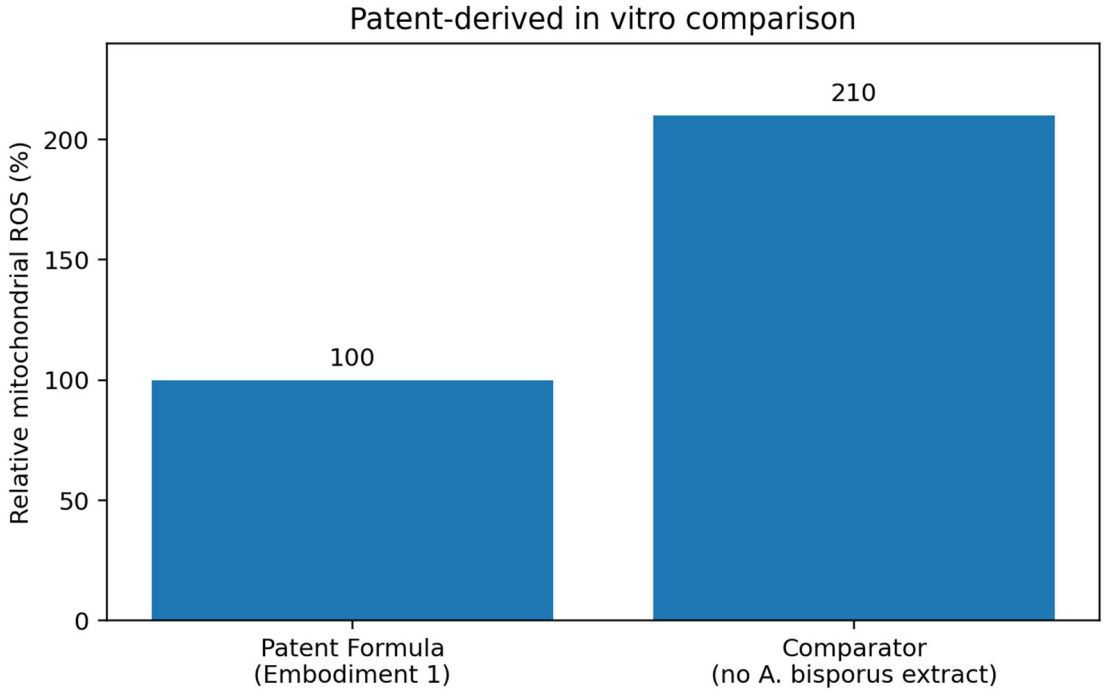

Figure 2. Retained original figure: relative mitochondrial ROS comparison

3.2. Human clinical evidence

Among the three ingredient domains, PQQ currently has the most developed human intervention base. In a crossover study in healthy adults, short-term PQQ supplementation lowered plasma C-reactive protein and interleukin-6 and produced urinary metabolomic changes interpreted as consistent with enhanced mitochondria-related function [1]. In later randomized trials, daily PQQ supplementation for 12 weeks improved composite memory and verbal memory in adults with age-associated forgetfulness [2,3], improved lower-limb extension strength, grip strength, and walking-based physical-function tests in healthy volunteers [4], and increased skeletal-muscle PGC-1alpha in untrained men even when overt aerobic-performance advantages were not detected [5]. Taken together, these findings support the view that PQQ is a clinically relevant mitochondrial-supporting anchor of the combination.

Human evidence for the mushroom-derived ergothioneine axis is newer but increasingly coherent. Ergothioneine from Agaricus bisporus is bioavailable in humans after mushroom ingestion [6], which is directly relevant to the translational plausibility of the mushroom fraction in the composition. In older adults with mild cognitive impairment, ergothioneine supplementation improved learning-related performance and stabilized plasma neurofilament light chain over one year without safety concerns [7]. In healthy older adults with subjective memory complaints, 10 mg and 25 mg daily ergothioneine were safe and produced exploratory benefits in prospective memory and sleep initiation, although the primary memory endpoint did not separate from placebo [8]. In healthy women, oral intake of an ergothioneine-rich mushroom preparation providing 25 mg/day for 12 weeks improved skin hydration and some facial-condition outcomes, with stronger signals in participants who had lower baseline plasma ergothioneine [9].

By contrast, the direct human efficacy base for AKG in healthy-aging settings remains less mature than the evidence for PQQ and ergothioneine. A placebo-controlled randomized protocol has been published for sustained-release calcium AKG in biologically older middle-aged adults, but completed efficacy results for that trial were not yet available in the public literature at the time of writing [10]. Earlier AKG-related human intervention studies in other contexts, such as l-arginine alpha-ketoglutarate in trained men, suggest that alpha-

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ketoglutarate-containing salts can be administered safely and may influence selected performance-related measures [11], but these studies cannot be taken as direct proof of geroprotective efficacy. This asymmetry in the human evidence base is important for a fair interpretation of the full formulation.

