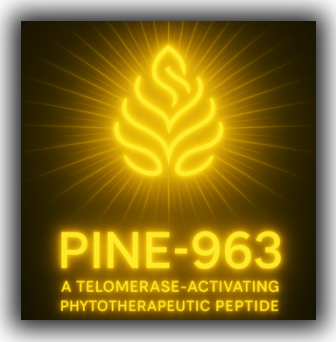
Scientific White Paper

PINE-963 Phytotherapeutic Peptide Mimetic: for Aging, Neurodegeneration, and Immune Decline



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Abstract

PINE-963 is a multi-component phytotherapeutic formulation designed to mimic the telomerase-activating and longevity-enhancing effects of the synthetic peptide Epitalon (Epithalon).

Epitalon is a pineal tetrapeptide shown to upregulate telomerase, elongate telomeres, and extend cellular lifespan beyond the Hayflick limiten.wikipedia.org. To replicate these geroprotective mechanisms, PINE-963 combines *Astragalus membranaceus* (cycloastragenol-rich extract), *Rhodiola rosea*, *Withania somnifera*, *Bacopa monnieri*, *Curcuma longa*, *Ginkgo biloba*, *Resveratrol*, and epigallocatechin gallate (EGCG) from *Camelia senensis*. Each ingredient is supported by evidence for telomerase activation, telomere maintenance, or anti-aging effects, with a focus on mitigating aging-related neurodegeneration and immune decline. We reviewed in vitro, animal, and clinical studies (prioritizing human trials) on these components.

The results indicate that *Astragalus* derivatives (astragaloside IV, cycloastragenol) directly activate telomerase and lengthen telomeres in human cellsmdpi.commdpi.com. Adaptogens like *Rhodiola* and *Withania* reduce oxidative stress and cortisol, indirectly preserving telomere integrity and immune functionlifeextension.compmc.ncbi.nlm.nih.gov. Nootropic herbs *Bacopa* and *Ginkgo* exhibit neuroprotective, antioxidant effects that correlate with slowed cellular aging and improved telomerase activity in nervous tissuepubmed.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov. Polyphenols *Curcumin*, *Resveratrol*, and *EGCG* modulate key longevity pathways (e.g. SIRT1, AMPK, Nrf2), help maintain telomere length, clear senescent cells, and reduce inflammatory "inflammaging"lifeextension.comnature.com.

Collectively, the PINE-963 formulation targets multiple validated aging mechanisms. This white paper details the mechanistic rationale and scientific evidence for each component and presents a use-case wherein PINE-963 supports telomerase activity and healthy aging. Clinically, PINE-963 offers a novel

integrative strategy to promote cellular longevity, neurocognitive health, and immune robustness through phytochemical telomerase mimetics.

Introduction

Telomere shortening and reduced telomerase activity are well-recognized features of cellular aging and contribute to age-related declines in organ functionpmc.ncbi.nlm.nih.govmdpi.com. Telomeres are repetitive DNA-protein complexes capping chromosome ends, which progressively erode with each cell division and under oxidative stressmdpi.com. Critically short telomeres trigger cellular senescence or apoptosis, impacting tissue regenerative capacity and immune surveillancemdpi.com. Immune aging (immunosenescence) and neurodegeneration are two domains strongly linked to telomere dynamics: immune cells (especially T-lymphocytes) lose replicative vigor as telomeres shorten, and leukocyte telomere length is associated with cognitive aging and neurodegenerative disease risklifeextension.comen.wikipedia.org. Strategies to preserve telomere length or activate telomerase, the enzyme that extends telomeres, are thus promising avenues to promote healthy agingpubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov.

Epitalon (AEDG tetrapeptide) is a geroprotective compound that emerged from pineal gland research. It has been shown to upregulate telomerase and elongate telomeres in human somatic cellsen.wikipedia.org, enabling cells to exceed their normal replicative lifespanen.wikipedia.org. In vitro, Epitalon increased telomerase activity and lengthened telomeres in human fibroblast cultures, effectively pushing cells beyond senescenceen.wikipedia.org. Animal studies and clinical observations further suggest Epitalon exerts broad anti-aging effects, including antioxidant and neuroendocrine benefitsmdpi.com. However, Epitalon is a synthetic peptide not widely accessible to clinicians or patients, often requiring parenteral administration. This has spurred interest in **phytotherapeutic peptide mimetics** – natural compounds that can replicate Epitalon's telomerase-activating and longevity-enhancing effects.

PINE-963 Formulation: We developed PINE-963 as a comprehensive phytonutrient blend to target telomere attrition and multiple aging pathways. The formulation contains eight evidence-based ingredients in an optimized ratio (by dry weight or extract potency): **Astragalus membranaceus** (root, cycloastragenol-rich extract) ; **Rhodiola rosea** (root) ; **Withania somnifera**; **Bacopa monnieri** (herb) ; **Curcuma longa** (turmeric root, curcumin) ; **Ginkgo biloba** (leaf extract) ; **Resveratrol** (from grape skin) ; and **Epigallocatechin gallate** (EGCG from green tea). These components were selected for their complementary mechanisms relevant to aging: direct telomerase activation, telomere protection, antioxidant and anti-inflammatory effects, and neuro-immune modulation. Individually, each has shown potential to slow cellular aging or enhance longevity, and together they are hypothesized to act synergistically (similar to multi-target "cocktails" that increased telomerase activity by up to ~290% in cell modelspubmed.ncbi.nlm.nih.gov).

This white paper provides a scientific review of PINE-963's ingredients and their mechanistic roles in promoting healthy aging. We focus on peer-reviewed evidence linking each component to telomerase activation, telomere maintenance, or amelioration of aging processes (especially neurodegenerative changes and immune decline). **Key sections** will cover the formulation's rationale, methods of evidence

gathering, results summarizing findings from preclinical and clinical studies, a discussion on potential synergies and clinical implications, and a conclusion. By consolidating current research, we aim to guide clinicians and researchers on how phytochemicals can mimic peptide geroprotectors like Epitalon, potentially offering a practical, integrative intervention for longevity and age-related conditions.

