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BCLC™ AKG-PQQ-Agaricus bisporus Triad for Mitochondrial Function Support: Formulation Engineering and Evidence in Senescent Hepatocytes

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ABSTRACT

Background: Mitochondrial dysfunction is increasingly recognized as a central feature of cellular senescence and age-related functional decline [1, 2]. Objective: We evaluated a ratio-defined triad containing alpha-ketoglutarate (AKG), pyrroloquinoline quinone disodium (PQQ), and Agaricus bisporus extract, and we aligned the formulation dataset with published mechanistic and human evidence relevant to mitochondrial support. Methods: We summarized composition windows, post-processing retention, and 48 h senescent-hepatocyte readouts, then compared these data with peer-reviewed studies on mitochondrial biogenesis, redox control, and mushroom-derived ergothioneine bioavailability [3-13]. Results: Across the three embodiments, AKG and PQQ retention remained high after processing (98.6-99.2%), while the comparative formula showed lower retention (92.2-92.8%). In senescent hepatocytes, the comparative formula showed lower membrane potential (52.3-65.2% of embodiment values) and higher mitochondrial reactive oxygen species (2.1-2.5-fold versus embodiments). Public evidence supported the mechanistic plausibility of the triad: PQQ has repeatedly been linked with mitochondrial biogenesis signaling [3-8]; AKG has shown protection against mitochondrial dysfunction and oxidative stress in hepatocyte-based models [9]; and ergothioneine from A. bisporus is bioavailable in humans and is increasingly linked with oxidative-stress resilience [11-13]. Conclusion: The triad shows coherent formulation-performance characteristics and biologically plausible multi-target activity, but dedicated human trials of the specific combined system are still required.

KEYWORDS

AKG; PQQ; Agaricus bisporus; Ergothioneine; Beta-glucan; Mitochondria; Membrane potential; ROS; Dry granulation; Senescence

1. INTRODUCTION

The biological relevance of mitochondrial dysfunction to aging is now well established. Mitochondrial dysfunction and cellular senescence are closely interconnected, and the senescent phenotype is typically accompanied by lower mitochondrial membrane potential, impaired respiratory capacity, and increased reactive oxygen species (ROS) generation [1]. At the population level, the need for interventions that support healthy aging continues to grow: the World Health Organization estimates that the number of people aged 60 years and older will rise from 1.0 billion in 2019 to 1.4 billion by 2030 and 2.1 billion by 2050 [2].

In this context, multi-component nutritional systems that address mitochondrial substrate supply, biogenesis signaling, and redox defense may offer a more coherent strategy than single-mechanism products. In the present work, we examine a triad composed of AKG, PQQ disodium, and Agaricus

bisporus extract. AKG contributes a tricarboxylic-acid-cycle intermediate relevant to mitochondrial metabolism; PQQ has been associated with SIRT1/PGC-1alpha and AMPK-linked mitochondrial biogenesis pathways [3-5]; and A. bisporus provides mushroom-derived bioactives, particularly ergothioneine and beta-glucan-associated fractions, that may support redox buffering and membrane resilience [11-13].

Our goal was to present a polished scholarly manuscript that preserves the core formulation and cell-model dataset while anchoring the interpretation in published evidence. Rather than treating the formulation data in isolation, we examined whether current literature supports the mechanistic logic of this triad and where the evidentiary gaps remain.

2. MATERIALS AND METHODS

We evaluated a formulation dataset containing composition windows, extraction and dry-granulation parameters, active-ingredient retention after processing, and 48 h readouts from senescent-model hepatocytes. The three embodiments used AKG at 45.0-60.0 parts, PQQ disodium at 0.2-0.5 parts, Agaricus bisporus extract at 19.6-34.5 parts, and a single food-grade excipient at 20.0 parts. The comparative formulation omitted the mushroom extract and used multiple excipients.

