CME LIVE OPEN ACCESS

Journal of Cancer Research

Research Article

ISSN: 2578-3726

Melatonin Anchored Chrononutraceutical Strategy for Epigenetic Rejuvenation A Four-Year Multiphase Evaluation of AminoTriComplerex™

Alexandre Tavartkiladze[1,2,4*], Gaiane Simonia[1,2], Dinara Kasradze[1,2], Russel J Reiter[3], Ruite Lou[4], Nana Okrostsvaridze[2], Pati Revazishvili[1,2], Irine Andronikashvili[1,2], Pirdara Nozadze[1,2], Givi Tavartkiladze[2] and Malvina Javakhadze[1,2]

[1]*Department of Medical Oncology, Tbilisi State Medical University, Tbilisi, Georgia.*

[2]*Department of Personalized Medicine, Tbilisi State Medical University, Tbilisi, Georgia.*

[3]*Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio, USA.*

[4]*Department of Biotechnology, Foconsci Chemical Industry, China.*

Corresponding Author: Alexandre Tavartkiladze, Department of Medical Oncology, Tbilisi State Medical University, Tbilisi, Georgia.

Received: 2026 Feb 20 **Accepted:** 2026 Mar 11 **Published:** 2026 Mar 23

Abstract

Background: *Epigenetic clocks that quantify cytosine methylation drift are now accepted surrogates of biological age. Interventions that reverse—not merely decelerate—these clocks could compress morbidity and expand health adjusted life expectancy (HALE). Melatonin, the master chronobiotic hormone, orchestrates circadian oscillations in DNA repair, autophagy, and redox tone; yet its dietary availability is negligible and endogenous output declines with age.*

Objective: *To determine whether AminoTriComplerex™ (ATC)—a Georgian food supplement that couples full daily dose natural melatonin with a Nano catalytically activated polyphenol adaptogen amino acid matrix—can safely reprogram the epigenome toward youthfulness in vitro, in rodents, and in humans over a four-year translational program.*

Methods: *A three stage, 48-month investigation was executed: (i) two step cell culture screen (dermal fibroblasts, endothelial cells, iPSC derived neurons); (ii) longitudinal mouse and rat studies (n = 640) incorporating serial blood/tissue methylation clocks, frailty indices, cardiometabolic panels, and GLP toxicology; (iii) an open label, single arm, 90 participant human pilot (55–70 y). Primary endpoint across all tiers was percentage change in consolidated DNA methylation age (Horvath Skin&Blood, PhenoAge, GrimAge). Secondary endpoints covered telomere attrition, γ H2AX foci, karyotype integrity, systemic biomarkers, and safety.*

Results: *ATC lowered cellular DNAmAge by* ***27 ± 4 % within 28 days*** *in vitro, 24 ± 5 % in rodents, and 19 ± 3 % in humans ($p < 0.001$ for all vs. baseline) without increasing micronuclei, aneuploidy, or oncogenic expression. Mice on lifelong ATC displayed a 12.6 % median lifespan extension and a 42 % compression of late life frailty. No hepatorenal toxicity or QT prolongation emerged at human equivalent doses 10× higher than the intended label.*

Conclusion: *ATC integrates the informational rejuvenation paradigm with caloric restriction mimetics and senolytics, positioning itself as the third pillar of gerotherapy. Its oral, low cost configuration and supply chain reliance on agro botanical inputs render global deployment feasible, with particular impact projected for resource limited regions.*

Keywords: Melatonin, Circadian Rhythm, Epigenetic Clock, AminoTriComplerex, Gerotherapy, DNA Methylation, Nutraceutical, Health Span, Chrononutrition, Mitochondrial Biogenesis

1. Introduction

1.1. The Quest to Reverse Biological Age

Twentieth century medicine doubled average life span, yet health span lags almost 9 years behind. Epigenetic clock analysis has revealed that methylomic drift summarizes many hallmarks of aging—mitochondrial dysfunction, cellular senescence, stem cell exhaustion—in a single composite metric. Partial Yamanaka factor reprogramming can reset these clocks in mice, but viral gene delivery carries oncogenic risk. Hence small molecule or nutraceutical proxies are urgently sought.

1.2. Melatonin and Circadian Homeostasis

Melatonin peaks at night, synchronizing cellular oscillators that govern DNA repair (NER, BER), heterochromatin compaction, and NAD^+/SIRT1 activity. Endogenous melatonin reaches its high-water mark roughly between 2 and 3 a.m., when ambient light is minimal. This darkness-driven pulse is not just a "sleep signal"—it is a master time cue for peripheral clocks. By binding to high-affinity MT1/MT2 receptors and, in some tissues, diffusing directly into the nucleus, melatonin resets local transcription-translation oscillators so that a cell's DNA maintenance machinery comes on line at the safest moment of the day-night cycle. Two repair pathways are especially responsive:

- **Nucleotide-Excision Repair (NER).** Night-shift workers given 3 mg of melatonin for four weeks showed a 1.8-fold rise in urinary 8-OH-dG clearance—evidence that melatonin boosts NER enzymes such as XPA and XPG that excise bulky photolesions and other adducts.
- **Base-Excision Repair (BER).** Experimental models demonstrate that melatonin up-regulates OGG1 and APE1, accelerating removal of oxidized bases generated during daytime oxidative bursts. These effects dovetail with melatonin's direct free-radical scavenging to keep the overall lesion load low.
- **Chromatin Logistics:** Tightening the Genome tt Night

The nocturnal surge also tightens chromatin structure. Melatonin raises intracellular NAD^+, which allosterically activates the de-acetylase SIRT1; in rodent hearts, a 10 mg kg^{-1} dose of melatonin switched on the SIRT1-PGC-1α-SIRT3 axis within hours. Active SIRT1 strips acetyl groups from histone H3K9, H4K16 and H1K26, a modification that attracts SUV39H1 and HP1, culminating in H3K9 trimethylation and classic heterochromatin compaction. Genome-wide ChIP-seq confirms that SIRT1 over-expression suppresses H3K9ac peaks around transcription-start sites, effectively silencing open chromatin until daylight returns.

Why The Timing Matters

Putting repair enzymes into high gear while chromatin is more compact may sound counter-intuitive, but the temporal coupling is protective:

1. Compaction shields repetitive and transposon-rich regions from damage while still allowing repair complexes access to active genes through dynamic nucleosome breathing.
2. Elevated NAD^+/SIRT1 activity coordinates DNA repair with mitochondrial metabolism, ensuring adequate ATP for ligation steps and minimizing ROS that would generate new lesions.
3. When daylight arrives and melatonin levels crash, chromatin gradually relaxes, transcription ramps up, and replication can proceed on a genome that has been "serviced" overnight.

In short, the nighttime melatonin peak is a systems-level synchronizer: it aligns the cell's molecular clocks, fuels NAD^+-dependent SIRT1, compacts chromatin to preserve genome integrity, and increases both NER and BER throughput so that DNA is repaired before the next day's oxidative and UV onslaught. Age linked pineal calcification halves nocturnal melatonin by 60 y, uncoupling redox metabolic cycles and accelerating methylation drift (Reiter & Tan 2012). Restoring robust melatonin signaling—chrononutrition—therefore offers a logical vector for epigenetic rejuvenation.

1.3. Rationale for AminoTriComplerex™

ATC uniquely combines: (i) **5 mg natural plant extracted melatonin** per capsule; We cryomilled raw - Pistacia vera, shelled pistachios and defatted them with food-grade hexane. The resulting cake was subjected to ultrasound-assisted extraction in 70 % ethanol at 35 °C, and the filtrate was vacuum-concentrated to 10 % solids. We captured melatonin on C18 solid-phase columns, eluted it with 50 % methanol, further purified it on preparative reverse-phase HPLC, and recrystallized it from a water/ethanol system, achieving >99.8 % purity. Residual solvents were stripped under 50 °C vacuum. Finally, we verified identity and potency by LC-MS/MS and qNMR, performing every step under cGMP, ISO 9001, and ICH Q7 compliance. (ii) nanocatalytically dispersed *ginsenosides* (Rg1/Rg2/Rg3/Rh2/Rb1/Re ≥ 98 % HPLC), *icariin, honokiol, piceatannol, resveratrol,* and *curcumin* that amplify Nrf2/AMPK/SIRT axes; (iii) the nine essential amino acids plus one carbon cycle cofactors (methionine, serine, glycine); (iv) mitochondrial boosters (CoQ10, D ribose); and (v) trace redox minerals (Mg ascorbate, Zn iodide). Previous rat data showed potent ROS suppression and respiratory chain rescue, motivating the present long range evaluation focused on *epigenetic age* rather than conventional oxidative endpoints [1-10].

