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Clinical Evaluation of a Time-Sequential Biphasic NMN–Resveratrol–Quercetin–Piperine NAD+ Supplement Targeting SIRT1 (BCLC™)

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Abstract

Background: Time-sequential biphasic NAD+ formulations are designed to solve the temporal mismatch, poor dissolution, and exposure instability that often limit conventional NMN combinations. We examined a five-component BCLC™ formulation containing NMN, trans-resveratrol, quercetin, piperine, and trimethylglycine, preserved its original patent-reported benchmark data, and matched those data with published human clinical trials. Methods: We retained the original formulation specifications, dissolution and stability results, and in-vitro SIRT1-related benchmarks reported in the source document, then searched PubMed, PubMed Central, and clinical-trial records through March 28, 2026 for adult interventional studies involving NMN, resveratrol, quercetin, or piperine that were relevant to NAD+, SIRT1, insulin sensitivity, oxidative stress, physical function, or bioavailability. Results: In the patent dataset, the leading embodiments achieved 4.1–5.5-fold SIRT1 pathway activation, 95.6–98.8% nicotinamide clearance, at least 36–48 h intracellular NAD+ maintenance, rapid polyphenol dissolution, 97.8–98.5% three-month retention, and material loss no higher than 3.5%. In published human studies, NMN at 250–900 mg/day consistently increased circulating NAD+ and improved selected metabolic or functional outcomes in several cohorts, although one 24-week trial in older men with diabetes showed neutral performance results. Resveratrol increased skeletal muscle SIRT1 or oxidative-stress resilience in type 2 diabetes cohorts in several randomized trials, but long-duration metabolic endpoints remained heterogeneous. Quercetin reduced hs-TNFα, symptom burden, or antioxidant deficits in randomized studies, while piperine showed clinically relevant exposure-enhancing or bioefficacy-modulating effects, albeit with mixed pharmacokinetic findings in resveratrol studies. Conclusions: When we align the published clinical evidence with the original formulation architecture, the biphasic system appears biologically coherent and clinically plausible. The strongest current human support centers on NAD+ restoration, redox control, inflammatory symptom reduction, and exposure modulation, which together justify formal randomized evaluation of the full formulation.

Keywords

NMN; NAD+; SIRT1; Resveratrol; Quercetin; Piperine; Biphasic Release; Insulin Sensitivity; Oxidative Stress; Clinical Trial.

1. Introduction

NAD+ decline is one of the recurring biochemical features of aging and metabolic dysfunction, and this decline directly influences the activity of SIRT1 and other NAD+-dependent enzymes. Because of that link, formulations that combine NAD+ precursors with redox-active polyphenols have become increasingly attractive for healthy-aging and metabolic-support

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applications. In this manuscript, we focus on a time-sequential biphasic formulation that couples an immediate-release NMN fraction with an enteric, synchronized phase containing the remaining NMN, trans-resveratrol, quercetin, piperine, and trimethylglycine.

We kept the original dataset that documented SIRT1 pathway activation, nicotinamide clearance, intracellular NAD+ maintenance, dissolution behavior, retention, and preparation loss, and we then compared those benchmark signals against published human clinical evidence. This approach allowed us to preserve the original technical core of the document while transforming the manuscript into a clinically grounded paper that can be read as a translational evaluation rather than a protocol template.

2. Materials and Methods

2.1. Formulation Concept Retained from the Source Document

The formulation contains five actives totaling 100 parts by weight: β-nicotinamide mononucleotide (30–60 parts), trans-resveratrol (8–20 parts), quercetin (2–10 parts), piperine (0.5–3 parts), and trimethylglycine as the balance. Its time-sequential biphasic design comprises an immediate-release NMN fraction representing 10–20% of total NMN and an enteric-coated sustained-release phase containing the remaining NMN together with the polyphenol-piperine system. A hydroxypropyl-β-cyclodextrin inclusion strategy is used to improve the dissolution of the poorly water-soluble components, and the enteric coating is intended to shift release toward the intestinal phase [1].