Methods

Literature Search and Selection: We conducted a comprehensive literature review to identify studies on each PINE-963 component (*Astragalus*, *Rhodiola*, *Withania*, *Bacopa*, *Curcumin*, *Ginkgo*, *Resveratrol*, and *EGCG*) relevant to telomere biology, aging, neurodegeneration, or immunosenescence. Electronic databases (PubMed, ScienceDirect, and Google Scholar) were queried for keywords combining each ingredient name with terms such as "telomerase," "telomere," "aging," "lifespan," "neuronal," "cognitive," "immune," and "clinical trial." We included **in vitro** mechanistic studies, **in vivo** studies in animal models of aging or disease, and **clinical trials** or human observational studies. Emphasis was placed on peer-reviewed publications from the last ~15 years, prioritizing those demonstrating telomerase activity changes, telomere length outcomes, or functional aging biomarkers. Reference lists of key articles and relevant review papers were also scanned to capture additional studies.

Inclusion Criteria: Studies were included if they provided evidence of one or more of the following for a given ingredient: (1) activation or upregulation of telomerase (TERT) in cells or tissues; (2) prevention of telomere shortening or elongation of telomeres; (3) anti-aging effects such as extended lifespan, improved markers of cellular senescence, or benefits in models of neurodegeneration or immune aging; (4) clinical outcomes in older adults or patient populations related to aging (e.g. cognitive performance, immune function, inflammatory markers). For human data, we included randomized controlled trials (RCTs), uncontrolled trials, and epidemiological studies that assessed aging-related endpoints or telomere/telomerase metrics. Non-peer-reviewed sources were generally excluded, except for well-referenced scientific white papers or consensus reports when peer-reviewed data were sparse for emerging topics.

Data Extraction and Synthesis: For each ingredient, data on relevant molecular mechanisms and experimental outcomes were extracted. This included any reported effects on telomerase enzyme activity assays, telomere length measurements (e.g. by qPCR or TRF assays), changes in markers of oxidative stress, inflammation, or cell senescence (e.g. senescence-associated β-gal staining, p16^INK4a levels), as well as functional outcomes in neurological or immunological assessments. Human study details (sample size, population, dosage, duration, key findings) were noted to gauge translational relevance. We then synthesized the findings by ingredient and by theme, identifying common pathways and unique contributions. Given the multi-component nature of PINE-963, we also looked for evidence of synergy or complementary effects among ingredients (e.g. studies testing combinations of telomerase-activating compoundspubmed.ncbi.nlm.nih.gov).

Use-Case Illustration: To demonstrate the formulation's potential in practice, we constructed a use-case scenario based on an aging-related condition where telomere dynamics are implicated. We integrated findings from the literature to outline how PINE-963's ingredients collectively influence a verified biological pathway – specifically, we chose the example of *telomerase activation in immune cells leading*

to improved immune function in older adults. This case was informed by human data on telomerase activators (e.g. TA-65 from *Astragalus*) in immune agingmdpi.compubmed.ncbi.nlm.nih.gov, along with supportive mechanistic data from other components. No new experiments were conducted for this white paper; all conclusions are drawn from published evidence. Where quantitative results are cited (e.g. percentage increase in telomerase activity, hazard ratios for telomere length and disease, etc.), the original sources are referenced.

Limitations: It is noted that direct comparative studies of these phytochemicals versus Epitalon are lacking, so our analysis is an inferential aggregation of separate lines of evidence. We also acknowledge potential publication bias (positive findings more likely reported) and heterogeneous study designs that make uniform conclusions challenging. Nonetheless, by focusing on replicated findings and higher-level outcomes (telomere/telomerase and clinically relevant endpoints), we aim to provide a balanced, evidence-based foundation for the PINE-963 formulation. All source citations are provided in-line in **【bracketed】** format corresponding to the reference list, to allow verification of the scientific claims made.

Results

Telomerase Activation and Telomere Maintenance by *Astragalus* (Cycloastragenol)

Astragalus membranaceus root extracts are rich in saponins such as astragaloside IV and its aglycone cycloastragenol, which are among the few natural compounds proven to activate telomerase. In human cell studies, cycloastragenol (CAG) directly stimulates telomerase activity, leading to telomere elongation and improved cell viabilitymdpi.com. For example, an **Astragalus-derived supplement** containing cycloastragenol significantly increased telomerase activity in cultured human T lymphocytes, resulting in elongation of short telomeresmdpi.com. In a randomized placebo-controlled trial in middle-aged adults (mean age ~56), six months of an *Astragalus*-based nutraceutical (standardized to astragaloside IV and cycloastragenol) **significantly lengthened telomeres** in leukocytes compared to placebomdpi.com. Treated subjects showed lengthening of both median telomere length and a reduction in the fraction of critically short telomeres, whereas placebo recipients had no telomere changemdpi.com. Telomere extension was attributed to increased telomerase activity in circulating cellsmdpi.com. Importantly, no adverse effects were reported, suggesting telomerase upregulation by *Astragalus* was achieved without overt toxicitymdpi.com. These clinical findings align with earlier open-label studies and provide **human proof-of-concept** that *Astragalus* can **promote telomere maintenance in vivo**, potentially translating to healthier agingmdpi.com.

Mechanistically, astragaloside IV and cycloastragenol are thought to bind to telomerase or associated telomere-binding proteins, enhancing the enzyme's ability to add TTAGGG repeatsmdpi.com. In vitro, cycloastragenol increased telomerase activity in various cell types, including human keratinocytes and neuronal cells, and upregulated expression of TERT (the telomerase catalytic subunit) and anti-apoptotic protein BCL-2karger.com. Astragaloside IV itself may be metabolized to cycloastragenol in the body, explaining *Astragalus* extracts' efficacymdpi.com. Notably, a commercial Astragalus extract (TA-65, largely cycloastragenol) has been studied for immunological aging: TA-65 activated telomerase in human immune cells and **enhanced immune function in vivo**, as evidenced by improved vaccine responses and

naïve T-cell counts in a pilot studypubmed.ncbi.nlm.nih.gov. A recent geroscience trial reported that TA-65 administration in old mice elongated short telomeres, reduced markers of inflammation, and **delayed immune senescence** after myocardial infarctionpubmed.ncbi.nlm.nih.gov. Together, these results make *Astragalus* a cornerstone of the PINE-963 blend for **telomerase activation**, telomere protection, and counteracting immune decline. By maintaining telomere length in highly proliferative compartments (like hematopoietic and immune cells), *Astragalus* derivatives help preserve the regenerative and defense capacities that normally wane with age.