Table 3. Overview of published human clinical evidence

Ingredient/domain	Population and design	Dose and duration	Main findings	Relevance to the formulation
PQQ	10 healthy adults; crossover human study	0.2 mg/kg single dose and 0.3 mg/kg/day short-term	Lower CRP and IL-6; metabolomic shifts consistent with enhanced mitochondria-related function	Supports inflammation and mitochondrial-signaling rationale [1]
PQQ	64 adults with age-associated forgetfulness; randomized, double-blind, placebo-controlled	21.5 mg/day for 12 weeks	Improved composite memory, verbal memory, attention-related domains, and MMSE-J/DECO scores	Supports cognition-oriented positioning [2]
PQQ	Adults 20-65 years; double-blind, placebo-controlled	20 mg/day for 12 weeks	Improved composite memory and verbal memory; age-stratified benefits differed by age group	Suggests broad cognitive relevance across adult age strata [3]
PQQ	64 healthy adults; randomized, double-blind, placebo-controlled	21.5 mg/day for 12 weeks	Improved leg extension strength, grip strength, and walking-based physical-function tests; no adverse events	Supports function and resilience claims relevant to aging [4]
PQQ	23 untrained men; randomized, placebo-controlled training study	20 mg/day for 6 weeks	Increased skeletal-muscle PGC-1alpha but did not significantly outperform placebo for aerobic performance	Supports a biomarker-level mitochondrial signal with restrained efficacy interpretation [5]
Agaricus/ergothioneine	10 healthy men; randomized crossover postprandial study	Mushroom test meal containing 8 g and 16 g mushroom powder	Ergothioneine from Agaricus bisporus was bioavailable; attenuated postprandial triglyceride response was observed	Directly anchors the translational relevance of the mushroom fraction [6]
Ergothioneine	19 older adults with mild cognitive impairment; randomized, double-blind, placebo-controlled	25 mg per capsule, 3 times weekly for 1 year	Improved learning-related performance and stabilized neurofilament light chain without clinical safety concerns	Supports neuroprotective positioning in at-risk older adults [7]
Ergothioneine	Healthy adults 55-79 years with subjective memory complaints; randomized, double-blind, placebo-controlled	10 or 25 mg/day for 16 weeks	Primary memory endpoint did not differ from placebo; exploratory benefits were seen in prospective memory and sleep initiation; no adverse events	Supports safety and nuanced cognitive-sleep positioning [8]
Ergothioneine-rich mushroom	80 healthy women; randomized, double-blind, placebo-controlled	25 mg ergothioneine/day for 12 weeks	Improved skin moisture and selected facial-condition outcomes; stronger subgroup signal at low baseline plasma ergothioneine	Extends resilience relevance to skin-barrier aging outcomes [9]
AKG-related evidence	Healthy-aging Ca-AKG RCT program and earlier AAKG exercise trial	Ca-AKG 1 g/day for 6 months in protocol; AAKG 12 g/day for 8 weeks in trained men	Healthy-aging RCT efficacy results are pending; earlier AAKG study suggested safety and selected performance effects	Shows translational interest but highlights the need for direct randomized evidence for AKG itself [10,11]

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4. Discussion

When the formulation data and the human literature are interpreted together, a coherent translational picture emerges. The retained in vitro dataset suggests that the mushroom-containing version of the composition is associated with a more favorable mitochondrial phenotype than the comparator, while the public human literature indicates that PQQ and ergothioneine-related interventions already have measurable effects in domains that are biologically linked to mitochondrial resilience, including inflammation, cognition, physical function, and skin barrier support.

The strongest clinical pillar of the composition is presently PQQ. The consistency across biomarker, cognition, and function-oriented trials is notable because it spans several populations and outcome domains. The second pillar is the ergothioneine-bearing mushroom fraction. Here, the evidence is less extensive but still clinically meaningful: human bioavailability has been demonstrated directly for Agaricus bisporus, and both purified ergothioneine and ergothioneine-rich mushroom interventions have shown favorable safety and signal-level efficacy in older adults and healthy women. Those findings are especially relevant because they help explain why removal of the mushroom fraction in the formulation comparison was associated with a weaker mitochondrial profile.

The weakest clinical pillar remains AKG. That does not imply that AKG lacks mechanistic importance; rather, it means that direct randomized efficacy evidence in the specific setting of healthy aging is still catching up with preclinical enthusiasm. In practical terms, this makes the full composition scientifically plausible but not yet clinically closed. The most defensible conclusion is that the formulation deserves a registered, double-blind, head-to-head trial with prespecified mitochondrial, inflammatory, functional, and patient-reported endpoints.

A publication-ready interpretation should therefore be balanced. We can state that the full formulation is supported by strong mechanistic logic, retained nonclinical differentiation, and ingredient-level human evidence of varying maturity. We should not state that a completed human superiority trial of the exact AKG-PQQ-Agaricus bisporus composition has already established clinical efficacy, because the public record does not support that claim.

5. Conclusion

We conclude that the AKG-PQQ-Agaricus bisporus composition has a credible mitochondria-centered clinical positioning for healthy-aging research. Its retained formulation data support favorable membrane-potential preservation and ROS control, while the published human literature provides convergent support for PQQ and ergothioneine-related biology in domains relevant to resilience and function. At the same time, the clinical evidence is not equally mature across the three ingredient pillars, and direct randomized superiority data for the exact full formulation are still absent. The next decisive step is a well-powered, registered, double-blind trial designed specifically around the complete composition.

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