

RESEARCH MONOGRAPH . COMPOUND PROFILE

Cycloastragenol

A naturally occurring triterpenoid aglycone derived from Astragalus membranaceus, identified as the bioactive sapogenin of astragaloside IV and the principal small-molecule telomerase activator in the TA-65 formulation, with expanding preclinical evidence in anti-inflammatory, neuroprotective, cardioprotective, and anti-senescence applications.

DOCUMENT	KDC-MN-1611
ISSUED	2026-05-20
REVISION	1.0
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COMPOUND CLASS	Lanostane-type tetracyclic triterpenoid sapogenin with telomerase-activating, anti-inflammatory, and antioxidant activity

ABSTRACT

Cycloastragenol (CAG) is a lanostane-type tetracyclic triterpenoid sapogenin obtained by acid or enzymatic hydrolysis of astragaloside IV, the principal bioactive saponin of *Astragalus membranaceus* (Huangqi), a plant with extensive use in traditional Chinese medicine. The compound gained prominence following a systematic screen of natural product libraries at Geron Corporation in the early 2000s that identified it as a small-molecule activator of human telomerase reverse transcriptase (hTERT), the catalytic subunit of telomerase. This discovery led to the development and commercialization of TA-65, a proprietary cycloastragenol-containing nutraceutical formulation marketed by T.A. Sciences for telomere health and anti-aging applications. The telomerase-activating mechanism involves upregulation of hTERT gene expression, enhanced nuclear localization of the hTERT protein via upregulation of the Hsp90 chaperone complex, and activation of the cAMP response element binding protein (CREB) signaling axis. At the cellular level, cycloastragenol activates telomerase in multiple cell types including peripheral blood mononuclear cells, CD4-positive and CD8-positive T lymphocytes, fibroblasts, and neuronal cells, with functional consequences including telomere elongation, reduced replicative senescence, and enhanced proliferative capacity. A 2016 randomized, double-blind, placebo-controlled clinical trial of TA-65 in 117 cytomegalovirus-positive subjects aged 53 to 87 years demonstrated dose-dependent telomere lengthening in the low-dose group (530 plus or minus 180 base pairs; p equals 0.005) over 12 months, with the placebo group losing telomere length (290 plus or minus 100 base pairs; p equals 0.01). The compound

additionally exhibits pharmacological activities independent of the telomerase mechanism. Preclinical studies have characterized anti-inflammatory effects through inhibition of NF-kappaB signaling and pyroptosis pathways; neuroprotective activity through upregulation of SIRT1 expression, activation of the Nrf2/HO-1 pathway, and promotion of BDNF/p-TrkB/CREB signaling; cardioprotective effects through promotion of myocardial autophagy via inhibition of AKT1-RPS6KB1 signaling; anti-fibrotic activity in hepatic and pulmonary models; and antioxidant effects through activation of the Nrf2/ARE transcriptional pathway. Pharmacokinetics in the rat model show oral bioavailability of approximately 25.7 percent following acid hydrolysis-mediated absorption, substantially higher than the parent compound astragaloside IV (2.2 percent), with extensive first-pass hepatic metabolism limiting systemic exposure. In human liver microsomes, only 8.2 percent of cycloastragenol remained after 30 minutes of incubation, indicating rapid phase I metabolism. A 91-day subchronic toxicity study in rats at doses up to 150 mg/kg/day by oral gavage produced no treatment-related mortalities, no cardiac effects, and no evidence of genotoxicity or carcinogenicity. Clinical safety data from TA-65 studies over 12 months of supplementation report no serious adverse events, with mild gastrointestinal discomfort as the principal dose-dependent adverse effect. The theoretical concern of telomerase activation promoting oncogenesis has not been substantiated in preclinical cancer bioassays or in clinical observation, though the mechanism warrants continued surveillance. This monograph reviews the chemistry and structural classification of cycloastragenol; its discovery as a telomerase activator and subsequent commercial development; the molecular pharmacology across telomerase, anti-inflammatory, neuroprotective, and cardioprotective

pathways; the pharmacokinetic profile including metabolism and bioavailability; the preclinical evidence base; the clinical evidence from TA-65 trials and related human studies; sourcing, quality verification, and reconstitution considerations; stack interactions; adverse events and safety signals; and a comparative assessment of five telomerase-modulating or astragalus-derived compounds against cycloastragenol on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Cycloastragenol.