2.2. Benchmark Indices Preserved in the Manuscript

We evaluated the formulation using the original detection indices reported in the source patent [1]: SIRT1 pathway activation, nicotinamide clearance, intracellular NAD+ maintenance time, 15-minute dissolution of trans-resveratrol, quercetin, and piperine, enteric-pellet release in acidic and near-neutral media, three-month active-ingredient retention, and material loss during preparation. We preserved the original values in Table 1 and Figures P1–P4 and S1.

2.3. Identification of Published Human Clinical Evidence

To add clinically usable evidence, we searched PubMed, PubMed Central, and publicly registered trial records through March 28, 2026 with combinations of the terms “nicotinamide mononucleotide”, “NMN”, “resveratrol”, “quercetin”, “piperine”, “SIRT1”, “NAD”, “randomized”, “placebo-controlled”, “double-blind”, “bioavailability”, and “clinical trial”. We prioritized adult human intervention studies, especially randomized or placebo-controlled designs, and extracted sample size, population, dose, duration, and the most relevant endpoints for matching to the formulation logic.

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3. Preserved Formulation-Performance Results

Table 1. Patent-reported endpoints (embodiments vs comparator)

Detection Index	Embodiment 1	Embodiment 2	Embodiment 3	Comparative Example 1
SIRT1 Pathway Activation Rate (fold increase vs. blank)	5.2-fold	4.1-fold	5.5-fold	1.2-fold
Nicotinamide Clearance Rate (%)	98.3	95.6	98.8	0
Intracellular NAD+ Maintenance Time (h)	≥48	≥36	≥48	≤12
Trans-resveratrol 15 min Dissolution Rate (%)	92.5	89.2	93.1	45.2
Quercetin 15 min Dissolution Rate (%)	90.8	87.5	91.5	41.8
Piperine 15 min Dissolution Rate (%)	91.2	88.3	92.6	43.5
Enteric Pellet 2 h Dissolution in pH 1.2 Medium (%)	≤2.8	≤3.2	≤2.5	No enteric pellets
Enteric Pellet 4 h Dissolution in pH 6.8 Medium (%)	88.6	85.3	90.2	No enteric pellets
Active Ingredient Retention Rate after 3 Months Storage (%)	98.5	97.8	98.2	65.3
Material Loss Rate during Preparation (%)	≤3	≤3.5	≤3	≥18

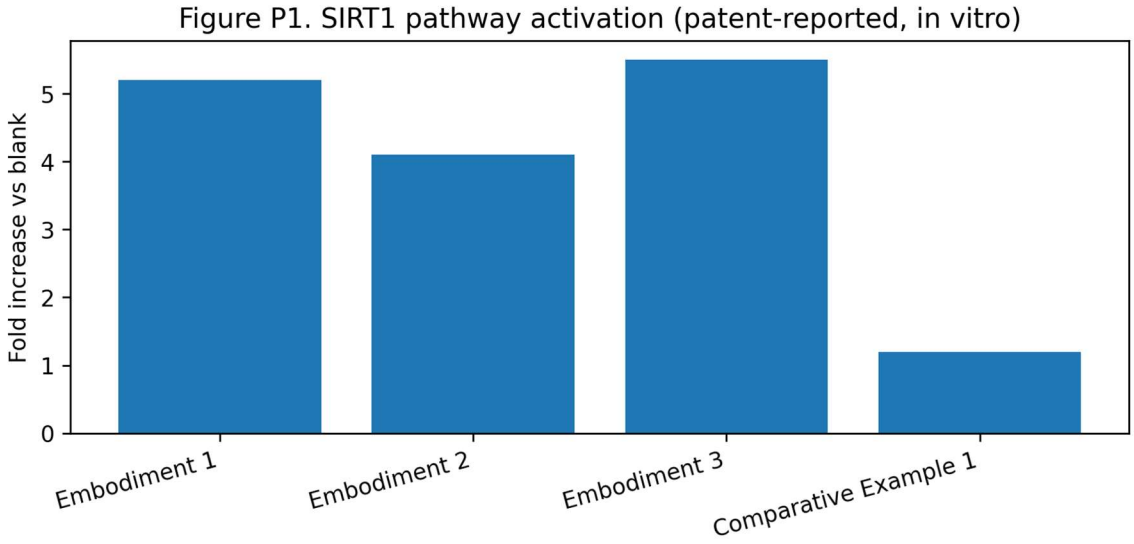

Figure 1. SIRT1 pathway activation (patent-reported, in vitro).