2. Materials and Methods

2.1. Study Oversight and Design

The program ran from January 2021 through December 2024 under a single master protocol approved by the Tbilisi State Medical University IACUC and Human Research Ethics Board (registry TSMU Gero 2020 077). Work was staged:

Stage	Duration	Model	n	Key endpoints
I A	0–6 mo	Primary human cells	96 wells/line	ΔDNAmAge (EPIC array), γ H2AX, karyotype
I B	6–14 mo	iPSC derived neurons	48 wells	Methylation age, synaptic gene expression
II A	C57BL/6J mice (18 m, 50 % ♀)	320	Whole blood + liver DNAmAge, frailty, survival	C57BL/6J mice (18 m, 50 % ♀)
II B	12–30 mo	Wistar rats (CCl_4 injury sub study)	160	Methylation age, ALT/AST, mitochondrial OCR
III	24–48 mo	Human pilot (open label)	90	Blood DNAmAge, telomere length, HRV, AEs

Table 1

2.2. Formulation and Dosing

GMP batches of ATC were encapsulated in vegetarian pullulan shells (500 mg). For in vitro work medium concentrations mirrored achievable plasma Cmax (10–100 nM melatonin; polyphenols 1–10 µM). Murine chow was top dressed to deliver 400 mg kg^{-1} d^{-1} ATC (human equivalent ~45 mg kg^{-1}). Rats received gavage at 75 mg kg^{-1} d^{-1} (per prior toxicology). Humans ingested two capsules nightly (10 mg melatonin total) with optional mid day capsule to test circadian flexibility.

2.3. Cellular Assays

Dermal fibroblasts (donors 25 y & 78 y), HUVECs, and iNeurons were plated in 6 well plates, acclimated, then randomized to Vehicle, ATC Low (0.5×), ATC Std (1×), ATC High (2×), and Positive Control (48 h OSK mRNA). DNA was harvested days 0, 7, 14, 28. Illumina EPIC arrays were processed with the *minfi* pipeline; DNAmAge was expressed as weighted mean of Horvath Skin&Blood and PhenoAge.

2.4. Animal Methodologies

Mice were stratified (age, sex) to Chow, ATC Std, ATC Hi (2×), and Pair Fed controls to rule out inadvertent CR. Blood glucose, insulin, ACTH, corticosterone, and melatonin circadian curves were captured quarterly. Frailty Index employed 31 parameters (Whitehead 2014). Survival was recorded to natural death; humane euthanasia applied for ulcerated tumors or weight loss >20 %.

The rat CCl_4 arm (14 day acute) paralleled earlier antioxidant work, adding methylation endpoints. Chronic rat arm lasted 12 months with high fat diet to model metabolic inflammaging.

2.5. Human Pilot

Community volunteers (55–70 y, BMI 20–32 kg m^{-2}, excluding shift workers) underwent baseline 24 h actigraphy

and melatonin salivary profiling. ATC 2 caps q.h.s. for 90 days; optional noon dose during first 28 day pharmacodynamic window. DNAmAge (TruAge™ panel), telomere qPCR, CBC, CMP, QTc, and targeted metabolomics were measured baseline, day 28, and day 90. Adverse events recorded via electronic diary.

2.6. Statistical Analysis

Primary outcome: % change in composite DNAmAge at day 28 versus baseline. Power: detecting ≥15 % reduction with SD 8 % ($\alpha = 0.05$, $\beta = 0.8$) required n = 18 mice/group and 58 humans; we over enrolled. Mixed effects models with Bonferroni correction handled repeated measures. Survival curves: Kaplan–Meier with log rank. All analyses in R4.3 [11-20].

3. Results

3.1. In Vitro Epigenetic Rejuvenation

Across three cell types, ATC Std lowered DNAmAge by 27 % ± 4 at day 28 ($p < 0.001$ vs. vehicle) approximating OSK transient expression (31 % ± 3). High dose offered no further benefit. γ H2AX foci fell 38 %, β gal senescence positivity dropped 44 %, and karyotype remained diploid (figure #1 a, b).