Synonyms: Astramembrangenin, Cyclogalegigenin, CAG, 20R,24S-epoxy-9,19-cyclolanostane-3 β ,6 α ,16 β ,25-tetraol.

Chemical Abstracts Service registry numbers: 78574-94-4 (primary CAS number used by Sigma-Aldrich, PubChem, and most chemical suppliers), 84605-18-5 (secondary CAS number used by some vendors including Santa Cruz Biotechnology and Selleck Chemicals). The discrepancy between the two CAS numbers reflects the historical independent characterization of the compound from different botanical sources; 78574-94-4 is the canonical registry entry in most current pharmacological and analytical literature.

PubChem compound identifier: CID 13943286.

International Union of Pure and Applied Chemistry name: (1S,3R,6S,8R,9S,11S,12S,14S,15R,16R)-15-[(2R,5S)-5-(2-hydroxypropan-2-yl)-2-methyloxolan-2-yl]-7,7,12,16-tetramethylpentacyclo[9.7.0.0(1,3).0(3,8).0(12,16)]octadecane-6,9,14-triol.

Commercial product designation: The compound is the principal active constituent of TA-65, a proprietary nutraceutical formulation marketed by T.A. Sciences, Inc. (New York, United States) for telomere health applications. TA-65 is a purified extract of *Astragalus membranaceus* root enriched for cycloastragenol content; the exact concentration and formulation excipients are proprietary [1].

1.2 Structural class and chemistry

Cycloastragenol is a lanostane-type tetracyclic triterpenoid belonging to the cycloartane subclass, characterized by the presence of a 9,19-cyclopropane ring fused to the lanosterol skeleton. The compound is the aglycone (sapogenin) of astragaloside IV, the major saponin of *Astragalus membranaceus* root. The structural class places cycloastragenol within the broader family of plant-derived cycloartane

triterpenoids, a group that includes cycloartenol (the plant equivalent of lanosterol in sterol biosynthesis) and numerous hydroxylated and epoxidated derivatives with diverse biological activities [2].

Molecular formula: C₃₀H₅₀O₅.

Molecular weight: 490.72 g/mol (monoisotopic mass 490.3658).

Physical properties: White to off-white amorphous or crystalline powder. Soluble in dimethyl sulfoxide, methanol, and ethanol; sparingly soluble in water. Melting point is approximately 224 to 226 degrees Celsius. The compound is optically active with multiple stereocenters across the tetracyclic ring system and the tetrahydrofuran side chain.

Stereochemistry: Cycloastragenol possesses eight defined stereocenters within its pentacyclic framework (including the cyclopropane ring and the tetrahydrofuran side chain). The natural configuration is 3 β ,6 α ,16 β ,25-tetrahydroxy with a 20R,24S-epoxy bridge forming the tetrahydrofuran ring. The 9,19-cyclopropane ring is a signature structural feature of the cycloartane triterpenoid class and is essential for the biological activity profile; ring-opened derivatives show substantially reduced telomerase activation [3].

Functional groups: The molecule contains four hydroxyl groups (at C-3, C-6, C-16, and C-25 positions), a cyclopropane ring (C-9 to C-19), and a tetrahydrofuran ring (C-20 to C-24 epoxide). The hydroxylation pattern and the tetrahydrofuran ring distinguish cycloastragenol from other cycloartane triterpenoids and are critical for receptor and enzyme binding interactions.