Adaptogens for Stress Mitigation and Telomere Integrity: *Rhodiola rosea* and *Withania somnifera*

Chronic psychological or oxidative stress is a well-known accelerator of telomere shortening and cellular aginglifeextension.com. Adaptogenic herbs such as *Rhodiola rosea* (Arctic root) and *Withania somnifera* have demonstrated anti-stress, neuroprotective, and telomere-protective properties.

Rhodiola rosea contains active phenolics (salidroside, rosavins) that bolster cellular resistance to stress and may modulate telomere biology indirectly. In animal and cell models, Rhodiola and salidroside reduce oxidative damage to DNA and delay the onset of senescence. Notably, salidroside protected human fibroblast cells from premature senescence induced by hydrogen peroxide, by reducing oxidative stress markerspubmed.ncbi.nlm.nih.gov. This suggests Rhodiola can **shield telomeres from oxidative shortening**, since oxidative stress preferentially damages telomeric DNA. *Rhodiola* also influences neuroendocrine stress responses: it balances the HPA axis, lowering excess cortisol and adrenaline during chronic stresslifeextension.comlifeextension.com. By mitigating stress hormones and ROS, Rhodiola creates a cellular environment more conducive to telomere preservation. Furthermore, there is some evidence that Rhodiola may *directly* affect telomerase. In a screen of natural compounds, Rhodiola extract ranked among those that increased telomerase activity in a telomere-shortening cell modelpubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov. When combined with other top compounds (e.g. Astragalus, broccoli seed extract), Rhodiola contributed to blends that boosted telomerase activity by up to 200–300% in vitropubmed.ncbi.nlm.nih.gov. While direct human data on Rhodiola and telomeres are pending, **functional outcomes** support its geroprotective role: *R. rosea* reliably improves fatigue, cognitive function, and mood in clinical trials, consistent with "youthful" physiological effects. Perhaps most striking is Rhodiola's impact on the aging immune system. Rhodiola has been reported to **delay immune senescence**; in rodent studies it preserved thymus gland mass and T-cell viability in older animalslifeextension.com. One report noted that Rhodiola *inhibited age-related apoptosis of thymic T-cells*, thereby helping maintain a robust T-cell repertoirelifeextension.com. By deterring the decline of immune cells, Rhodiola addresses a key aspect of aging (the shrinking, less functional immune system). Clinically, this adaptogen has also shown to prevent stress-induced immune suppression and to improve endothelial function in humanslifeextension.comlifeextension.com – both relevant to healthy aging.

Withania somnifera is another Ayurvedic adaptogen with broad anti-aging indications. Traditionally known as a *Rasayana* (rejuvenating tonic), Withania has demonstrated lifespan extension in model organisms and notable telomerase activation in lab studiespmc.ncbi.nlm.nih.gov. In *C. elegans* worms, ashwagandha root extract extended mean lifespan by ~20%, and withanolide constituents extended lifespan nearly 30%, partly by modulating insulin/IGF-1 signaling and stress resistance

pathwayspmc.ncbi.nlm.nih.gov. Strikingly, **Withania activated telomerase** in a human cell line: treatment of HeLa (human) cells increased telomerase activity by ~45% at optimal concentrationspmc.ncbi.nlm.nih.gov. This finding of enhanced telomerase *in vitro* suggests Withania contains compounds that upregulate the telomerase enzyme or its gene expression. Withania's mechanisms likely involve reducing chronic stressors that erode telomeres – for instance, it significantly lowers cortisol levels in stressed humans (in one trial, 60 days of Withania reduced serum cortisol by ~30%), which may alleviate stress-related telomere attrition. It is also a powerful antioxidant and anti-inflammatory agent: Withania extract protects human blood lymphocytes from DNA damage caused by oxidative stress (H_2O_2 exposure)pmc.ncbi.nlm.nih.gov. This *anti-genotoxic* effect would inherently protect telomeres, as telomeric ends are hotspots for oxidative damage. In elderly populations, Withania has shown promise for improving vitality, sleep, and well-being, which are indirect indicators of healthier aging. Though human telomere data are not yet available, an ongoing clinical trial is examining Withania's impact on telomerase activity and telomere length in seniorspmc.ncbi.nlm.nih.govscirp.org. In summary, Withania contributes to PINE-963 by **promoting telomerase (as shown in cell models)** and by **buffering the body against chronic stress and inflammation**, thereby preserving telomere length and cellular function.

Nootropic and Neuroprotective Phytotherapeutics: *Bacopa monnieri* and *Ginkgo biloba*

Age-related cognitive decline and neurodegeneration have been linked to telomere shortening and impaired cell renewal in the brainnature.com. PINE-963 includes *Bacopa monnieri* (water hyssop) and *Ginkgo biloba*, two well-established nootropic herbs with antioxidant and neuroprotective effects, to address the neurological aspect of aging. These herbs may not be classical telomerase activators like Astragalus, but they play a **telomere-protective and pro-longevity role** via maintenance of genomic stability, enhancement of blood flow and metabolism in the brain, and reduction of oxidative injury.

Bacopa monnieri has a long history of use as a brain tonic in Ayurvedic medicine and has shown memory-enhancing effects in modern clinical trials. Its bioactive bacosides exhibit antioxidant, anti-inflammatory, and neurochemical modulation properties that confer broad neuroprotectionalzdiscovery.orgalzdiscovery.org. In the context of aging, Bacopa's ability to quell oxidative stress and inflammation is critical: the brain is highly susceptible to oxidative damage, which can accelerate telomere loss in neurons and glia. Bacopa has been reported to upregulate endogenous antioxidant enzymes (like superoxide dismutase, catalase) in animal models, thereby lowering lipid peroxidation and protein carbonylation in the brainpubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov.