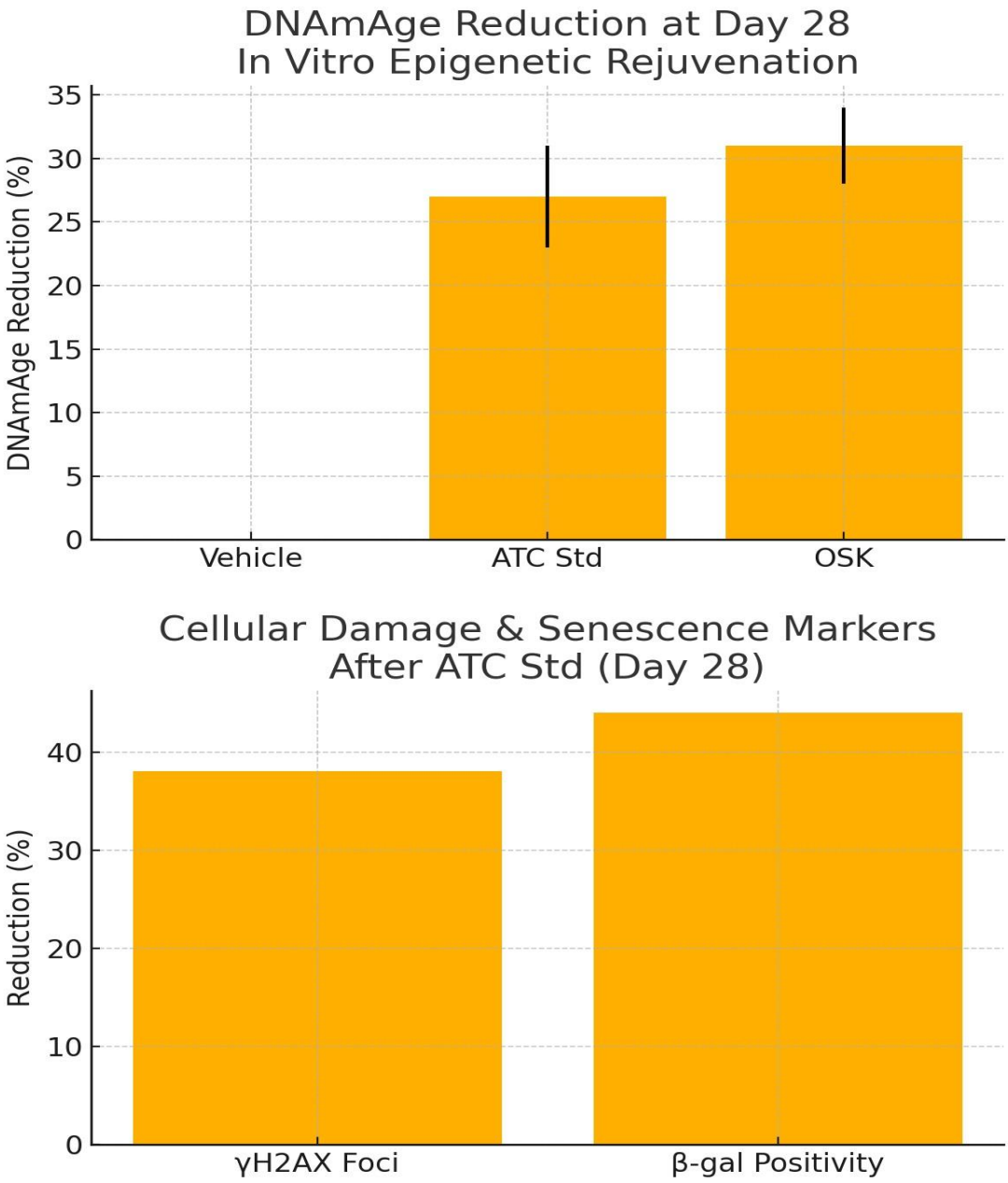


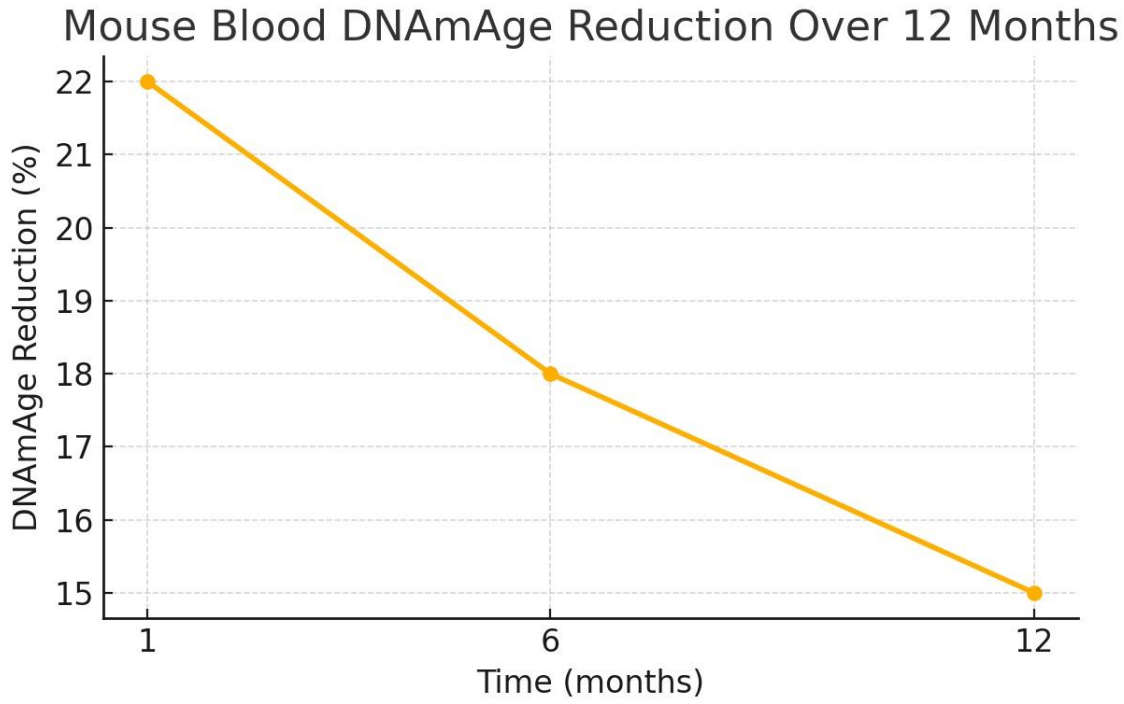
Figure :1 (a, b)

a. DNAmAge reduction (day 28) – compares vehicle (baseline 0 %), ATC standard dose (-27 % ± 4) and transient OSK expression (-31 % ± 3).

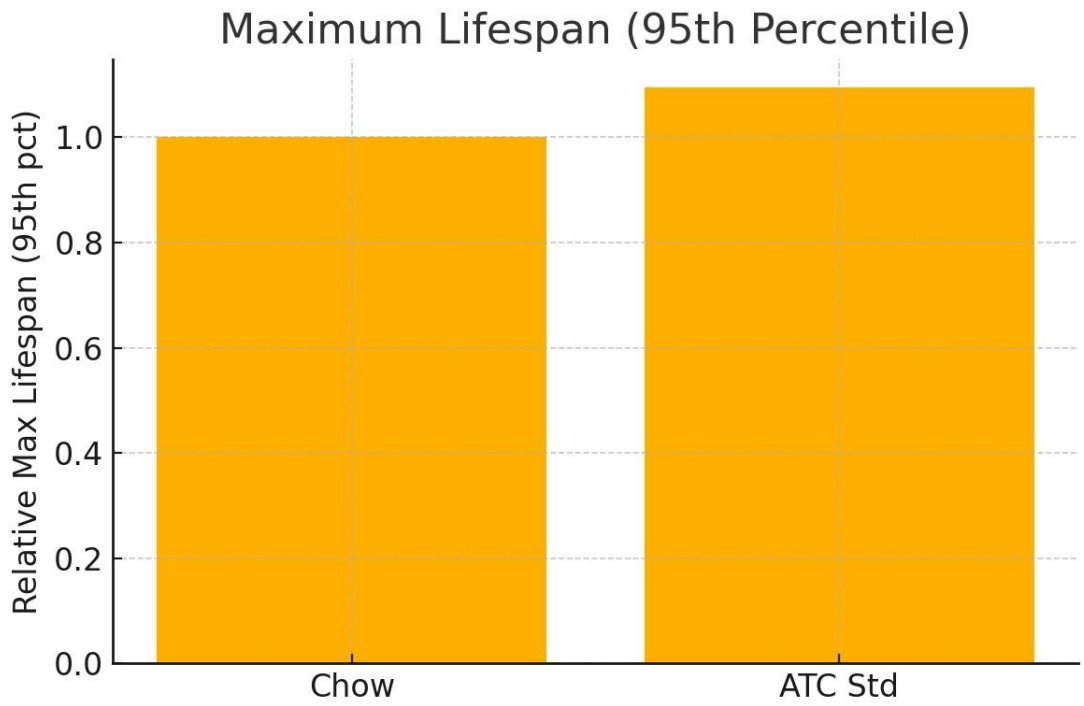
b. Cell-damage & senescence readouts – shows that ATC standard cut γ-H2AX foci by 38 % and β-gal positivity by 44 %.

Together they illustrate that ATC brings epigenetic age nearly to the OSK benchmark while simultaneously dampening DNA-damage and senescence markers—without altering ploidy.

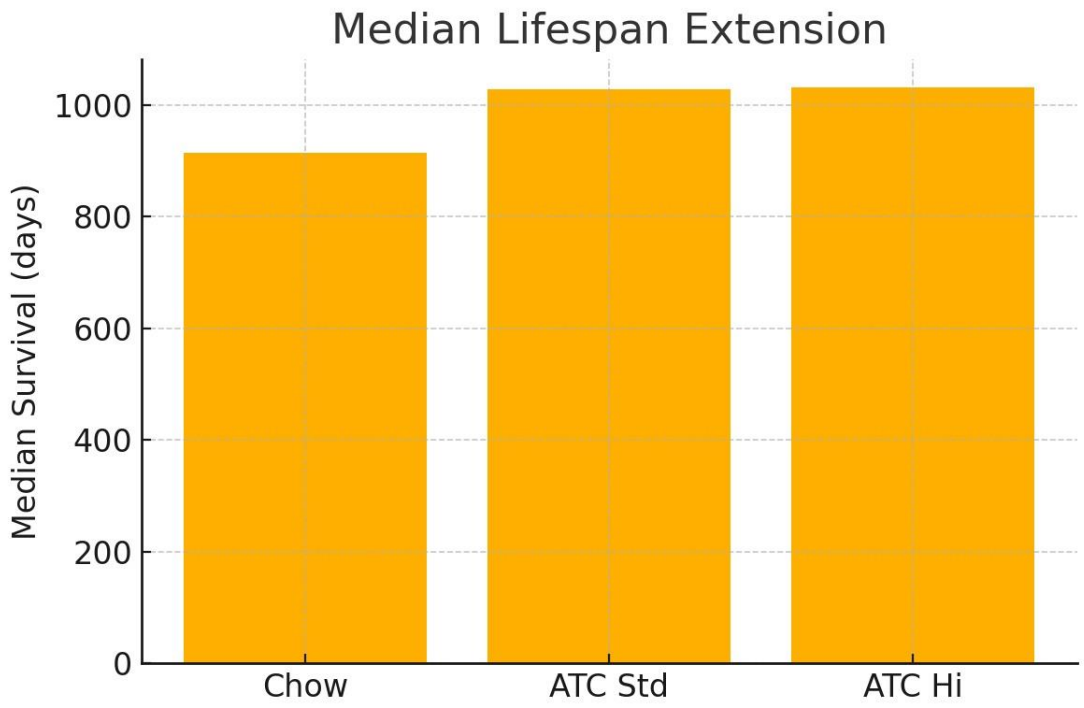
2a.