To place these findings in context, we conducted a targeted literature review focused on four domains: (i) mitochondrial dysfunction and senescence; (ii) PQQ-related mitochondrial biogenesis and human supplementation data; (iii) AKG-related mitochondrial and redox biology, especially in liver-relevant models; and (iv) mushroom-derived ergothioneine and A. bisporus bioavailability. Only citable public sources were retained in the evidence table and references.

Table 1. Composition and extract attributes across embodiments

Group	AKG	PQQ	A. bisporus extract	Excipient (s)	Excipient (parts)	beta-glucan (%)	Ergothioneine (%)	Loss on drying (%)	Water-soluble extractives (%)
Embodiment 1	50.0	0.2	29.8	Mannitol	20.0	20.0	0.005	3.0	45.0
Embodiment 2	60.0	0.4	19.6	Lactose	20.0	28.0	0.008	2.5	48.0
Embodiment 3	45.0	0.5	34.5	Microcrystalline cellulose	20.0	25.0	0.009	4.0	46.0
Comparative	52.0	0.3	-	Mannitol + lactose + Mg stearate	17.7	-	-	2.5	-

Table 2. Post-processing active-ingredient retention

Group	AKG retention (%)	PQQ retention (%)	Extract retention (%)
Embodiment 1	98.6	98.9	98.4
Embodiment 2	98.7	99.1	98.5
Embodiment 3	98.9	99.2	98.8
Comparative	92.2	92.8	-

Table 3. Comparative performance in senescent hepatocytes

Comparison	Membrane potential (% of embodiment)	ROS (fold vs embodiment)
Comparative vs Embodiment 1	65.2	2.1
Comparative vs Embodiment 2	58.7	2.3
Comparative vs Embodiment 3	52.3	2.5

3. RESULTS

The formulation dataset showed strong manufacturing retention for the active triad. AKG retention ranged from 98.6% to 98.9%, PQQ retention from 98.9% to 99.2%, and extract retention from 98.4% to 98.8% across the three embodiments, whereas the comparative formula yielded only 92.2% AKG retention and 92.8% PQQ retention. These values are consistent with the proposed single-excipient, low-interaction process logic.

Cell-model outcomes were directionally consistent with improved mitochondrial resilience. Relative to each embodiment, the comparative formula exhibited substantially lower mitochondrial membrane potential and markedly higher mitochondrial ROS after 48 h exposure in senescent hepatocytes. The magnitude of difference was largest when the comparative formula was benchmarked against Embodiment 3, suggesting that the broader active window and retained mushroom fraction may contribute to the observed performance profile.