1.3 Relationship to astragaloside IV

Astragaloside IV (AG-IV), the glycosylated precursor of cycloastragenol, is a cycloartane-type triterpenoid saponin bearing xylose and glucose sugar moieties at the C-3 and C-6 hydroxyl positions. Acid or enzymatic hydrolysis cleaves these glycosidic bonds to yield the aglycone cycloastragenol. The relationship is pharmacokinetically significant: astragaloside IV has an oral bioavailability of approximately 2.2 percent in the rat, while cycloastragenol achieves approximately 25.7 percent, a 12-fold improvement attributable to the removal of the sugar residues and the resulting increase in lipophilicity and membrane permeability [4, 5]. It has been proposed that a portion of orally administered astragaloside IV is hydrolyzed

to cycloastragenol by intestinal microflora and gastric acid prior to absorption, and that cycloastragenol is therefore the systemically active metabolite of astragaloside IV *in vivo*.

1.4 Synthesis and extraction

The primary industrial and laboratory source of cycloastragenol is acid-catalyzed hydrolysis of astragaloside IV extracted from the dried roots of *Astragalus membranaceus* (synonym: *Astragalus mongholicus*). The extraction and purification sequence typically involves: (1) ethanol/water gradient extraction of dried root material to yield a crude saponin fraction; (2) chromatographic isolation of astragaloside IV from the crude extract using silica gel column chromatography or preparative high-performance liquid chromatography; (3) acid hydrolysis (hydrochloric acid or sulfuric acid in aqueous methanol, reflux, 2 to 6 hours) to cleave glycosidic bonds and yield the aglycone; and (4) purification of cycloastragenol by recrystallization or by preparative HPLC to achieve greater than 98 percent purity [6]. Enzymatic hydrolysis using beta-glucosidase and beta-xylosidase preparations represents an alternative approach with potentially milder reaction conditions and higher stereochemical fidelity. Total chemical synthesis of cycloastragenol has been reported but is not commercially viable owing to the complexity of the tetracyclic ring system and the density of stereocenters; the compound is produced exclusively by semisynthesis from botanical precursors. Chinese patent CN106083979A describes an optimized extraction and preparation method for high-purity cycloastragenol from *Astragalus* root.

2. Abstract

Cycloastragenol (CAG) is a cycloartane-type tetracyclic triterpenoid sapogenin derived from the hydrolysis of astragaloside IV, the principal saponin of *Astragalus membranaceus* root. The compound is the most extensively characterized small-molecule telomerase activator in the published literature, identified through a systematic natural product screen at Geron Corporation and subsequently developed as TA-65 by T.A. Sciences for nutraceutical applications [1, 7].

The telomerase-activating mechanism operates through transcriptional upregulation of the human telomerase reverse transcriptase (hTERT) gene, the rate-limiting catalytic subunit of the telomerase holoenzyme. Cycloastragenol increases hTERT mRNA expression and promotes nuclear translocation of the hTERT protein through upregulation of the Hsp90 chaperone complex. The upstream signaling involves activation of the cAMP response element binding protein (CREB) pathway; pharmacological blockade of CREB expression reduces basal telomerase activity and abolishes cycloastragenol-induced telomerase activation [8, 9]. More recently, the NRF2 transcription factor has been identified as an additional mediator of cycloastragenol-induced hTERT expression, linking the telomerase-activating and antioxidant mechanisms through a shared transcriptional node [10].

Functionally, cycloastragenol activates telomerase in multiple human cell types. In peripheral blood mononuclear cells, the compound increases telomerase activity and produces measurable telomere elongation on chronic exposure. In neonatal human keratinocytes, cycloastragenol extends replicative lifespan and delays senescence. In neuronal cell lines (SH-SY5Y and PC12), it activates telomerase with potency in the low-micromolar range and has been proposed as a candidate for depression management on the basis of the telomere-depression association [8]. In human mesenchymal stromal cells and senescent fibroblasts, both cycloastragenol and astragaloside IV activate telomerase and increase telomere length, with the combination producing effects greater than either agent alone [11].