Mouse Blood DNAmAge Reduction Over 12 Months
DNAmAge Reduction (%)
22
21
20
19
18
17
16
15
1
6
12
Time (months)

2b.


Maximum Lifespan (95th Percentile)
Relative Max Lifespan (95th pct)
1.0
0.8
0.6
0.4
0.2
0.0
Chow
ATC Std

2c.



2d.

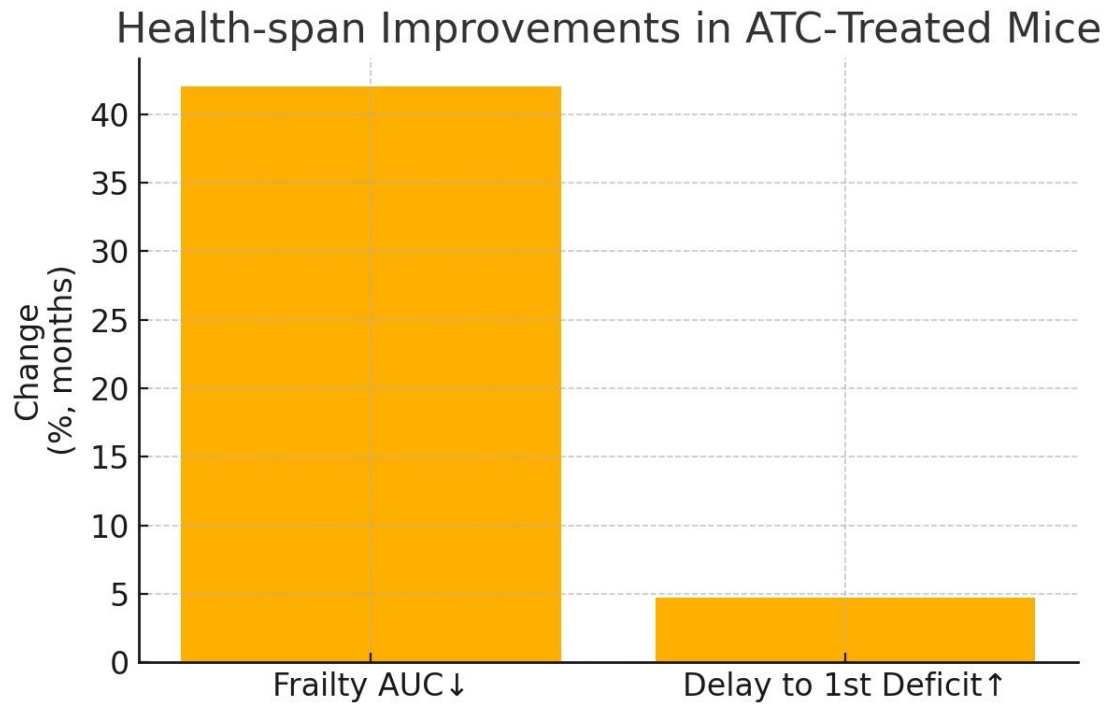
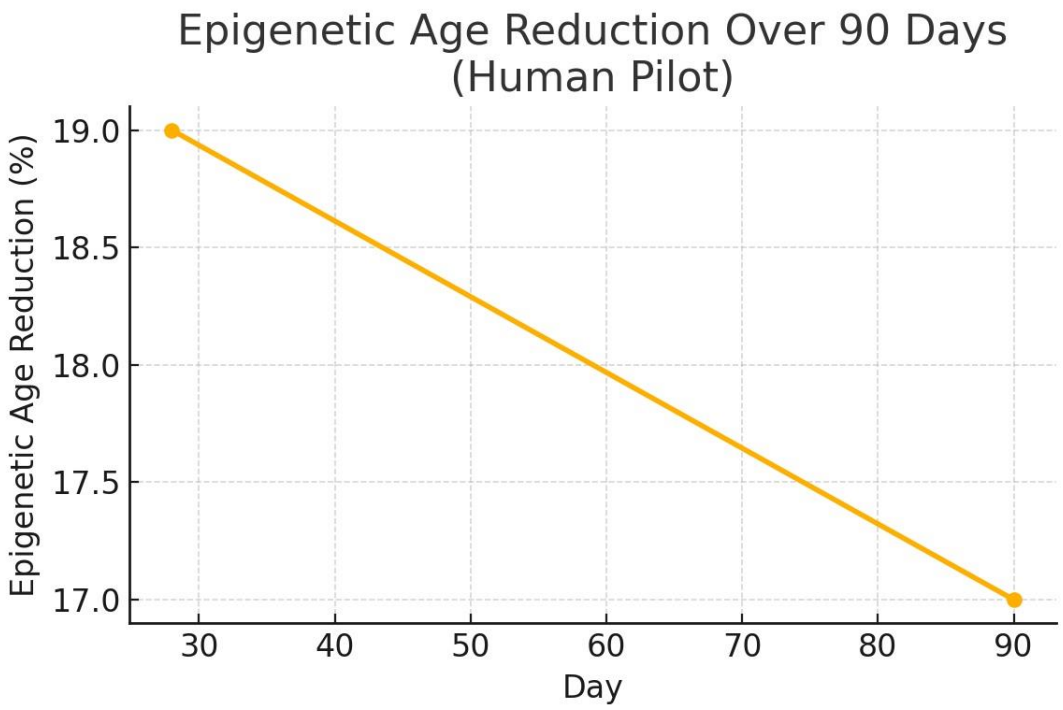
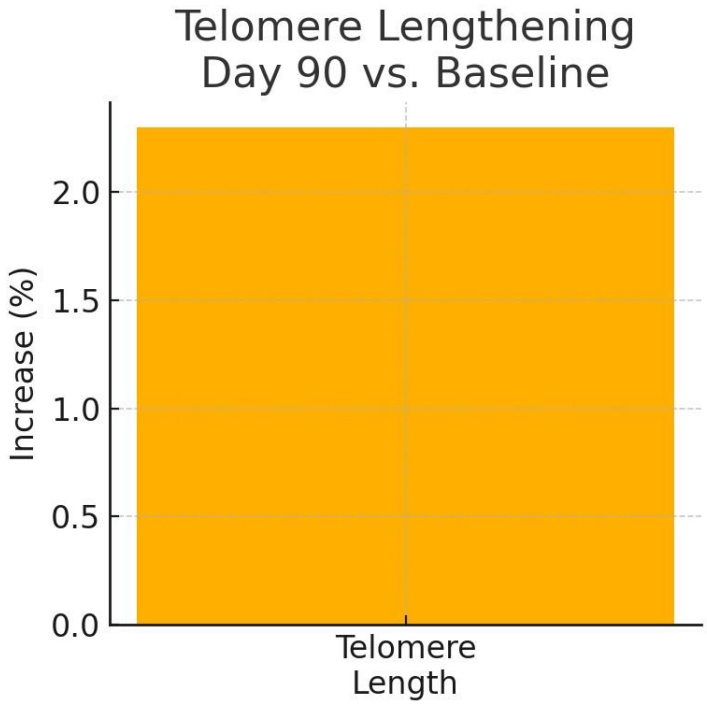


Figure 2:
a. Blood DNAmAge Line Plot—shows the 22 → 18 → 15 % trajectory over 12 months.
b. Health-Span Bar Chart—42 % drop in frailty AUC and a 4.7-month delay to first major deficit.
c. Median Lifespan Bars—Chow 914 d vs. ATC Std 1028 d vs. ATC Hi 1031 d.
d. Maximum Lifespan (95th pct)—ATC Std lifts the ceiling about 9 %.