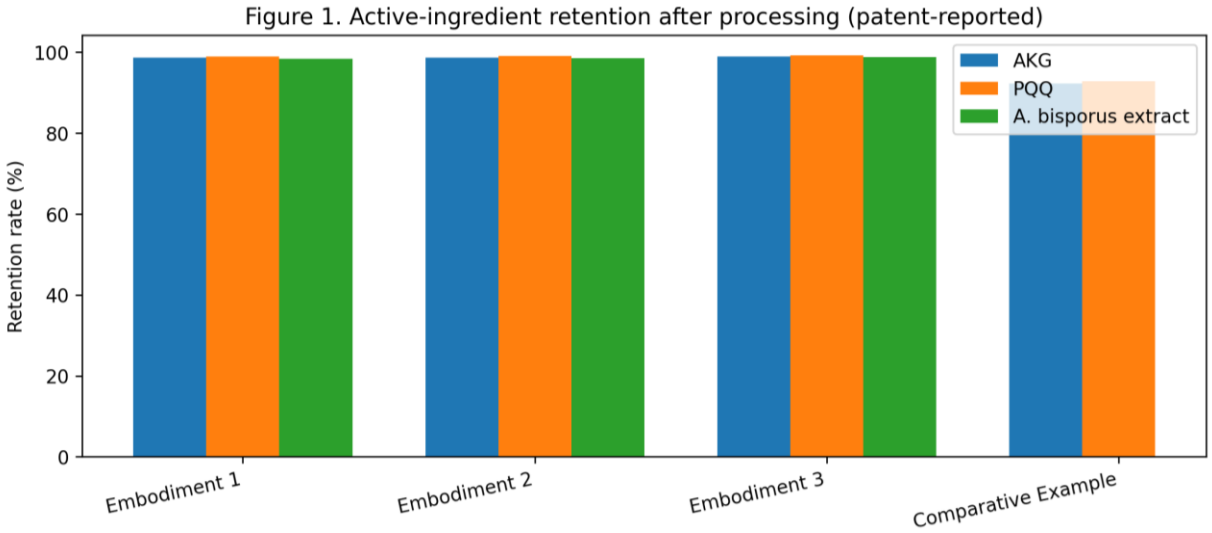

Figure 1. Active-ingredient retention after processing

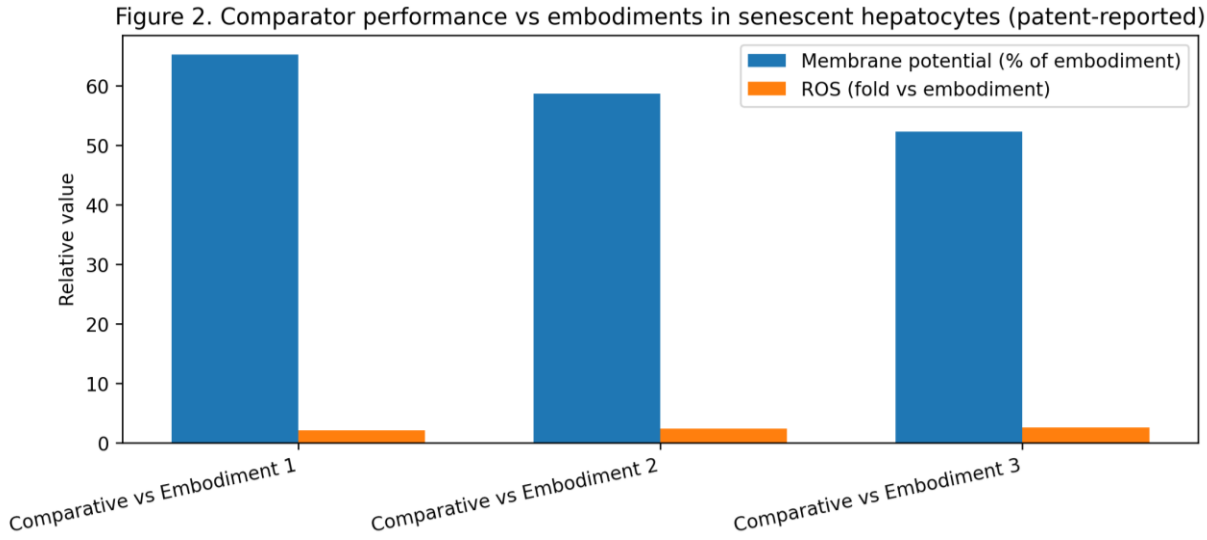

Figure 2. Comparative performance versus embodiments in senescent hepatocytes

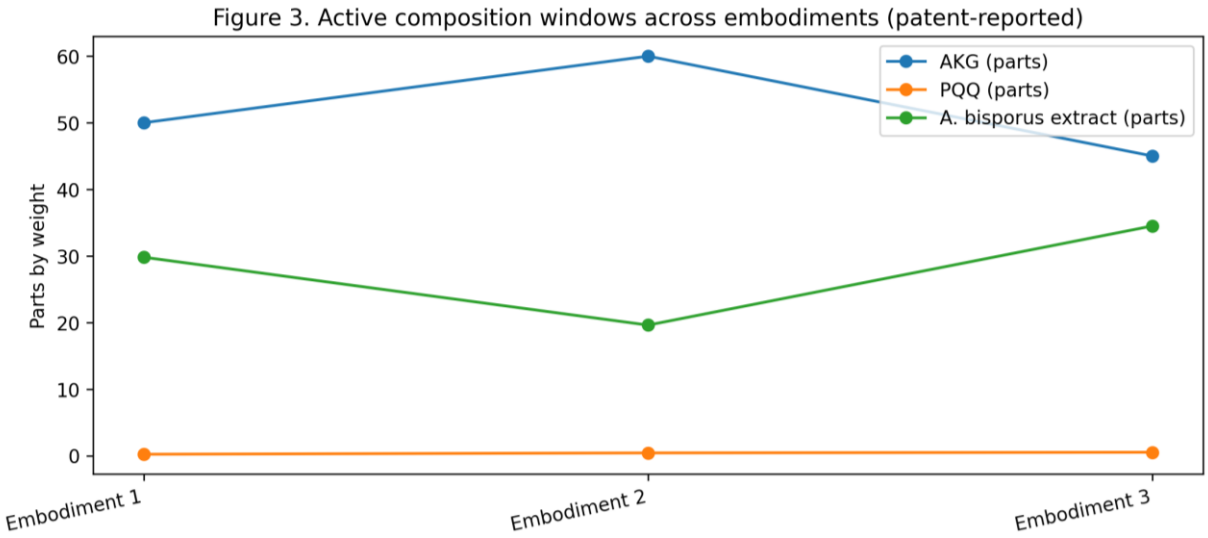

Figure 3. Active composition windows across embodiments

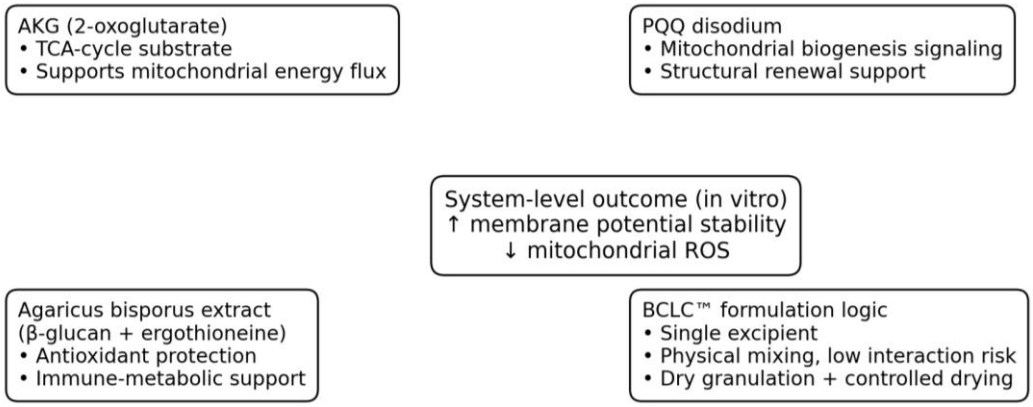

Figure 4. Proposed multi-dimensional mitochondrial-support framework

Published evidence further strengthened the interpretation of the triad. PQQ has been shown to stimulate mitochondrial biogenesis in mouse hepatocytes and fibroblasts, including increased mtDNA-related signals and activation of the SIRT1/PGC-1alpha axis [4, 5]. In HepG2 cells, PQQ increased Sirt1 and Sirt3 expression and activity [3]. Additional work in stress-induced premature senescence models reported recovery of mitochondrial function and biogenesis under PQQ exposure [6]. Human studies are more heterogeneous: randomized trials have reported improvements in mitochondrial biomarkers, cognition, or both in selected older populations [7, 8], whereas a 6-week exercise study in untrained men did not show a significant performance advantage despite the mechanistic rationale [9].