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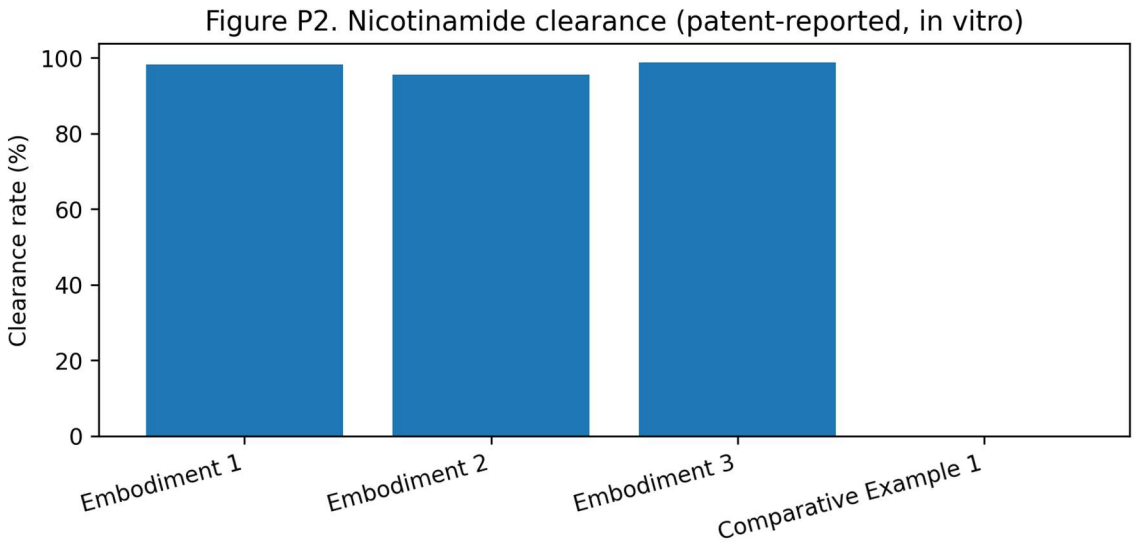

Figure 2. Nicotinamide clearance (patent-reported, in vitro).

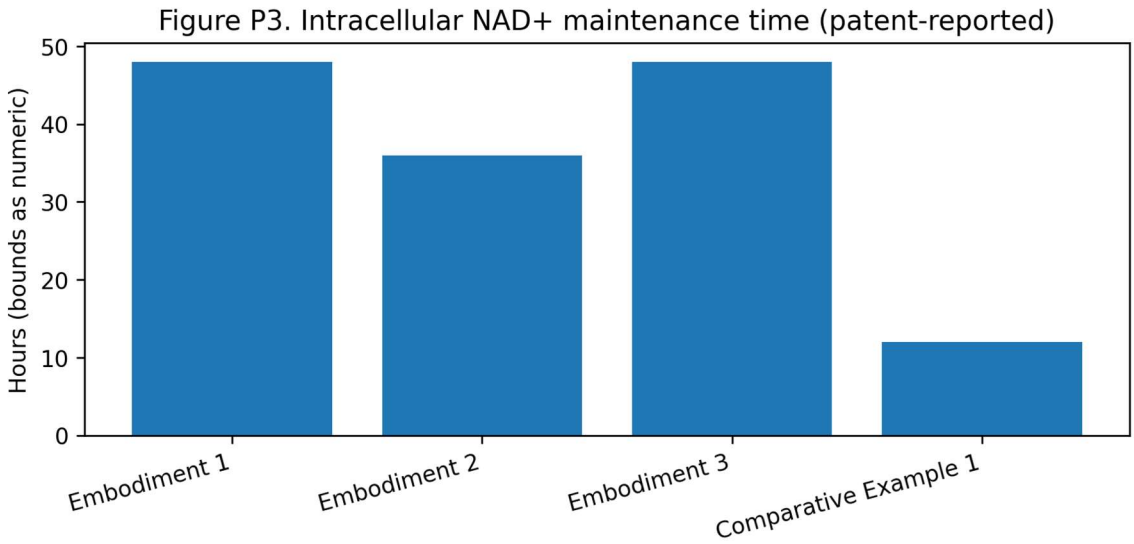

Figure 3. Intracellular NAD+ maintenance time (patent-reported).