Beyond telomerase activation, cycloastragenol exhibits a broad pharmacological profile including anti-inflammatory activity (NF-kappaB inhibition, pyroptosis suppression, cholinergic anti-inflammatory pathway modulation), neuroprotective effects (SIRT1 upregulation, Nrf2/HO-1 pathway activation, BDNF signaling enhance-

ment), cardioprotective effects (AKT1-mTOR-RPS6KB1 pathway modulation, myocardial autophagy promotion), anti-fibrotic activity (hepatic and pulmonary models), antioxidant effects (Nrf2/ARE activation), and immunomodulatory properties [2, 12, 13]. These activities are mediated through ERK/JNK, Wnt/beta-catenin, AKT1-mTOR-RPS6KB1, and JAK/STAT3 signaling pathways.

The clinical evidence base rests primarily on two controlled human studies of the TA-65 formulation. The Salvador et al. (2016) randomized, double-blind, placebo-controlled trial in 117 cytomegalovirus-positive subjects demonstrated dose-dependent telomere lengthening in immune cells over 12 months [14]. The Harley et al. (2011) observational study in 114 subjects reported increases in median telomere length and reductions in critically short telomeres after 12 months of TA-65 supplementation [7]. Both studies reported favorable safety profiles with no serious adverse events.

Pharmacokinetics are characterized by moderate oral bioavailability (approximately 25.7 percent in rats), extensive first-pass hepatic metabolism, and dose-dependent systemic exposure. The safety profile in the 91-day subchronic rat toxicity study at doses up to 150 mg/kg/day is favorable, with no treatment-related mortalities, organ toxicity, or genotoxicity signal [15].

3. Discovery and Development History

3.1 Ethnobotanical context

Astragalus membranaceus (Huangqi) has been used in traditional Chinese medicine for over 2,000 years as a qi-tonifying herb, prescribed for fatigue, immune support, wound healing, and general vitality. The dried root is one of the 50 fundamental herbs in the traditional Chinese pharmacopoeia and is among the most commercially significant medicinal plants in global botanical trade. The saponin fraction of *Astragalus* root, of which astragaloside IV is the most abundant component, was identified in the mid-twentieth century as the source of the immunomodulatory and anti-inflammatory activities attributed to the herb in traditional practice [16].

3.2 Identification as a telomerase activator

In the early 2000s, Geron Corporation (Menlo Park, California) conducted a systematic screen of natural product libraries for small-molecule activators of human telomerase. The screen was motivated by the hypothesis that telomere attrition drives age-related immune decline and cellular senescence, and that pharmacological reactivation of telomerase in somatic cells could delay or partially reverse these processes. The Geron screen identified cycloastragenol as the most potent small-molecule telomerase activator in the *Astragalus membranaceus* extract library, with activity at low-micromolar concentrations in human keratinocytes and peripheral blood mononuclear cells [1, 7]. The intellectual property was subsequently licensed to T.A. Sciences, Inc. (New York), which developed the compound into TA-65, a proprietary nutraceutical formulation. TA-65 received a patent (United States Patent 7,846,904) covering the use of cycloastragenol for telomerase activation and telomere maintenance.

3.3 Commercialization as TA-65

T.A. Sciences launched TA-65 commercially in approximately 2007 as a dietary supplement marketed for telomere health and cellular anti-aging. The product is sold as oral capsules at various dosing units (100 U, 250 U, and 1000 U, where "U" desig-

nates a proprietary dosing unit). The company has sponsored or co-funded several clinical studies to substantiate telomere-lengthening claims, including the Harley et al. (2011) observational study and the Salvador et al. (2016) randomized controlled trial [7, 14]. TA-65 is sold as a dietary supplement in the United States and is not classified or approved as a pharmaceutical drug by the United States Food and Drug Administration.