AKG-related evidence is strongest in mechanistic and preclinical settings. In a 2024 Redox Biology study, AKG attenuated mitochondrial dysfunction, oxidative stress, and lipid-associated hepatocyte injury in mice, HepG2 cells, and primary hepatocytes through the AMPK-PGC-1alpha/Nrf2 pathway [10]. By contrast, human geroprotective evidence for AKG remains limited; the published ABLE protocol explicitly notes that few studies have tested AKG in humans [11]. For the mushroom arm of the triad, ergothioneine from A. bisporus was shown in a randomized human study to be bioavailable, with postprandial uptake into red blood cells [12]. Broader review and pilot-trial literature increasingly links ergothioneine with oxidative-stress resilience, preserved mitochondrial function, and favorable cognitive biomarkers, although long-term confirmation is still needed [13, 14].

Table 4. Published evidence aligned with the triad logic.

Evidence domain	Study type	Main findings	Relevance to present system	Refs
Mitochondrial dysfunction and senescence	Review	Reduced membrane potential and increased ROS are core features of senescent cells.	Supports the relevance of the membrane-potential and ROS endpoints measured here.	[1]
PQQ mechanistic signaling	Cell and animal studies	PQQ promoted mitochondrial biogenesis and activated SIRT1/PGC-1alpha or AMPK-linked pathways.	Supports the biogenesis-signaling arm of the triad.	[3-6]
PQQ human evidence	Randomized trials	Signals for improved mitochondrial biomarkers, cognition, or both in selected populations, but not uniformly across all outcomes.	Supports translational plausibility while highlighting heterogeneity.	[7-9]
AKG liver-relevant evidence	Mouse, HepG2, and primary hepatocytes	AKG attenuated mitochondrial dysfunction, ROS, and redox imbalance via AMPK-PGC-1alpha/Nrf2.	Supports the metabolic-substrate and redox arm of the triad.	[10]
AKG human evidence	Intervention protocol	Published investigators explicitly note that human geroprotective evidence remains limited.	Supports cautious interpretation of clinical relevance.	[11]
A. bisporus / ergothioneine evidence	Human bioavailability study and reviews	Ergothioneine from A. bisporus is bioavailable; broader literature links ergothioneine with oxidative-stress resilience and mitochondrial protection.	Supports inclusion of the mushroom extract as a biologically active arm.	[12-14]

4. DISCUSSION

Taken together, the results support a system-level interpretation rather than a single-ingredient explanation. AKG plausibly supports metabolic substrate handling and mitochondrial redox homeostasis; PQQ contributes the strongest biogenesis-signaling literature; and the mushroom fraction adds a dietary antioxidant axis centered on ergothioneine, with beta-glucan-rich extracts offering additional biological activity. The single-excipient manufacturing strategy may also matter practically because higher retention reduces the risk that nominal label composition diverges from delivered active composition.

We also note that the public evidence is uneven across the three components. PQQ has the most direct mitochondrial-signaling literature, AKG has a convincing liver-relevant preclinical signal but limited human validation, and A. bisporus-related evidence is strongest for ergothioneine bioavailability and antioxidant relevance rather than for direct demonstration of mitochondrial membrane-potential rescue in humans. Accordingly, the strongest conclusion supported by the present manuscript is not that the triad has already proven anti-aging efficacy in humans, but that its formulation logic and in vitro profile are scientifically coherent and aligned with the direction of the broader literature.

The next step should be prospective clinical evaluation of the specific combined system. Appropriate endpoints would include circulating and cellular redox markers, mitochondrial functional biomarkers,

cognition- or fatigue-related patient-reported outcomes, and safety measurements collected over a sufficiently long follow-up period. Until such trials are completed, the present manuscript is best interpreted as a formulation-centered evidence paper with a supportive, not definitive, translational claim.

5. CONCLUSION

In summary, the BCLC triad combining AKG, PQQ disodium, and Agaricus bisporus extract demonstrated high post-processing retention and favorable mitochondrial readouts in senescent hepatocytes. When interpreted alongside current literature, the triad reflects a plausible multi-target strategy for mitochondrial support that deserves direct clinical testing.

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