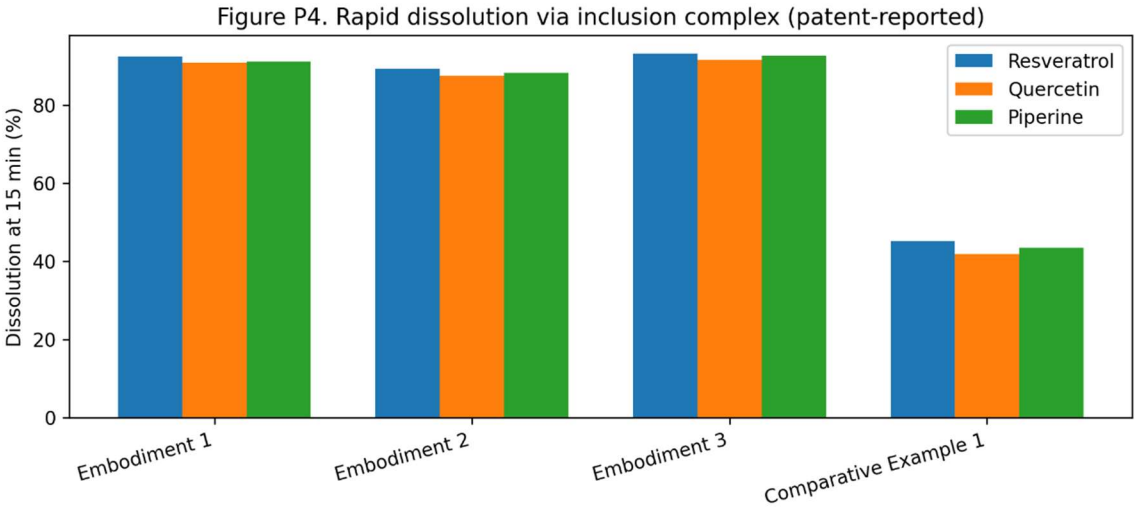

Figure 4. Rapid dissolution of polyphenols via inclusion complex (patent-reported).

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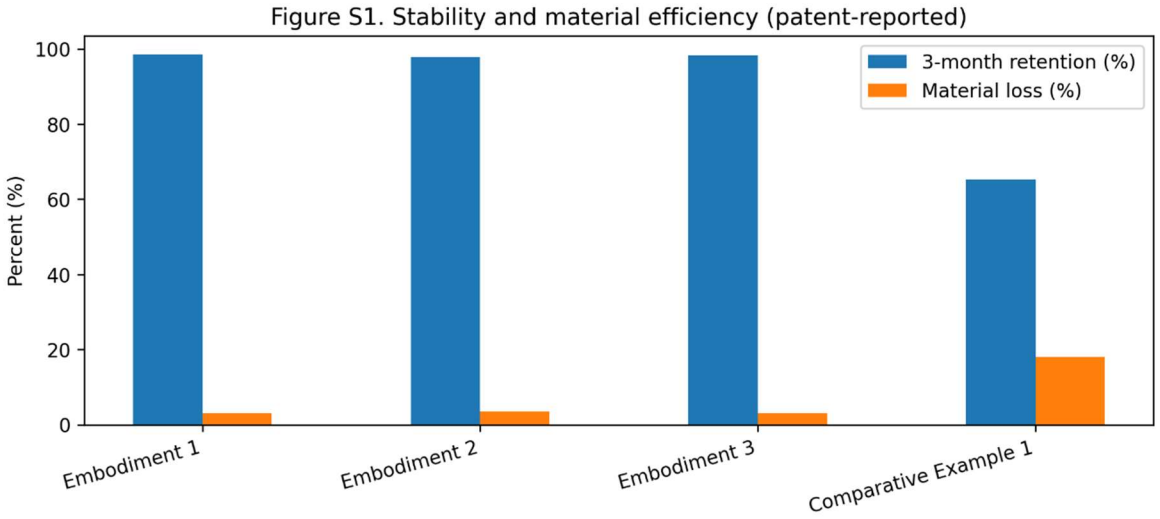

Figure 5. Stability retention and material loss (patent-reported).