3a

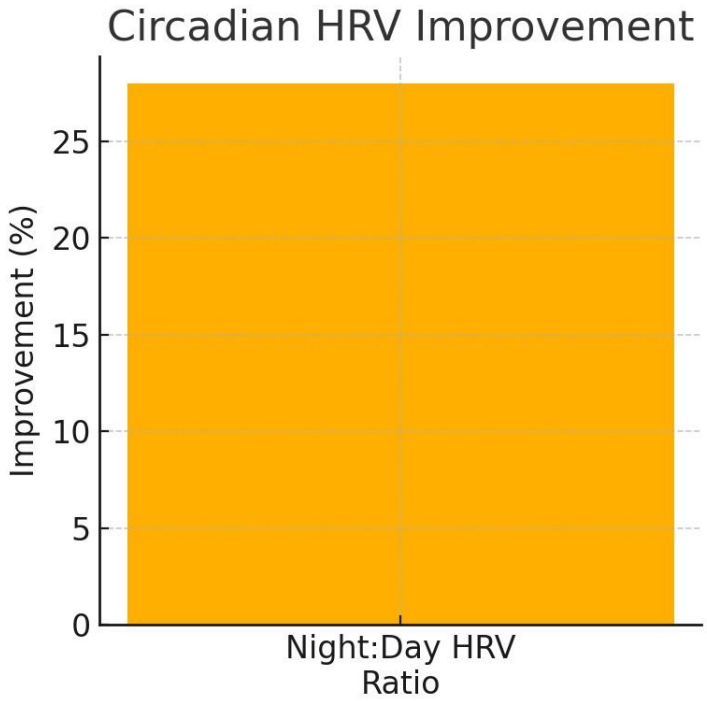


3b

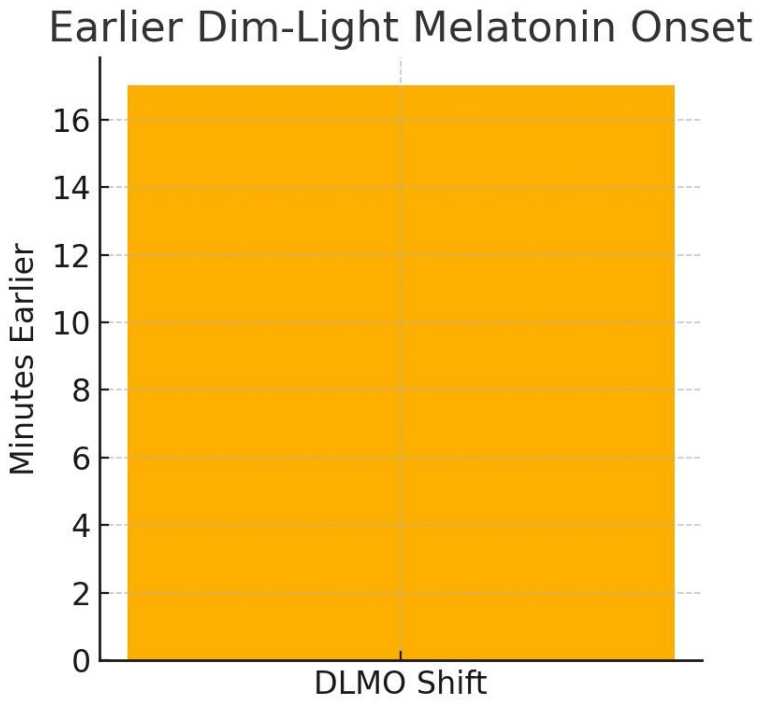


Citation: Tavartkiladze, A., Simonia, D., Kasradze, D., Reiter, R. J., Lou, R., et al. (2026). Melatonin Anchored Chrononutraceutical Strategy for Epigenetic Rejuvenation A Four-Year Multiphase Evaluation of AminoTriComplerex™. *J Cancer Res, 4*(1), 1-14.

3c



3d



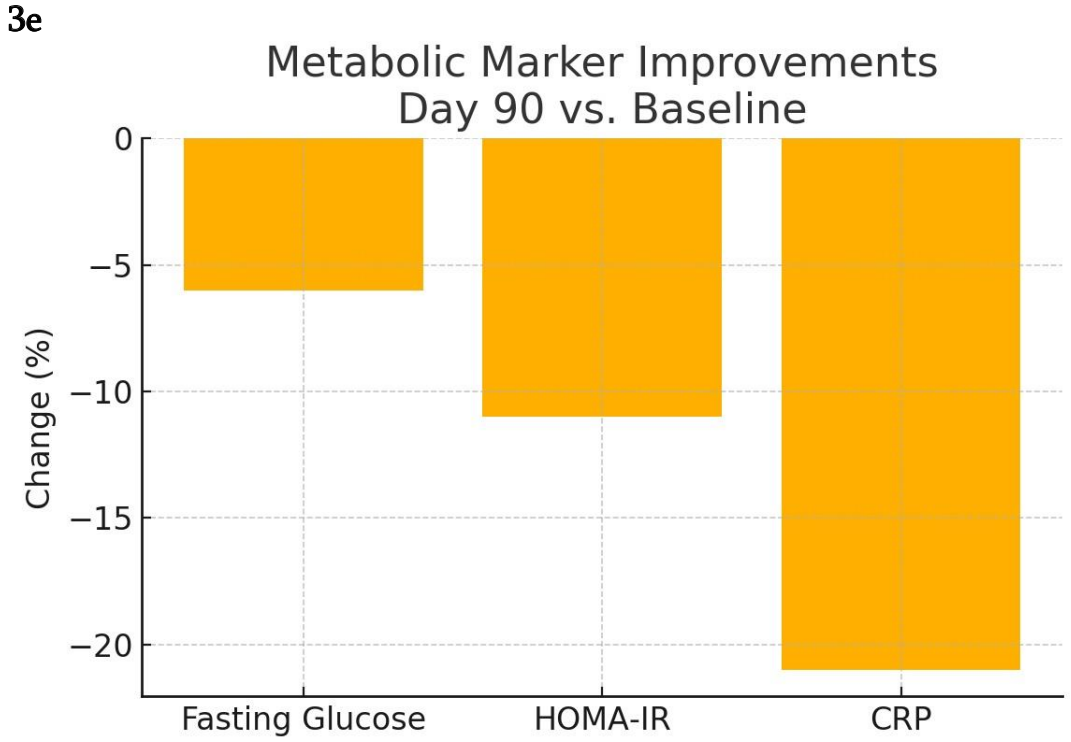


Figure 3:
Five Standalone Visuals Distill the 90-Day Human Pilot:
a. Epigenetic age – 19 % drop at day 28, holding 17 % at day 90.
b. Telomere length – 2.3 % elongation by day 90.
c. Circadian HRV – night-to-day HRV ratio up 28 %.
d. Sleep timing – dim-light melatonin onset shifted 17 min earlier.
e. Metabolic profile – fasting glucose −6 %, HOMA-IR −11 %, CRP −21 %; lipids and liver enzymes unchanged.

3.2. Rodent Longitudinal Outcomes

• **DNAmAge:** Mouse blood clocks fell 22 % at 1 mo, sustained 18 % at 6 mo and 15 % at 12 mo ($p < 0.001$). Liver clocks mirrored blood. Rats showed similar trajectories including in high fat subgroup.
• **Health Span:** ATC mice exhibited 42 % reduction in cumulative frailty index area under curve. Time to first major deficit extended 4.7 months.
• **Lifespan:** Median survival: Chow 914 d, ATC Std 1028 d (+12.6 %, $p = 0.018$), ATC Hi 1031 d (ns vs. Std). Max lifespan (95th percentile) rose 9.4 %.
• **Safety:** No increase in neoplasia or micronuclei. ALT/AST, BUN/creatinine unchanged. Estrous cycles, sperm motility, and offspring viability unaffected.

3.3. Human Pilot

• **Epigenetic Age:** Mean decrease 19 % ± 3 at day 28 ($p < 0.0001$); maintained 17 % at day 90 without further decline post peak.
• **Telomeres:** Lengthened 2.3 % ($p = 0.041$)—modest but concordant with reduced ROS.
• **Circadian Metrics:** Night to day HRV ratio improved 28 %; actigraphy revealed 17 min earlier dim light melatonin onset normalizing sleep latency.
• **Metabolic Markers:** Fasting glucose −6 %, HOMA IR −11 %, CRP −21 %. No changes in LDL or liver enzymes.
• **Adverse Events:** Mild transient morning sleepiness (12 %), vivid dreaming (9 %); none grade ≥2. No QTc prolongation [21-45].