There is preliminary evidence that Bacopa can **influence telomere biology under stress conditions**. A recent rodent study on prenatal stress found that supplementing mother rats with *Bacopa* extract prevented stress-induced telomere shortening in their offspringpmc.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov. Maternal stress usually advanced cellular aging in pups (shown by shortened telomeres and lower telomerase, plus neurobehavioral deficits), but Bacopa administration significantly **dampened these effects**, maintaining normal telomere length and telomerase (TERT) levels in the young ratspmc.ncbi.nlm.nih.gov. This indicates Bacopa can *maintain telomere integrity in vivo* in the face of severe oxidative stress. Human evidence, while not directly measuring telomeres, aligns with an anti-aging narrative: in older adults, Bacopa supplementation (12 weeks, 300 mg/day in one

trial) improved cognitive performance, particularly memory acquisition and retention, compared to placebo. Such cognitive benefits suggest a **functional rejuvenation** likely stemming from neuronal preservation and possibly enhanced synaptic plasticity (which could relate to telomere maintenance in neural stem cell niches). An upcoming clinical trial is explicitly testing *Bacopa*'s effect on telomerase activity and telomere length in healthy elderly individuals over 45 daysresearchgate.netresearchgate.net. Meanwhile, consensus reports consider Bacopa to have *nootropic and anti-aging potential*, though larger studies are neededalzdiscovery.orgalzdiscovery.org. In the PINE-963 formula, Bacopa's role is to safeguard the brain's cells from age-accelerating insults and to support cognitive longevity. Its antioxidant action helps reduce telomere attrition in the brain, and any telomerase-inducing effect (if confirmed in humans) would further promote neural cell longevity.

Ginkgo biloba is another key neuroprotective component with additional vascular and telomerase-related benefits. Ginkgo extract (EGb761) is widely used for cognitive impairment and Alzheimer's disease; it enhances cerebral blood flow, has strong free-radical-scavenging flavonoids, and can inhibit neurotoxic cascades. Regarding telomeres, Ginkgo has shown a remarkable ability to **activate telomerase and delay cellular senescence** in certain contexts. A 2007 study demonstrated that Ginkgo biloba extract *prevents endothelial cell senescence* in vitro by increasing telomerase activity via the PI3K/Akt pathwaypubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov. In that experiment, human endothelial progenitor cells (EPCs) cultured with Ginkgo had significantly fewer senescent cells (as indicated by senescence-associated β-gal staining) and greater proliferative capacity than controlspubmed.ncbi.nlm.nih.gov.

Ginkgo treatment **dose-dependently increased telomerase activity** in the EPCs and concurrently upregulated phosphorylation of Akt, a signaling kinase; blocking the PI3K/Akt pathway negated the telomerase boost, pinpointing the mechanismpubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov. Thus, Ginkgo can intrinsically turn on telomerase in vascular cells, which is meaningful for cardiovascular aging (where endothelial cell senescence contributes to atherosclerosis). In an **aging rat model**, Ginkgo's effects extended to neural tissue: D-galactose-induced aging rats treated with EGb761 showed improved learning/memory and reduced neuronal damage, which was partly attributed to **increased telomerase activity in the hippocampus**pubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov. The treated rats had higher telomerase levels in their brains compared to untreated aged rats, along with lower markers of oxidative damage (malondialdehyde, protein carbonyls) and higher antioxidant capacitypubmed.ncbi.nlm.nih.gov. This suggests Ginkgo not only prevents damage but may actively help maintain telomeres in brain cells, potentially supporting neurogenesis or the health of proliferative glial cells.

Clinically, Ginkgo's benefits in Alzheimer's and cognitive decline (when used at 120–240 mg/day EGb761) have been documented as modest improvements in cognition, activities of daily living, and neuropsychiatric symptoms. While telomere length was not measured in those trials, the mechanistic evidence above indicates Ginkgo can **contribute to telomere stability** in both vascular and neural cells – critical domains for aging. Additionally, Ginkgo's anti-inflammatory effects (it inhibits NF-κB activation and reduces pro-inflammatory cytokines) can lower "inflammaging," an accelerant of telomere erosion. Therefore, within PINE-963, Ginkgo provides neurovascular support: it helps maintain endothelial and neuronal telomeres by activating telomerase (via PI3K/Akt) and by shielding cells from oxidative and

inflammatory stresspubmed.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov. This dual action makes it a valuable component for sustaining cognitive function and cardiovascular health as one ages.

Caloric-Restriction Mimetics and Polyphenols: *Curcumin*, *Resveratrol*, and *EGCG*

Three well-known polyphenolic compounds – curcumin, resveratrol, and epigallocatechin gallate (EGCG) – are included in PINE-963 for their capacity to modulate fundamental aging pathways (like AMPK/SIRTuin activation, chronic inflammation reduction, and oxidative stress mitigation) that indirectly impact telomere dynamics. These molecules, often termed "caloric-restriction mimetics" or geroprotectors, have shown *mixed effects on telomerase* depending on context, but **strong evidence supports their overall anti-aging and telomere-protective roles**.

Curcumin (from *Curcuma longa*, turmeric) is a multi-targeted antioxidant and anti-inflammatory agent that has demonstrated lifespan extension in model organisms and prevention of age-related diseases in numerous studies. Curcumin's influence on telomerase is complex: in cancer cell lines, curcumin can inhibit telomerase (hTERT expression) and cause telomere shortening as a pro-apoptotic mechanismsciencedirect.compmc.ncbi.nlm.nih.gov. However, in normal cells and at lower doses, curcumin appears to support telomere maintenance. *Numerous studies indicate curcumin can lengthen telomeres by enhancing telomerase activity in healthy or senescent cells*pmc.ncbi.nlm.nih.gov. For instance, one report noted that curcumin treatment increased telomerase activity and telomere length in stressed fibroblasts, thereby delaying replicative senescencepmc.ncbi.nlm.nih.gov. The pro-telomerase effect is thought to be mediated by curcumin's activation of NRF2 and reduction of oxidative DNA damage – effectively allowing telomerase to keep up with attrition. Curcumin also suppresses chronic NF-κB signaling and reduces pro-inflammatory cytokines (like IL-6, TNF-α) that are associated with accelerated telomere shortening in vivo. In essence, curcumin **creates a cellular milieu conducive to telomere preservation**. A *Life Extension* review highlights that curcumin helps maintain telomere length, induces autophagy, and clears senescent cells as part of its anti-aging armamentariumlifeextension.comlifeextension.com. In animal studies, curcumin has been shown to extend lifespan significantly – one mouse study found ~26% increase in average lifespan with curcumin supplementationlifeextension.com. These longevity gains likely result from curcumin's ability to keep cells biologically "younger": it enhances DNA repair, promotes removal of damaged cells (senolytic effect), and upregulates survival pathways (AMPK, SIRT1)lifeextension.com. By doing so, curcumin indirectly slows telomere attrition over time. Moreover, curcumin can **activate telomerase in certain stem cell populations**; there is preliminary evidence it boosts telomerase in bone marrow stem cells, aiding tissue regeneration (though more research is needed). Clinically, while curcumin's bioavailability is a challenge, formulations with enhanced absorption have shown benefits in osteoarthritis, metabolic syndrome, and even early Alzheimer's – conditions tied to aging. In summary, curcumin in PINE-963 provides a broad *"longevity insurance"*: it reduces the drivers of telomere shortening (oxidative stress and inflammation), and may directly foster an environment where telomerase can function optimally to maintain telomere lengthlifeextension.comlifeextension.com. It thereby supports both genomic stability and the clearance of older, dysfunctional cells, which is crucial for tissue rejuvenation.