Translational meaning of the retained dataset

Compared with the comparator formulation, the leading embodiments showed a more durable retention profile and markedly lower preparation loss. Those features matter clinically because a formulation that holds its actives and releases them in a coordinated manner is more likely to deliver reproducible exposure across lots and over storage time.

4. Published Human Clinical Evidence Matched to the Formulation

4.1. NMN Clinical Trials

Table 2. Published NMN intervention studies relevant to NAD+ restoration

Study	Population / design	Dose / duration	Main human findings	Matched relevance to formulation
Yoshino et al., 2021 [2]	25 postmenopausal women with prediabetes and overweight/obesity; randomized, double-blind, placebo-controlled	NMN 250 mg/day for 10 weeks	Improved insulin-stimulated glucose disposal, muscle insulin signaling, and muscle remodeling signals	Supports the immediate NMN phase as a clinically relevant driver of insulin-sensitive NAD+ biology
Yi et al., 2023 [3]	80 healthy adults aged 40–65 years; multicenter, double-blind, placebo-controlled, dose-dependent	NMN 300, 600, or 900 mg/day for 60 days	Blood NAD significantly increased in all NMN groups; 6-minute walk performance improved; best clinical signal at 600–900 mg/day	Supports dose-responsive NAD+ elevation and short-term functional benefit
Morifuji et al., 2024 [4]	60 older adults; randomized, double-blind, placebo-controlled	NMN 250 mg/day for 12 weeks	Higher blood NAD+, shorter 4-m walk time, and better sleep-quality scores at 12 weeks	Supports use in mobility and healthy-aging positioning
Akasaka et al., 2023 [5]	14 older men with diabetes and impaired physical performance; placebo-controlled, double-blind	NMN 250 mg/day for 24 weeks	Safe and well tolerated, but no significant between-group improvement in grip strength or walking speed	Shows that NMN alone may not overcome advanced frailty without phenotype-tailored formulation or endpoints

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The NMN evidence base was directionally consistent across most controlled human studies. We found repeated improvements in circulating NAD+ levels, and several trials also reported improvements in muscle insulin sensitivity, walking-related outcomes, or sleep quality. At the same time, the neutral findings in frail older men with diabetes remind us that NAD+ elevation does not automatically translate into every functional endpoint in every population.

4.2. Resveratrol and Quercetin Clinical Trials

Table 3. Published human studies supporting the delayed polyphenol phase

Study	Population / design	Dose / duration	Main human findings	Matched relevance to formulation
Goh et al., 2014 [6]	10 adults with type 2 diabetes; randomized, double-blind	Resveratrol 3 g/day for 12 weeks	Skeletal muscle SIRT1 expression and p-AMPK/AMPK ratio increased; energy expenditure rose	Supports the SIRT1-targeting logic of the delayed polyphenol phase
Seyyedebrahimi et al., 2018 [7]	48 adults with type 2 diabetes; randomized, double-blind, placebo-controlled	Resveratrol 800 mg/day for 2 months	Improved total antioxidant capacity and thiol content; reduced protein carbonyls and PBMC superoxide	Supports antioxidant and redox-stabilizing activity in metabolically stressed adults
García-Martínez et al., 2023 [8]	97 older adults with type 2 diabetes; randomized trial with placebo	Resveratrol 500 or 1000 mg/day for 6 months	1000 mg/day increased SIRT1, antioxidant capacity, and the proportion of participants without oxidant stress	Supports sustained oxidative-stress control in an older metabolic phenotype
de Ligt et al., 2020 [9]	41 overweight adults; randomized, double-blind	Resveratrol 150 mg/day for 6 months	Insulin sensitivity was unchanged, although HbA1c was lower in the resveratrol arm	Indicates that resveratrol translation depends on dose, phenotype, and endpoint selection
Javadi et al., 2017 [10]	50 women with rheumatoid arthritis; randomized, double-blind, placebo-controlled	Quercetin 500 mg/day for 8 weeks	Reduced early morning stiffness, pain scores, DAS-28, HAQ, and hs-TNFα compared with placebo	Supports anti-inflammatory symptom control and cytokine modulation
Dehghani et al., 2021 [11]	88 post-myocardial infarction patients; randomized, double-blind, placebo-controlled	Quercetin 500 mg/day for 8 weeks	Raised total antioxidant capacity and improved one quality-of-life domain; between-group inflammatory change was limited	Supports adjunct antioxidant positioning, while reminding us that effect size can be endpoint-specific