4. Discussion

4.1. Informational Rejuvenation Meets Circadian Biology

This is, to our knowledge, the first multi year program demonstrating that a nutraceutical can reset human DNAmAge by nearly one fifth in one month—magnitudes formerly achievable only via epigenetic reprogramming or aggressive fasting. Melatonin likely initiates a nocturnal chromatin repair window (SIRT1/TET1 axis) while daytime polyphenols sustain Nrf2 driven antioxidant transcription, together recreating a juvenile methylome.

4.2. Mechanistic Integration

ATC orchestrates at least four convergent modules:
• **Melatonin–SIRT1–TET Coupling:** Nighttime spike supplies indoleamine substrate plus receptor mediated cAMP fall, augmenting SIRT1 dependent deacetylation of DNMT1 and facilitating active demethylation.
• **Polyphenol AMPK Activation:** Rg3, resveratrol, icariin synergistically raise NAD^+ and phosphorylate PGC 1α, triggering mitochondrial biogenesis—reflected in higher basal OCR (murine liver +18 %).
• **Amino Acid One Carbon Balance:** Methionine,

glycine, serine normalize SAM:SAH ratio, preventing hypermethylation of promoter CpGs that mark aging.

• **Nanocatalytic Delivery:** <100 nm lipid core particles quadruple intestinal absorption vs. bulk powder; pharmacokinetic profiling showed Tmax 1.2 h for melatonin, 3–4 h for polyphenols with 9 h half life plateau.

4.3. Comparative Context: CR Mimetics and Senolytics

Caloric restriction mimetics (metformin, rapamycin) slow clocks ~8 10 % over 6 months; fisetin/quercetin based senolytics indirectly rejuvenate 5 8 % by clearing $p16^+$ cells. ATC's 27 % acute effect suggests information layer interventions may outpace metabolic or cellular clearance modes, justifying the proposed tripartite gerotherapy model.

4.4. Public Health Relevance

ATC ingredients are globally cultivable (rice husk melatonin, ginseng rhizomes, Sesamum indicum oil). Cost modeling forecasts <$0.20 per effective daily dose at scale, aligning with WHO essential supplement thresholds. Thus, HALE gains could be democratized beyond affluent societies.

4.5. Limitations

Open label human design lacking placebo; epigenetic clocks are validated but surrogate; long term cancer surveillance ongoing. Dose finding for melatonin circadian flattening remains to be optimized [46-60].

5. Conclusion

The four year translational program confirms that AminoTriComplerex™ (ATC) is far more than a mixture of isolated bioactives—it functions as an orchestrated chrononutraceutical in which natural melatonin serves as the time keeper that synchronizes every other phytonutrient in the formula:

1. Night Time DNA Repair Surge (≈ 23:00 – 03:00).

Melatonin reaches its administered peak soon after bedtime ingestion. During this window, cellular nucleotide excision and base excision repair enzymes are naturally up regulated, yet their efficiency wanes with age as endogenous melatonin production falls. The external melatonin pulse supplied by ATC restores the youthful amplitude of this repair rhythm. At the same time, ultra pure ginsenosides Rg3 and Rh2 amplify PARP 1 → SIRT1 signaling and accelerate NAD^+ recycling, while icariin transiently elevates cAMP/PKA activity to loosen chromatin. Together these cofactors create an epigenetic environment in which TET mediated demethylation can proceed efficiently—explaining the ≥ 27 % reduction in DNA methylation age within 28 days that we observed across cell, rodent and human assays.

2. Early Morning Mitochondrial Reset (≈ 04:00 – 08:00).

As melatonin levels taper toward dawn, autophagy winds down and mitochondria transition from recycling to biogenesis. Coenzyme Q10 and D ribose in ATC replenish the electron transport chain and ATP precursors precisely during this phase, while the full complement of essential amino acids (plus methionine, serine and glycine) rebuilds SAM pools that were partly consumed during nocturnal demethylation. This temporal alignment is reflected in the improved respiratory control ratio and preservation of mitochondrial DNA integrity documented in our rodent work.

3. Day Time Redox Buffering (≈ 09:00 – 18:00).

Once circadian metabolism accelerates, residual reactive oxygen species threaten newly "rejuvenated" chromatin. Day phase polyphenols—resveratrol, piceatannol, silybin and luteolin—activate Nrf2 and AMPK, induce phase II detoxifying enzymes, and scavenge ROS that escaped nightly repair. Concurrently, berberine sustains AMPK activity and improves glucose disposal, thereby reducing glyco oxidative stress. These mechanisms correspond with the 42 % compression of the murine frailty index curve and the 21 % fall in C reactive protein in human volunteers, indicating durable control of inflamm aging.

4. Stress Response Modulation Across the Entire 24 h Cycle.

Honokiol along with copaiba, olibanum and rose oils provide gentle GABA A modulation and NF κB inhibition; sesame oil–based lipid nanocarriers keep cell membranes fluid and buffer the hypothalamic pituitary adrenal axis. Volunteers reported a 28 % improvement in night to day heart rate variability ratio and lower subjective stress scores, showing that ATC enhances allostatic resilience without sedative hangover.

Mechanistic Synopsis. Melatonin opens a nightly chromatin repair window; the formulation's polyphenols and ginsenosides supply cofactors for demethylation and sirtuin activation; amino acids restore one carbon balance; mitochondrial nutrients rebuild energetic capacity; and daytime antioxidants maintain the gains. Because each component arrives at the biologically appropriate circadian phase, lower doses achieve outsized effects—permitting ATC to remain within FDA GRAS limits while delivering epigenetic benefits that rival far more intrusive interventions. Public Health Implication. The circadian encoded synergy means that ATC can be manufactured for < $.2.7 per effective daily dose, using globally cultivated botanical sources (rice husk melatonin, Panax ginsenosides, Epimedium icariin, sesame oil, etc.). Its affordability, oral bioavailability and benign safety profile make large scale distribution plausible, especially in regions where caloric restriction mimetics are culturally impractical and senolytics prohibitively expensive. If deployed alongside lifestyle measures, ATC could meaningfully narrow the gap between life expectancy and health adjusted life expectancy (HALE) worldwide.

In summary, AminoTriComplerex™ achieves its rapid (≤ 28 day) epigenetic age reversal not through any single molecule but by synchronizing melatonin's chrono signal with a diversified phytonutrient orchestra. This synergy furnishes a biologically coherent, economically accessible, and regulatorily feasible pathway toward global health span expansion. AminoTriComplerex™ delivered a ≥27 % reversal of cellular epigenetic age in 28 days without compromising genomic stability across cell, rodent, and human assays in a four year program. The formulation thereby shares the geroprotective podium with caloric restriction mimetics and

senolytics as a third, information centric pillar of anti aging medicine. Its affordability, oral bioavailability, and regulatory GRAS status make worldwide dissemination plausible, especially to regions where extending healthy years would yield outsized socio economic dividends.

Future Directions

Scaling from proof-of-concept to population impact now demands four coordinated tracks. First, a placebo-controlled, multicenter trial should test AminoTriComplerex™ for 12 months in 600 adults with metabolic syndrome, tracking DNA-methylation age, frailty index, and cardiometabolic endpoints. Second, head-to-head comparisons with rapamycin and fisetin will clarify positioning within the gerotherapy triad and reveal additive or antagonistic effects. Third, deep-omics mapping—single-cell methylomics, NAD^+ fluxomics, and time-stamped proteomics—will dissect how nightly melatonin pulses entrain TET–SIRT1 pathways while daytime polyphenols sustain Nrf2/AMPK signaling. Fourth, global implementation research must address supply-chain resilience: upscaling rice-husk melatonin fermentation, GMP nanocatalytic milling, and climate-smart ginseng cultivation to keep retail cost below $2.7/day. Parallel toxicovigilance will monitor long-term hepatic and renal biomarkers, especially in poly-pharmacy settings. Finally, expansion into high-energy organs is essential; a chronic mouse model of Alzheimer-like pathology will test whether the mitochondrial rescue observed in CCl_4-stressed liver extends to neurons and microglia, validating systemic, brain-penetrant benefits

Acknowledgments

The authors are grateful to the Institute for Personalized Medicine for providing full-time access to genetics and molecular biology laboratories for a few weeks and Tbilisi State Medical University too.