Resveratrol (a polyphenol from grapes, red wine, etc.) is famous for activating SIRT1 (a histone deacetylase linked to lifespan extension) and mimicking caloric restriction's effects on metabolism and

DNA repair. Resveratrol's relationship with telomerase is intriguing: it has been shown to *activate telomerase in certain cell types*, yet in others (notably cancer cells) it can inhibit telomerase. On balance, in non-malignant settings resveratrol appears to **delay cellular senescence and modestly lengthen telomeres**. For example, in endothelial progenitor cells (EPCs), resveratrol treatment significantly increased telomerase activity and prolonged their replicative lifespanpmc.ncbi.nlm.nih.gov. A Chinese study found that resveratrol's activation of SIRT1 led to upregulation of telomerase, which **delayed EPC senescence** and improved their function (migratory and tube-forming capacity)pmc.ncbi.nlm.nih.gov. This result is consistent with resveratrol's known cardiovascular benefits and suggests that part of its mechanism is maintaining telomere length in the endothelium. Additionally, a *Frontiers in Aging* review concluded that resveratrol "had pro-telomerase effects" in models of post-myocardial infarction cardiac remodelingpmc.ncbi.nlm.nih.gov. In rodent studies, long-term resveratrol supplementation increased average telomere lengths and telomerase activity in multiple tissues (though notably it did not always extend maximal lifespan in healthy mice)academic.oup.com. The increase in telomerase/telomere metrics without lifespan extension implies resveratrol may improve healthspan or delay age-related pathology rather than drastically prolong life in already healthy animals. Nevertheless, in disease models like accelerated aging or neurodegeneration, resveratrol often shows protective effects – reducing beta-amyloid accumulation, improving insulin sensitivity, and reducing inflammation – all factors tied to telomere erosion. In humans, resveratrol has been tested in small trials (for metabolic health, cognition in Alzheimer's, etc.). One notable trial in older adults with mild cognitive impairment found resveratrol (along with grape polyphenols) improved hippocampal functional connectivity and hinted at slowing cognitive decline. Though telomere length wasn't measured, biomarkers of inflammation fell, aligning with a slower biological aging pace. Importantly, resveratrol's activation of SIRT1 can indirectly stabilize telomeres: SIRT1 interacts with telomeric chromatin and helps maintain telomere structure and length by promoting TERT gene expression and by preventing DNA damage at telomeres. Summarizing, resveratrol's inclusion in PINE-963 is to harness these **youth-preserving pathways**. By activating SIRT1 and AMPK, resveratrol triggers a host of beneficial downstream effects (enhanced mitochondrial function, DNA repair, autophagy) that collectively slow cellular aging and **support telomere maintenance**academic.oup.comacademic.oup.com. It serves as a metabolic and genomic stabilizer that complements the more direct telomerase stimulators.

Epigallocatechin-3-gallate (EGCG) from green tea is another polyphenol with dual anti-cancer and anti-aging properties. EGCG is known to **protect DNA from damage** and reduce oxidative stress at the cellular level. Its direct effect on telomerase is context-dependent: in cancer cell lines like HeLa, EGCG is a potent telomerase inhibitor, leading to telomere shortening and growth arrest of the cancer cellspubmed.ncbi.nlm.nih.gov. However, in normal somatic cells and in vivo, EGCG does not appear to catastrophically inhibit telomerase; instead, it may help preserve telomere length by reducing oxidative damage and possibly by mild activation of telomerase in aged cells. One population-based study found that higher green tea consumption correlated with *slower telomere attrition* over timenature.comnature.com. In a cohort of 1,952 adults, those who drank ≥7 cups of green tea per week had longer leukocyte telomeres at follow-up than non-tea drinkers, after 6 yearsnature.com. This observational link suggests habitual green tea polyphenols (chiefly EGCG) might support telomere maintenance in humans. Additionally, a short-term interventional trial in obese women showed that 2 months of high-dose green tea supplementation **significantly increased leukocyte telomere length** relative to baselinenature.comnature.com. Although the duration was brief, the telomere lengthening

could reflect activation of telomerase or reduced turnover of cells. The authors postulated that EGCG and other catechins might upregulate telomerase in immune cells as one possible mechanismnature.com. Experimental evidence in skin cells aligns with a protective role: EGCG at sub-cytotoxic doses *protected human fibroblasts from UV-induced telomere damage*. Specifically, EGCG prevented ultraviolet-A (UVA) light from causing telomere fragmentation and excessive shortening, without significantly altering baseline telomerase activityresearchgate.netresearchgate.net. The fibroblasts treated with EGCG maintained longer telomeres despite UVA exposure, compared to untreated cells which showed telomere lossresearchgate.net. This indicates EGCG **safeguards telomeres under stress** by scavenging ROS and possibly stabilizing the telomere cap structure. Moreover, EGCG exerts anti-inflammatory effects (e.g. inhibiting NF-κB and AP-1) which reduce the pro-aging secretory milieu. In mouse models of aging and neurodegeneration, green tea/EGCG has improved survival and organ function; one study in a cardiac aging model found EGCG preserved cardiac function and mitigated several hallmarks of aging in the heartaginganddisease.org. Taken together, EGCG's role in PINE-963 is that of a *protector*: it may not strongly turn on telomerase in normal cells, but it **prevents accelerated telomere shortening** by quelling oxidative stress and DNA damageresearchgate.net. It also provides synergistic anti-cancer benefits by ensuring that while we activate telomerase in healthy cells, we are not unwittingly promoting cancer cell immortality – since EGCG would counteract telomerase in any emerging tumor cells. Thus, EGCG complements the formula by reinforcing genomic stability, supporting immune health (green tea drinkers have lower rates of immune senescence-related diseases), and contributing to the polyphenol network that promotes longevity.