3.4 Expansion of the research literature

Beginning approximately 2010, the research literature on cycloastragenol expanded beyond telomerase activation to encompass anti-inflammatory, neuroprotective, cardioprotective, anti-fibrotic, and anti-senescence applications. The compound is now characterized in over 100 peer-reviewed publications spanning molecular pharmacology, preclinical efficacy, pharmacokinetics, and safety. A comprehensive review by Yu et al. (2022) in the *European Journal of Medicinal Chemistry Reports* catalogued the biological activities, mechanisms, and structure-activity relationships of cycloastragenol and its synthetic derivatives [2]. A 2025 review by Wang et al. in *Frontiers in Pharmacology* specifically addressed the anti-inflammatory pharmacology and translational prospects of cycloastragenol across multiple disease models [12].

4. Mechanism of Action

Cycloastragenol is a multi-target agent. Its principal molecular activities, characterized in cell-based systems and confirmed in animal models, span telomerase activation, anti-inflammatory signaling, antioxidant pathway induction, neuroprotective signaling, and cardioprotective autophagy modulation. These activities are mediated through several interconnected signaling pathways and operate at functionally relevant concentrations achievable by oral administration.

4.1 Telomerase activation

The telomerase holoenzyme consists of the catalytic subunit human telomerase reverse transcriptase (hTERT) and the RNA template component (hTERC/hTR). In most somatic cells, hTERT expression is the rate-limiting determinant of telomerase activity; hTERC is constitutively expressed. Cycloastragenol activates telomerase primarily through transcriptional upregulation of the hTERT gene [8].

The molecular mechanism involves several interconnected pathways. First, cycloastragenol activates the cAMP response element binding protein (CREB) through phosphorylation at Ser133. Phosphorylated CREB binds to CRE elements in the hTERT promoter region and drives transcription. Pharmacological blockade of CREB (using dominant-negative CREB constructs or the CREB inhibitor KG-501) abolishes cycloastragenol-induced telomerase activation, confirming the requirement for CREB signaling [8]. Second, cycloastragenol upregulates the Hsp90 chaperone complex, which is required for proper folding, stabilization, and nuclear translocation of the hTERT protein. Inhibition of Hsp90 (using geldanamycin or 17-AAG) blocks cycloastragenol-induced nuclear accumulation of hTERT and reduces telomerase activity [9]. Third, the NRF2 transcription factor has been identified as an additional mediator of hTERT induction. Cycloastragenol stabilizes NRF2 by inhibiting its Keap1-dependent proteasomal degradation, permitting nuclear translocation and binding to antioxidant response elements (ARE) in the hTERT promoter and in cytoprotective gene promoters. This mechanism links the telomerase-activating and antioxidant pathways through a shared transcriptional node [10].

The functional consequence of telomerase activation is the enzymatic addition of TTAGGG hexanucleotide repeats to chromosome 3-prime termini, counteracting the progressive telomere shortening that occurs with each cell division in the absence of telomerase. In cell culture models, cycloastragenol treatment at 0.1 to 10 micromolar concentrations for 1 to 4 weeks produces measurable increases in mean telomere length by quantitative fluorescence in situ hybridization (Q-FISH) or quantitative polymerase chain reaction (qPCR), delays the onset of replicative senescence (measured by beta-galactosidase staining), and extends replicative lifespan by 1 to 3 population doublings depending on cell type [7, 11].

4.2 Anti-inflammatory signaling

Cycloastragenol inhibits multiple nodes of the inflammatory signaling cascade. The principal characterized mechanisms include:

NF-kappaB pathway inhibition. Cycloastragenol suppresses phosphorylation and nuclear translocation of the NF-kappaB p65 subunit, reduces IkappaB-alpha degradation, and consequently decreases transcription of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6) [12, 13].

Pyroptosis suppression. In models of psoriatic dermatitis and ischemic brain injury, cycloastragenol inhibits NLRP3 inflammasome assembly and reduces caspase-1-mediated cleavage of gasdermin D, thereby suppressing the pyroptotic cell death pathway that amplifies inflammatory tissue damage [12].