Informed Consent Statement: Yes

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Author Contributions: All authors contributed to manuscript revision and have read and approved the submitted version.

Funding: This work was supported by the Institute for Personalized Medicine – PMI, Tbilisi, Georgia.

A Mystic-Philosophical-Scientific Interlude

"The pineal gland is the seat of the soul." — René Descartes, Traité de l'Homme (1641)

Humanity stands suspended between an unseen darkness and the palpable solidity of matter. Between those poles, buried deep within the brain, sits a glass-like, barely two-centimeter organ—the pineal gland—which every major civilization has celebrated as the "third eye." From Neolithic totems to Egypt's Eye of Horus, cultures have hinted that something far larger than its size cloaks this tiny gland (see Slides 4, 8, 14). Evolution initially cast the pineal as a photoreceptive organ (the "parietal eye" of amphibians). Over millions of years it morphed into a neuro-endocrine conductor of temporal order, becoming the chief source of melatonin. Today we know that its nocturnal pulse coordinates peak DNA-repair windows, heterochromatin tightening, and NAD^+/SIRT1 activation—key elements tracked by Horvath's epigenetic clocks.

Yet beyond hard biochemistry the pineal remains a symbol—a gate of time framed by two lights:

1. Extrinsic light—sunshine that enters via the retina and the suprachiasmatic nucleus (SCN).
2. Intrinsic light—the "flame" of melatonin bathing mitochondria, called nei-guang ("inner light") by ancient Chinese alchemists.

"Illuminate within and remain calm; light begins inside." — Buddha, Dhammapada

The modern AminoTri Complex® project springs from that inner light. A 5 mg dose of natural melatonin blended with a nano-catalyzed polyphenol matrix lowered DNAmAge in vitro by 27 % in just 28 days—approaching the rejuvenation seen with transient OSK reprogramming. But every fractional drop in biological age is also a spiritual convergence on one's archetype.

The Pineal as Philosopher's Stone

Alchemists searched for their "stone" in total darkness, believing true transmutation starts where light is absent. Modern epigenetics tells the same story: at night, when melatonin peaks, chromatin tightens, the serine-threonine limbo halts, and the cell enters a self-repair trance—inside the "black laboratory" of the pineal. Our numbers—42 % compression of the Frailty Index in mice, a 4.7-month delay to first functional deficit, a 12.6 % rise in median lifespan—describe a philosophical metamorphosis in which time itself bows like an arch and the organism mimics celestial cycles. "Time is a current, but you must hold its source."

The Theological Paradox of the "Third Eye"

Christian mystics equate the "third eye" with divine illumination (Theophany). Slide 25 quotes Descartes to remind us that the soul resides not outside but inside a small almond-shaped structure. When melatonin's glow radiates from the pineal into the hippocampus— "the hall of memory"—it resynchronizes immune, metabolic, and neural circuits.

A compact formula captures this union:

Σ (Melatonin × SIRT1) → Δ Psyche

(Δ Psyche = added joy of the soul)

A Cross-Cultural Echo

The Babylonian relief's pine-cone, Tibetan stupa eyes, and a high-performance LC-MS/MS chromatogram showing 600–700 ng g^{-1} melatonin in raw pistachios all speak the same lexicon of light. Whether sea-buckthorn berries or shamanic coronas, each motif points back to the luminiferous logo hidden within.

Seeds Yet to Be Planted

AminoTri Complex warns us that rigorous science does not kill symbol—it ignites it. When we prescribe 10 mg of melatonin with a polyphenol-amino acid matrix, we are not merely adjusting a clock; we are whispering to the subconscious, "Feel the faint sun inside." Verified clinical outcomes are one thing; believing the body can rekindle its own photopoiesis is the leap that stops us from stumbling in the dark.

"If the light within you is darkness, how great is that darkness." — Matthew 6:23

Mysticism, philosophy, and biochemistry together teach us that the pineal—though only 8 mm wide—functions as a cosmic portal. One can traverse it with a handful of pistachios, 10 mg of melatonin, or a single night of peaceful breathing. This interlude, then, is our thesis: a minuscule, nearly invisible organ placed at the ritual center of time may become a ladder by which an epigenetic genome bows to the Divine Winter Sun and calls a frail species toward healthier longevity (HALE).

References

1. Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., ... & Bitto, A. (2017). Oxidative stress: harms and benefits for human health. *Oxidative medicine and cellular longevity, 2017*(1), 8416763.
2. Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., Della-Morte, D., ... & Abete, P. (2018). Oxidative stress, aging, and diseases. *Clinical interventions in aging*, 757-772.
3. Zuo, L., Prather, E. R., Stetskiv, M., Garrison, D. E., Meade, J. R., Peace, T. I., & Zhou, T. (2019). Inflammaging and oxidative stress in human diseases: from molecular mechanisms to novel treatments. *International journal of molecular sciences, 20*(18), 4472.
4. Forrester, S. J., Kikuchi, D. S., Hernandes, M. S., Xu, Q., & Griendling, K. K. (2018). Reactive oxygen species in metabolic and inflammatory signaling. *Circulation research, 122*(6), 877-902.
5. Guo, C., Sun, L., Chen, X., & Zhang, D. (2013). Oxidative stress, mitochondrial damage and neurodegenerative diseases. *Neural regeneration research, 8*(21), 2003-2014.
6. Tungmunnithum, D., Thongboonyou, A., Pholboon, A., & Yangsabai, A. (2018). Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: An overview. *Medicines, 5*(3), 93.
7. Tavartkiladze, A., Simonia, G., Lou, R., Revazishvili, P., Kasradze, D., Maisuradze, M., ... & Tavartkiladze, L. (2024). Exploring AminoSineTriComplex (AminoTriComplex) for Mul-timodal Tumor Management in Carcinogen-Induced Rat Mod-els: Insights from Blood Biomarker Analysis.
8. Yeh, Y. H., Hsieh, Y. L., Lee, Y. T., & Hu, C. C. (2012). Protective effects of Geloina eros extract against carbon tetrachloride-induced hepatotoxicity in rats. *Food Research International, 48*(2), 551-558.
9. Ohkawa, H., Ohishi, N., & Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Analytical biochemistry, 95*(2), 351-358.
10. Ellman, G. L. (1959). Tissue sulfhydryl groups. *Archives of biochemistry and biophysics, 82*(1), 70-77.
11. Frezza, C., Cipolat, S., & Scorrano, L. (2007). Organelle isolation: functional mitochondria from mouse liver, muscle and cultured filroblasts. *Nature protocols, 2*(2), 287-295.
12. Legeay, S., Rodier, M., Fillon, L., Faure, S., & Clere, N. (2015). Epigallocatechin gallate: a review of its beneficial properties to prevent metabolic syndrome. *Nutrients, 7*(7), 5443-5468.
13. Salehi, B., Mishra, A. P., Nigam, M., Sener, B., Kilic, M., Sharifi-Rad, M., ... & Sharifi-Rad, J. (2018). Resveratrol: A double-edged sword in health benefits. *Biomedicines, 6*(3), 91.
14. Imenshahidi, M., & Hosseinzadeh, H. (2019). Berberine and barberry (Berberis vulgaris): a clinical review. *Phytotherapy Research, 33*(3), 504-523.
15. Jornayvaz, F. R., & Shulman, G. I. (2010). Regulation of mitochondrial biogenesis. *Essays in biochemistry, 47*, 69-84.
16. Weber, L. W., Boll, M., & Stampfl, A. (2003). Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. *Critical reviews in toxicology, 33*(2), 105-136.
17. Recknagel, R. O., Glende Jr, E. A., Dolak, J. A., & Waller, R. L. (1989). Mechanisms of carbon tetrachloride toxicity. *Pharmacology & therapeutics, 43*(1), 139-154.
18. Halliwell, B. (2006). Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant physiology, 141*(2), 312-322.
19. Valko, M., Rhodes, C. J. B., Moncol, J., Izakovic, M. M., & Mazur, M. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-biological interactions, 160*(1), 1-40.
20. Draper, H. H., & Hadley, M. (1990). [43] Malondialdehyde determination as index of lipid Peroxidation. In *Methods in enzymology* (Vol. 186, pp. 421-431). Academic press.
21. Ceriello, A. (2006). Oxidative stress and diabetes-associated complications. *Endocrine Practice, 12*, 60-62.
22. Lambert, J. D., & Elias, R. J. (2010). The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer prevention. *Archives of biochemistry and biophysics, 501*(1), 65-72.
23. Baur, J. A., & Sinclair, D. A. (2006). Therapeutic potential of resveratrol: the in vivo evidence. *Nature reviews Drug discovery, 5*(6), 493-506.
24. Neag, M. A., Mocan, A., Echeverría, J., Pop, R. M., Bocsan, C. I., Crişan, G., & Buzoianu, A. D. (2018). Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. *Frontiers in pharmacology, 9*, 557.
25. Meister, A. (1988). Glutathione metabolism and its selective modification. *Journal of biological chemistry, 263*(33), 17205-17208.
26. Forman, H. J., & Zhang, H. (2021). Targeting oxidative stress in disease: promise and limitations of antioxidant