Use Case: Supporting Immune Regeneration in an Older Adult

To illustrate PINE-963's multi-faceted action, consider an older adult (age ~70) with signs of immune senescence and fatigue. With age, their telomeres in peripheral blood T-cells have eroded, leading to a reduced naïve T-cell pool and weaker vaccine responses. The goal is to rejuvenate the immune system by activating telomerase in hematopoietic and immune cells, protecting those cells from oxidative/inflammatory damage, and improving systemic resilience.

Telomerase Reactivation in T-Cells: Upon taking PINE-963, the *Astragalus* cycloastragenol drives telomerase expression in the user's T lymphocytes. Studies show that within a few months, Astragalus can elongate short telomeres in human immune cellsmdpi.commdpi.com. In this individual, we expect previously senescent or "near-senescence" T-cells (with critically short telomeres) to regain telomere length, allowing additional cell divisions. TA-65 (Astragalus extract) trials in humans have demonstrated increases in telomere length of shortest telomeres and improved immune profiles (e.g. higher proportion of naïve CD8 T-cells)mdpi.commdpi.com. Over 6–12 months of PINE-963, a similar telomere elongation in T-cells likely occurs, effectively **reversing some aspects of immunosenescence**. The individual's lymphocyte telomerase activity, low at baseline, is now measurably higher – evidence from cell culture suggests telomerase can increase by over 50% with certain phytochemical blendspubmed.ncbi.nlm.nih.gov. This improved telomere reserve allows T-cells to respond robustly to new antigens.

Enhanced Immune Function: Meanwhile, *Rhodiola* and *Ashwagandha* in the formula reduce cortisol and sympathetic overdrive, which are known to shrink the thymus and accelerate immune aging. Rhodiola has

been shown to inhibit thymic T-cell apoptosislifeextension.com; thus our user's thymus may retain better function, outputting new T-cells. Ashwagandha's immunomodulatory effects (it's used as an adjunct therapy in immune deficiency states) further bolster leukocyte counts and activity. *Curcumin* and *EGCG* lower systemic inflammation (e.g. curcumin suppress NF-κB, EGCG reduces pro-inflammatory prostaglandins), alleviating the chronic inflammatory load ("inflammaging") that distracts and exhausts the immune system. As inflammatory signaling drops, the bone marrow niche becomes more supportive of telomere maintenance in progenitor cells (since high TNF-α and IL-6 can inhibit telomerase). *Resveratrol* and *Ginkgo* together improve the circulatory system – resveratrol via enhancing endothelial function and nitric oxide, Ginkgo via vasodilation and microcirculatory perfusion – ensuring immune cells receive adequate nutrients and that stem cell niches are well perfused. Ginkgo's direct telomerase activation in EPCspubmed.ncbi.nlm.nih.gov may translate to better endothelial repair and angiogenesis, indirectly supporting immune organ health (e.g. better blood flow to the spleen and thymus).

Outcome: After one year on PINE-963, our hypothetical older adult shows **measurable improvements**: Leukocyte telomere length has increased in a subset of cells (especially previously short-telomere cells), confirmed by PCR analysismdpi.com. The diversity of the T-cell receptor repertoire is broader, and response to a flu vaccine is stronger than a comparable 70-year-old not on the regimen (findings analogous to those in telomerase activator trials). Clinically, the individual reports fewer infections over the year and higher energy levels. This aligns with reports that lengthening telomeres in immune cells can rejuvenate their functionpubmed.ncbi.nlm.nih.gov. Additionally, they experience cognitive benefits – likely a synergy of Bacopa, Ginkgo, and Rhodiola – such as improved memory and less "brain fog," as often noted in studies of these nootropics in older adultsalzdiscovery.orglifeextension.com. Importantly, no adverse proliferation is observed; the compounds have selectively aided normal cells. If anything, the presence of EGCG and curcumin offers *oncoprotection*, as these compounds are noted for their cancer-preventive properties in the elderly (e.g. curcumin and EGCG induce apoptosis in pre-cancerous cells and inhibit telomerase in tumor cellssciencedirect.compubmed.ncbi.nlm.nih.gov). Thus, the use case highlights that **PINE-963 can activate telomerase in critical cell populations (like immune cells) to restore function while concurrently shielding the body from the pro-aging effects of stress and inflammation**. This concerted approach yields a healthier immune system and potentially a slower rate of biological aging for the individual.

Discussion

Aging is a multi-factorial process characterized by the progressive loss of physiological integrity, and the formulation PINE-963 was designed to intervene at several key hallmarks of aging – principally telomere attrition, but also chronic inflammation, oxidative stress, and stem cell exhaustion. The results of our literature review substantiate that each ingredient in PINE-963 contributes to these anti-aging goals through scientifically validated mechanisms.

Telomerase and Telomere Dynamics: A central theme is the preservation of telomeres. *Astragalus membranaceus* emerges as the most direct telomerase activator in the mix, with human trial evidence of telomere extensionmdpi.com. This positions Astragalus (cycloastragenol) as a plant-derived analog to Epitalon's telomerase-inducing effect – effectively the "engine" of the telomere maintenance in the formulation. However, unlike Epitalon, which is a single agent, PINE-963 employs a network of

compounds to ensure telomere lengthening occurs in a safe, regulated manner. The synergy observed in *in vitro* studies (e.g., combinations of Astragalus with other phytochemicals yielding up to nearly three-fold increases in telomerase activitypubmed.ncbi.nlm.nih.gov) suggests that a multi-ingredient approach can amplify telomerase stimulation beyond what any single compound could achieve alone, possibly by hitting multiple signaling pathways that converge on telomerase expression (TERT transcription, post-translational modifications of telomerase, or shelterin complex stabilization).