JAK/STAT3 pathway modulation. Cycloastragenol inhibits Janus kinase-mediated phosphorylation of STAT3, reducing transcription of STAT3-dependent inflammatory and proliferative genes. This mechanism is relevant to the anti-inflammatory effects observed in hepatic and pulmonary inflammation models [2].

4.3 Neuroprotective signaling

Cycloastragenol has demonstrated neuroprotective activity through multiple mechanisms in cell-based and animal models of neurodegeneration and ischemic brain injury.

SIRT1 upregulation. In a rat model of cerebral ischemia-reperfusion injury, cycloastragenol upregulated sirtuin 1 (SIRT1) expression, attenuated neuronal apoptosis (reduced caspase-3 cleavage and cytochrome c release), and suppressed neuroinflammation (reduced microglial activation and pro-inflammatory cytokine release). The SIRT1-mediated mechanism is downstream of NAD-plus metabolism and links the neuroprotective effect to cellular metabolic state [17].

Nrf2/HO-1 pathway activation. Cycloastragenol reverses amyloid-beta-induced inhibition of the Nrf2/HO-1 antioxidant pathway in neuronal cells, reducing oxidative stress-mediated neuronal death. The same Nrf2 activation that mediates hTERT upregulation simultaneously induces heme oxygenase-1 (HO-1) and other phase II detoxification enzymes, providing cytoprotection against reactive oxygen species [10, 18].

BDNF/TrkB/CREB signaling. Cycloastragenol activates the brain-derived neurotrophic factor (BDNF) signaling axis through phosphorylation of the TrkB receptor and downstream CREB activation. This pathway promotes neuronal survival, synaptic plasticity, and neurite outgrowth. The convergence of BDNF/CREB signaling with the telomerase-activating CREB mechanism suggests a unified neuroprotective and telomere-maintenance pathway [18].

Glutamate excitotoxicity protection. A 2015 study demonstrated that cycloastragenol protected hippocampal neurons from glutamate-induced excitotoxicity in vitro, a mechanism relevant to ischemic stroke and neurodegenerative conditions characterized by excitatory amino acid dysregulation [19].

4.4 Cardioprotective signaling

Cycloastragenol ameliorates experimental cardiac damage through promotion of myocardial autophagy via inhibition of the AKT1-mTOR-RPS6KB1 signaling axis. Suppression of mTOR complex 1 (mTORC1) signaling de-represses the autophagy initiation complex (ULK1/ATG13/FIP200) and increases autophagic flux, facilitating clearance of damaged organelles and misfolded proteins in cardiomyocytes subjected to ischemia-reperfusion injury or doxorubicin-induced cardiotoxicity [20]. Additional cardioprotective mechanisms include reduction of cardiac fibrosis through TGF-beta/Smad pathway modulation and attenuation of oxidative stress through Nrf2-dependent antioxidant gene induction.

4.5 Additional pharmacological activities

Anti-fibrotic activity. Cycloastragenol has been characterized in models of hepatic fibrosis (carbon tetrachloride-induced and bile duct ligation models) and pulmonary fibrosis (bleomycin-induced model), with effects mediated through inhibition of the TGF-beta/Smad signaling pathway and reduction of collagen deposition [2, 12].

Immunomodulatory effects. Cycloastragenol modulates T-cell proliferation and differentiation, reduces immunosenescent CD8-positive CD28-negative T cells in human clinical studies (the Harley et al. observation), and enhances natural killer cell activity in preclinical models [7, 21].

Anti-viral activity. Preliminary evidence suggests activity against several viral pathogens, consistent with the broader anti-viral properties attributed to Astragalus-derived compounds in traditional Chinese medicine, though the mechanism and clinical relevance remain under investigation [2].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Cycloastragenol is absorbed through the intestinal epithelium with moderate efficiency. In vitro studies using Caco-2 monolayers demonstrated efficient transepithelial transport with apparent permeability coefficients consistent with passive transcellular absorption. The compound traverses the intestinal barrier without requirement for active transporter-mediated uptake [4].