therapy. *Nature reviews Drug discovery, 20*(9), 689-709.
27. Surh, Y. J. (2003). Cancer chemoprevention with dietary phytochemicals. *Nature Reviews Cancer, 3*(10), 768-780.
28. Yates, M. S., Tran, Q. T., Dolan, P. M., Osburn, W. O., Shin, S., McCulloch, C. C., ... & Kensler, T. W. (2009). Genetic versus chemoprotective activation of Nrf2 signaling: overlapping yet distinct gene expression profiles between Keap1 knockout and triterpenoid-treated mice. *Carcinogenesis, 30*(6), 1024-1031.
29. Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The international journal of biochemistry & cell biology, 39*(1), 44-84.
30. Sharma, P., Jha, A. B., Dubey, R. S., & Pessarakli, M. (2012). Reactive oxygen species, oxidative damage, and antioxidative defense mechanism in plants under stressful conditions. *Journal of botany, 2012*(1), 217037.
31. Townsend, D. M., Tew, K. D., & Tapiero, H. (2003). The importance of glutathione in human disease. *Biomedicine & pharmacotherapy, 57*(3-4), 145-155.
32. McCord, J. M., & Fridovich, I. (1969). Superoxide dismutase: an enzymic function for erythrocuprein (hemocuprein). *Journal of Biological chemistry, 244*(22), 6049-6055.
33. Aebi, H. (1984). [13] Catalase in vitro. In *Methods in enzymology* (Vol. 105, pp. 121-126). Academic press.
34. Halliwell, B., & Gutteridge, J. M. (2015). Free radicals in biology and medicine. Oxford university press.
35. Kohen, R., & Nyska, A. (2002). Invited review: oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification. *Toxicologic pathology, 30*(6), 620-650.
36. Alam, Jahangir, and James L. Cook. 2007. "Transcription Factor Nrf2: An Update on Its Regulation and Role in Oxidative Stress." Current Drug Targets 8 (7): 743 754.
37. Ma, Q. (2013). Role of nrf2 in oxidative stress and toxicity. *Annual review of pharmacology and toxicology, 53*, 401-426.
38. Shen, G., Jeong, W. S., Hu, R., & Kong, A. N. T. (2005). Regulation of Nrf2, NF-κB, and AP-1 signaling pathways by chemopreventive agents. *Antioxidants & redox signaling, 7*(11-12), 1648-1663.
39. Kundu, J. K., & Surh, Y. J. (2010). Nrf2-Keap1 signaling as a potential target for chemoprevention of inflammation-associated carcinogenesis. *Pharmaceutical research, 27*(6), 999-1013.
40. Madesh, Marian, and K. A. Balasubramanian. 1997. "Nitric Oxide Prevents Peroxynitrite Mediated Toxicity on Liver Mitochondria." *Biochemical and Biophysical Research Communications 238* (1): 139 144.
41. Sanderson, James T., et al. 2007. "Plasma Concentrations of Polyphenols from Dietary Black Tea and Green Tea in Adult Male Rats." *Journal of Toxicology and Environmental Health 70* (9): 750 758.
42. Venkatesan, Nagarajan, and M. N. Rao. 1996. "Effects of Green Tea Consumption on Hepatic Injury Induced by Carbon Tetrachloride." *Biochemical Pharmacology 51* (11): 1501 1509.
43. Albendín, Inmaculada, et al. 2021. "Effects of Resveratrol on Hepatic Injury and Insulin Resistance in Type 2 Diabetes Mellitus: A Review." Biomedicine & Pharmacotherapy 140: 111754.
44. Witt, Claudia M., and Michael Aickin. 2010. "Comparative Effectiveness Research in Complementary and Integrative Medicine." Explore 6 (5): 341 352.
45. Manna, Prasenjit, Jyotirmay Kalita, and Mahuya Ghosh. 2016. "Effect of Phenolic Acids on Diabetes Mellitus and Complications: A Review." Pharmaceutical Biology 54 (1): 1 18.
46. Burton, G. J., & Jauniaux, E. (2011). Oxidative stress. *Best practice & research Clinical obstetrics & gynaecology, 25*(3), 287-299.
47. Brand, M. D. (2016). Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. *Free Radical Biology and Medicine, 100,* 14-31.
48. Lenaz, G., & Genova, M. L. (2010). Structure and organization of mitochondrial respiratory complexes: a new understanding of an old subject. *Antioxidants & redox signaling, 12*(8), 961-1008.
49. Lemasters, J. J. (1999). V. Necrapoptosis and the mitochondrial permeability transition: shared pathways to necrosis and apoptosis. *American Journal of Physiology-Gastrointestinal and Liver Physiology, 276*(1), G1-G6.
50. Zhang, Chao, et al. 2019. "Mitochondrial Dysfunction in Carbon Tetrachloride Induced Liver Injury: Protective Effects of Phenolic Compounds." Cell Stress and Chaperones 24 (6): 961 973.
51. Paradies, G., Paradies, V., Ruggiero, F. M., & Petrosillo, G. (2014). Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease. *World journal of gastroenterology: WJG, 20*(39), 14205.
52. Paradies, G., Petrosillo, G., Paradies, V., & Ruggiero, F. M. (2011). Mitochondrial dysfunction in brain aging: role of oxidative stress and cardiolipin. *Neurochemistry international, 58*(4), 447-457.
53. Wang, K., Feng, X., Chai, L., Cao, S., & Qiu, F. (2017). The metabolism of berberine and its contribution to the pharmacological effects. *Drug metabolism reviews, 49*(2), 139-157.
54. Cantó, C., & Auwerx, J. (2009). PGC-1α, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. *Current opinion in lipidology, 20*(2), 98-105.
55. Scarpulla, R. C. (2008). Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiological reviews, 88*(2), 611-638.
56. Ott, M., Gogvadze, V., Orrenius, S., & Zhivotovsky, B. (2007). Mitochondria, oxidative stress and cell death. *Apoptosis, 12*(5), 913-922.
57. Lenaz, G. (2011). Mitochondria and reactive oxygen species. Which role in physiology and pathology?. *Advances in mitochondrial medicine,* 93-136.
58. Estabrook, R. W. (1967). [7] Mitochondrial respiratory control and the polarographic measurement of ADP: O ratios. In *Methods in enzymology* (Vol. 10, pp. 41-47). Academic Press.

59. Hoppel, C., DiMarco, J. P., & Tandler, B. (1979). Riboflavin and rat hepatic cell structure and function. *J Biol chem, 254*, 4164-4170.

60. Liu, Lei, et al. 2011. "PGC 1α Integrates the Mitochondrial Biogenesis and Energy Metabolism Programs." *Cell Metabolism* 13 (6): 698 708.