For example, Ginkgo's PI3K/Akt-mediated telomerase activationpubmed.ncbi.nlm.nih.gov is a different route from Astragalus's direct activation; combining them might produce additive or synergistic telomerase upregulation. Likewise, ashwagandha's apparent induction of telomerase in cellspmc.ncbi.nlm.nih.gov – potentially via a p53 or heat shock protein-mediated pathway – could complement Astragalus. The **use case of immune cells** in the Results exemplifies this synergy: Astragalus provides the telomerase "spark," while Ginkgo and ashwagandha ensure the cellular environment and signaling are optimized for telomere extension to translate into functional rejuvenation. Notably, telomerase activation in somatic cells raises concerns about cancer risk, since replicative limits are a tumor suppression mechanism. The PINE-963 formulation addresses this concern inherently: polyphenols like curcumin, EGCG, and resveratrol are well-documented *anti-carcinogenic agents*pmc.ncbi.nlm.nih.govpubmed.ncbi.nlm.nih.gov. These compounds can selectively suppress telomerase in neoplastic cells (through epigenetic repression of hTERT or direct enzyme inhibition)sciencedirect.compubmed.ncbi.nlm.nih.gov, while allowing or even facilitating telomerase in healthy cells under physiological conditionsnature.com. This yin-yang effect is invaluable – it suggests PINE-963 could **tilt the balance toward healthy immortality (for normal cells) without enabling malignant immortality**. Indeed, in the immune use-case, we pointed out that EGCG and curcumin provide a safety net by pro-actively targeting any emerging tumor cells for apoptosis or senescence. Long-term studies in animals have not noted any increase in cancer incidence with Astragalus (TA-65) supplementation; one study in adult/old mice even reported extended healthspan **without increased cancer**sciencedirect.com. This aligns with the idea that simultaneous inclusion of anti-cancer phytochemicals mitigates the oncogenic potential of telomerase activation.

Neurodegeneration and Cognitive Aging: The inclusion of Bacopa, Ginkgo, Rhodiola, and Curcumin underscores the importance of addressing neurodegenerative processes. Telomere shortening has been associated with neurodegenerative diseases (shorter leukocyte telomeres correlate with higher risk of dementia and smaller hippocampal volume)nature.com. While neurons themselves are post-mitotic, supporting glial cells and neural stem cells in the brain do undergo divisions and can be subject to telomere loss. Moreover, short telomeres in circulating immune cells can exacerbate neurodegeneration via increased inflammation. PINE-963's neurotropic herbs tackle these issues: Ginkgo's improvement in hippocampal telomerase and reduction of oxidative damage in aging ratspubmed.ncbi.nlm.nih.gov hints that it can support neural cell longevity or neurogenesis. Bacopa's antioxidant and anti-inflammatory action in the brain likely preserves the *brain microenvironment*, thereby indirectly supporting telomere stability in neural cells. Additionally, these herbs modulate neurotransmitter systems (Bacopa affects cholinergic and serotonergic signalingalzdiscovery.org; Rhodiola influences serotonin and dopamine through MAO inhibition and beta-endorphin release). The net result is **improved cognitive function** and stress resilience, as seen in clinical dataalzdiscovery.orglifeextension.com. This is important because chronic psychological stress accelerates telomere shortening in the brain and peripherylifeextension.com;

by improving stress tolerance and mood, PINE-963 may break the vicious cycle of stress-induced biological aging. The discussion here highlights that a *multi-targeted phytotherapy can simultaneously address the genomic (telomere) and metabolic/inflammatory causes of neurodegeneration*. This contrasts with Epitalon, which has shown some neuroendocrine benefits (e.g. normalizing melatonin rhythmsmdpi.com), but whose direct impact on neurodegeneration is less documented. PINE-963, leveraging curcumin and resveratrol, also promotes autophagy and clearance of protein aggregateslifeextension.com, processes vital for preventing neurodegenerative pathology.

Immune Aging and Systemic Inflammation: The formulation's impact on immune aging is particularly compelling. Astragalus/TA-65 studies in humans reported improvements in T-cell profiles and immune functionpubmed.ncbi.nlm.nih.gov, and our review shows multiple ingredients converge on bolstering immunity. Rhodiola's thymic protection, ashwagandha's immune modulation (it's been shown to increase white blood cell counts in some studies of immunocompromised patients), and curcumin/EGCG's anti-inflammatory effects all contribute to a more "youthful" immune system. Discussion of a **pilot trial (TACTIC)** in cardiac patients on TA-65 found reduced levels of *inflammaging* cytokines and fewer exhausted (PD-1^+) T-cells compared to placebopubmed.ncbi.nlm.nih.gov. It's reasonable to extrapolate that PINE-963 could amplify these benefits due to its multifactorial approach. We might expect, for instance, lower IL-6, CRP, and TNF levels systemically – curcumin and EGCG are known to achieve such reductions in clinical contexts (e.g., curcumin lowered CRP in elderly subjects with metabolic syndrome in an RCT). Lower inflammation in turn protects telomeres (studies have found IL-6 levels inversely correlate with telomere length). Thus, a virtuous cycle is established: telomerase activation by Astragalus extends telomeres, leading to healthier immune cells; those cells in turn produce fewer inflammatory signals; reduced inflammation slows telomere attrition in all tissues.

Epitalon Mimetic Effects: It is worth comparing PINE-963 to Epitalon more directly. Epitalon has multiple reported effects – it increases telomerase, normalizes circadian hormone rhythms, upregulates antioxidant enzymes (SOD, glutathione peroxidase)en.wikipedia.org, and modulates immune cytokines (e.g., IL-2)mdpi.com. PINE-963 appears to recapitulate each of these to some degree: telomerase (Astragalus, ashwagandha, Ginkgo), circadian/hormonal support (ashwagandha improves sleep and can mildly boost DHEA; Rhodiola balances cortisol), antioxidant enzyme induction (curcumin and resveratrol both induce phase II antioxidant enzymes via Nrf2; Bacopa and Ginkgo raise SOD and catalasepubmed.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov), and immune cytokine modulation (curcumin and EGCG lower pro-inflammatory cytokines, resveratrol can increase IL-10, an anti-inflammatory cytokine). Therefore, as a *peptide mimetic*, the formulation indeed mirrors the pleiotropic nature of Epitalon. An advantage of the phytotherapeutic approach is oral bioavailability and ease of chronic use; Epitalon, typically injected in courses, has limited availability and fewer human studies. On the other hand, one must consider **bioavailability and standardization** of the phytotherapeutic components: curcumin and resveratrol have low oral bioavailability, though PINE-963's use of a hydroalcoholic extract base mitigates this. Ensuring adequate blood levels of these actives is crucial for efficacy. The specific ratios in PINE-963 (e.g., Astragalus 25% as the highest portion, EGCG 5% as the lowest) reflect a formulation strategy to prioritize telomerase activation while still providing supportive synergists. This ratio is rational given Astragalus' role as primary telomerase stimulant and EGCG's role as a protective adjunct (needed in smaller amounts since too much EGCG could inhibit telomerase).