Oral bioavailability in the rat model is approximately 25.7 percent at a 10 mg/kg dose, with a mean absorption time of 5.70 plus or minus 1.62 hours. This bioavailability is substantially higher than the parent glycoside astragaloside IV (approximately 2.2 percent), reflecting the increased lipophilicity conferred by removal of the sugar residues during hydrolysis [4, 5].

In human studies, both peak plasma concentration (C_{max}) and area under the curve (AUC) increase with dose, indicating dose-dependent pharmacokinetics across the studied dose range. The human elimination half-life appears longer than in rats, though comprehensive human pharmacokinetic characterization with validated analytical methods remains limited in the published literature [12].

5.2 Distribution

The volume of distribution has not been precisely characterized in human subjects. Based on the lipophilic character of the triterpenoid scaffold (calculated LogP approximately 4.5) and the moderate plasma protein binding, the compound is expected to distribute into tissues. Preclinical tissue distribution studies of the parent compound astragaloside IV in rats and dogs demonstrated broad tissue distribution with accumulation in liver, kidney, and lung, and the aglycone cycloastragenol is expected to follow a similar pattern with potentially greater tissue penetration owing to its higher lipophilicity [22].

5.3 Metabolism

Cycloastragenol undergoes extensive first-pass hepatic metabolism. In vitro incubation studies demonstrated that only 17.4 percent of cycloastragenol remained after 30 minutes in rat liver microsomes and only 8.2 percent remained after 30 minutes in human liver microsomes, indicating rapid phase I oxidative metabolism in both species [4]. The metabolic rate is notably faster in human liver microsomes than in rat microsomes, suggesting that the oral bioavailability in humans may be lower than the 25.7 percent observed in rats.

The principal metabolic transformations include hydroxylation at multiple positions on the triterpenoid ring system, catalyzed by cytochrome P450 enzymes. Phase II conjugation reactions (glucuronidation and sulfation) of the hydroxylated metabolites facilitate renal elimination. The specific CYP isoforms responsible for cycloastragenol metabolism have not been definitively assigned, though CYP3A4 is a plausible candidate based on the structural similarity to other triterpenoid substrates of this enzyme [4, 23].

In the rat pharmacokinetic study, the principal urinary and fecal metabolites were identified by liquid chromatography-tandem mass spectrometry as mono- and di-hydroxylated derivatives and their glucuronide conjugates. Unchanged cycloastragenol accounted for a minor fraction of the total excreted material, consistent with extensive metabolic transformation prior to elimination [23].

5.4 Elimination

Elimination occurs primarily through hepatic metabolism and biliary excretion, with renal clearance of conjugated metabolites contributing a secondary pathway. The plasma elimination half-life in rats at 10 mg/kg oral dose is approximately 4 to 8 hours. In human studies using TA-65 supplementation, a longer elimination half-life has been suggested by the pharmacokinetic profile, though definitive human half-life data with intravenous reference dosing are not available in the published literature [12, 23].

5.5 Routes of administration

The compound is administered exclusively by the oral route in clinical and supplement applications. TA-65 is formulated as oral capsules at proprietary dosing units. Research-grade cycloastragenol is typically administered to animals by oral gavage

in suspension (carboxymethylcellulose or hydroxypropyl methylcellulose vehicle) or dissolved in dimethyl sulfoxide for in vitro applications. Intraperitoneal injection in dimethyl sulfoxide or corn oil vehicle has been used in rodent preclinical studies for pharmacokinetic bypass of first-pass metabolism and for mechanism-of-action investigations.

5.6 Formulation considerations

The relatively low aqueous solubility and extensive first-pass metabolism of cycloastragenol have motivated investigation of formulation strategies to improve oral bioavailability. Approaches under investigation include solid lipid nanoparticles, cyclodextrin inclusion complexes, phospholipid complexes, and self-emulsifying drug delivery systems. These formulation strategies aim to enhance intestinal absorption and reduce pre-systemic metabolism, though none has been validated in human pharmacokinetic studies at the time of monograph preparation [12].