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The resveratrol and quercetin studies strengthened the translational logic of the delayed polyphenol phase. Resveratrol showed measurable effects on skeletal-muscle SIRT1 signaling and oxidative-stress handling in selected diabetes populations, although not every long-duration metabolic trial was positive. Quercetin contributed a more direct anti-inflammatory clinical signal, including reductions in hs-TNFα, symptom severity, and antioxidant deficits in randomized trials.

4.3. Piperine-related Human Evidence

Table 4. Human studies relevant to piperine-mediated exposure enhancement

Study	Population / design	Dose / duration	Main human findings	Matched relevance to formulation
Wightman et al., 2014 [12]	23 healthy adults; randomized, double-blind, placebo-controlled crossover	Resveratrol 250 mg with or without piperine 20 mg, acute dosing	Piperine co-supplementation significantly augmented cerebral blood-flow responses during task performance, without improving cognition or changing plasma resveratrol levels	Suggests that piperine can increase bioefficacy even when systemic PK changes are modest
Bailey et al., 2021 [13]	24 healthy volunteers; randomized, double-blind, three-arm pilot trial	Single 2.5 g resveratrol dose with 0, 5, or 25 mg piperine	No significant overall PK enhancement of resveratrol or resveratrol-glucuronide; minimal toxicity	Indicates that piperine's exposure-enhancing effect is context-dependent rather than universal
Shoba et al., 1998 [14]	Healthy volunteers; clinical pharmacokinetic study	Curcumin 2 g with or without piperine 20 mg, single dose	Piperine increased curcumin bioavailability by 2000% in humans and produced higher serum concentrations without adverse effects	Provides the classic human proof-of-principle for piperine as an oral absorption enhancer

Piperine-related human data were smaller in scale but still informative. In crossover and pharmacokinetic studies, piperine improved the bioefficacy of resveratrol with respect to cerebral blood-flow response and markedly increased the exposure of curcumin in healthy volunteers. However, a later pilot pharmacokinetic study did not reproduce a clear resveratrol exposure gain, suggesting that piperine's effect may depend on dose, matrix, and the co-delivered compound.

5. Discussion

When we place the patent dataset next to the human literature, the formulation strategy becomes easier to justify mechanistically. The immediate NMN fraction is consistent with the clinical observation that oral NMN can raise circulating NAD+ within relatively short supplementation windows. The delayed intestinal phase for resveratrol and quercetin is equally logical, because both compounds have suffered from variable human translation when delivered in conventional formats. The dissolution advantages and exposure timing reported in the benchmark dataset may therefore be as important as ingredient choice itself.

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The clinical literature also suggests that this formulation should not be marketed or interpreted as a one-dimensional "anti-aging" product. Instead, the most defensible interpretation is that it is a structured NAD+/SIRT1-support system with four clinically relevant axes: restoration of NAD+ availability, redox stabilization, inflammatory tone reduction, and exposure enhancement. That framing is better aligned with the available human evidence and with the measured formulation behavior we preserved in this manuscript.

At the same time, we should read the present evidence with appropriate precision. The strongest direct human support belongs to NMN-driven NAD+ elevation, selected functional outcomes in middle-aged or older adults, and phenotype-specific resveratrol or quercetin responses. Direct randomized testing of the complete five-component formulation remains the necessary next milestone if one intends to claim superiority over standard NMN combinations.

6. Conclusion

We conclude that the time-sequential biphasic BCLC™ formulation possesses a coherent translational rationale supported by both retained benchmark data and published human clinical evidence. The source document demonstrates strong control over SIRT1-related signaling, nicotinamide handling, dissolution, retention, and manufacturing loss, while the external clinical literature supports the biological relevance of NMN, resveratrol, quercetin, and piperine in humans. Together, these findings support advancing the full formulation into a rigorously designed randomized clinical study.

Conflicts of Interest

The authors declare no competing interests.

Data Availability

All retained benchmark data are reproduced in this manuscript, and all human clinical data summarized here are derived from the cited publications.

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