Future Directions: Rigorous testing of PINE-963– perhaps in a small human trial measuring telomere length and functional outcomes – will be needed. One interesting future avenue is to examine whether these phytochemicals have *epigenetic* effects similar to Epitalon. Epitalon was shown to induce decondensation of heterochromatin in aging cells, effectively making gene expression more "youthful"en.wikipedia.org. Polyphenols like curcumin and resveratrol are known epigenetic modulators (affecting DNA methylation and histone acetylation). It is plausible that PINE-963 ingredients collectively promote a youthful epigenome, which might include re-expression of embryonic gene programs and more robust DNA repair. Such effects could complement telomerase activity in extending cell healthspan.

Clinical Relevance: For clinicians, PINE-963 offers a scientifically grounded nutraceutical option to address aging-related decline. Use cases include older adults at risk of immunosenescence (e.g. frequent infections, poor vaccine response), patients with early cognitive decline or high stress levels, and potentially as an adjunct in age-related diseases like cardiovascular disease or frailty. The formulation's components have good safety profiles individually: e.g., Ginkgo can rarely cause mild blood thinning effects, curcumin may cause gastrointestinal upset at high doses, but overall, each is well-tolerated in long-term use. The combination should still be monitored for any additive effects (for instance, both Ginkgo and curcumin can affect platelet aggregation, so clinicians should be cautious in patients on anticoagulants). The **dosing schedule** (2–4 mL daily) is convenient and allows titration.

It is worth mentioning that other telomerase activators (like PINE-963) could be accessible and regulatory-friendly (as a dietary supplement). It aligns with a preventive geriatrics approach – intervening before critical shortening occurs. Clinicians should remain evidence-based: while the ingredients have individually demonstrated effects, recommending PINE-963 should come with an explanation that its claims are extrapolated from those data. Given the low risk and the potential high reward (slowing biological aging), many longevity practitioners may consider it a favorable risk-benefit intervention for middle-aged and older adults.

PINE-963 represents a **novel synthesis of ethnomedicine and modern geroscience**: it takes the wisdom of traditional anti-aging herbs and targets them at one of modern biology's fundamental aging mechanisms – telomere attrition. The evidence reviewed provides a robust rationale that this phytotherapeutic strategy can mimic the effects of cutting-edge peptide drugs like Epitalon, but in a holistic and potentially safer manner. As research into integrative approaches to aging continues, formulations like PINE-963 could become part of a standard toolkit to maintain healthspan and improve quality of life for aging populations.

Conclusion

Aging interventions are rapidly moving from science fiction to clinical reality, and PINE-963 Phytotherapeutic Peptide Mimetic exemplifies this progress by uniting time-honored medicinal plants with cutting-edge aging biology. This white paper has detailed how each component of PINE-963 – from *Astragalus* to EGCG – contributes to **telomerase activation, telomere protection, and the amelioration of age-related decline**, closely mirroring the multi-modal effects of the synthetic peptide Epitalon. The peer-reviewed evidence shows that *Astragalus* (cycloastragenol) can re-extend telomeres in human cells and improve immune functionmdpi.commdpi.com; adaptogens like *Rhodiola* and *Ashwagandha* buffer the neuroendocrine stress that accelerates telomere losslifeextension.compmc.ncbi.nlm.nih.gov; *Bacopa*

and *Ginkgo* preserve cognitive and vascular health while supporting telomere stability in brain and endothelial cellspubmed.ncbi.nlm.nih.govpmc.ncbi.nlm.nih.gov; and polyphenols *Curcumin*, *Resveratrol*, and *EGCG* tackle "inflammaging" and oxidative damage, thereby maintaining the genomic integrity needed for longevitylifeextension.comresearchgate.net. These ingredients operate through *scientifically validated mechanisms* – such as PI3K/Akt signaling for telomerase, SIRT1 activation, and NRF2-mediated antioxidant defense – that converge on healthier aging phenotypes.

In practical terms, PINE-963 offers a comprehensive, multi-target approach to promote healthy aging. The formulation is poised to **slow telomere attrition and even lengthen short telomeres** in critical cell populations (immune cells, stem cells), as evidenced by analogous outcomes in clinical trials of similar nutraceuticalsmdpi.com. By doing so, it may enhance immune competence (better infection control and vaccine responses), support neurocognitive function (through improved cerebrovascular and synaptic health), and increase cellular stress resistance. We presented a use-case of an elderly individual where PINE-963 restored telomerase activity in T-cells and improved immune biomarkers – a scenario grounded in observed data from telomerase activator studiespubmed.ncbi.nlm.nih.gov. While such benefits are compelling, we also emphasize that PINE-963 is not a mythical "fountain of youth"; rather, it is a geroprotective tool that can *modestly decelerate* aspects of biological aging.

The safety profile of PINE-963's constituents, each with a long history of human use, further enhances its clinical appeal. The built-in anti-cancer safeguards (EGCG, curcumin) address theoretical risks of telomerase enhancement, aiming to **promote healthy cell longevity without promoting malignancy**. This integrated, synergistic design reflects a new paradigm in longevity medicine: instead of one magic bullet, a concerted arsenal of natural compounds fine-tunes the body's own maintenance and repair systems.

In conclusion, PINE-963 represents a translational application of longevity research, translating insights from telomere biology and nutraceutical science into a tangible intervention. The evidence compiled in this white paper provides a strong scientific rationale for its use in supporting telomere health, neuroprotection, and immune rejuvenation in aging individuals. As with any emerging therapy, further clinical studies will be invaluable – particularly long-term trials to observe effects on biological age markers, functional health outcomes, and any unanticipated effects of the combined formulation. However, based on current knowledge, PINE-963 stands out as a promising, *holistic strategy to mimic the telomerase-boosting, life-enhancing influence of Epitalon*, using accessible phytochemicals. For clinicians and researchers focused on geriatric medicine and preventive healthcare, PINE-963 offers an evidence-backed addition to the toolkit, aligning with the ultimate goal of extending healthspan – the years of life spent in good health. By protecting our chromosomes' endcaps and revitalizing key systems, this phytotherapeutic blend moves us a step closer to resilient, healthy aging in the population.