6. Preclinical Pharmacology

6.1 Telomerase activation in cell-based models

The foundational preclinical observation is activation of telomerase in multiple human cell types. In neonatal human keratinocytes, cycloastragenol at 0.1 to 1 micromolar increased telomerase activity (measured by the telomeric repeat amplification protocol, TRAP) and extended replicative lifespan [7]. In peripheral blood mononuclear cells from healthy donors, the compound increased telomerase activity in CD4-positive and CD8-positive T lymphocytes and in monocytes. In SH-SY5Y neuroblastoma cells, cycloastragenol was characterized as a potent telomerase activator with EC₅₀ in the low-micromolar range, with functional consequences including telomere lengthening and enhanced cell viability under oxidative stress [8].

6.2 Anti-senescence activity

Cycloastragenol delays replicative senescence in fibroblasts, as measured by reduced senescence-associated beta-galactosidase staining, reduced p16INK4a and p21 expression, and extended population doubling capacity. In human mesenchymal stromal cells, the compound increases telomere length and telomerase activity in a dose-dependent manner. The combination of cycloastragenol with astragaloside IV produces synergistic effects on telomere length and telomerase activity that exceed either agent alone [11].

6.3 Anti-inflammatory models

In the ovalbumin-induced asthma model in mice, cycloastragenol reduced total leukocyte and eosinophil counts in bronchoalveolar lavage fluid, reduced serum levels of IL-4, IL-5, and IL-13 (Th2 cytokines), and attenuated airway hyperresponsiveness and goblet cell hyperplasia [12].

In the imiquimod-induced psoriatic dermatitis model, cycloastragenol reduced epidermal thickness, inflammatory cell infiltration, and expression of psoriasis-associated cytokines (IL-17A, IL-22, TNF-alpha) through inhibition of NLRP3 inflammasome-mediated pyroptosis [12].

In lipopolysaccharide-stimulated macrophage models, cycloastragenol inhibited NF-kappaB activation and reduced secretion of TNF-alpha, IL-1beta, and IL-6 at concentrations consistent with achievable plasma levels following oral administration [13].

6.4 Neuroprotection models

In the middle cerebral artery occlusion (MCAO) model of focal cerebral ischemia in rats, cycloastragenol (administered intraperitoneally at 20 mg/kg) reduced infarct volume, improved neurological deficit scores, and attenuated blood-brain barrier disruption. The protective mechanism involved upregulation of SIRT1 and downstream deacetylation of p53, reducing pro-apoptotic signaling [17].

In amyloid-beta-treated neuronal cultures, cycloastragenol reversed Nrf2/HO-1 pathway suppression and activated BDNF/TrkB/CREB signaling, reducing oxidative stress-mediated cell death and promoting neurite outgrowth [18].

In hippocampal neuron cultures exposed to glutamate excitotoxicity, cycloastragenol protected against neuronal death at concentrations of 1 to 10 micromolar, with the protective effect blocked by the telomerase inhibitor BIBR 1532, suggesting that telomerase activation contributes to the neuroprotective mechanism [19].

6.5 Cardioprotection models

In the doxorubicin-induced cardiotoxicity model in rats, cycloastragenol (administered at 10 to 40 mg/kg by oral gavage) reduced myocardial injury biomarkers (creatinine kinase-MB, lactate dehydrogenase, cardiac troponin I), improved cardiac function (ejection fraction, fractional shortening), and reduced histopathological evidence of cardiomyocyte necrosis. The mechanism involved promotion of myocardial autophagy through inhibition of the AKT1-mTOR-RPS6KB1 signaling axis [20].

6.6 Anti-fibrotic models

In the carbon tetrachloride-induced hepatic fibrosis model in rats, cycloastragenol reduced serum aminotransferase levels, decreased hepatic collagen deposition (measured by Masson trichrome staining and hydroxyproline content), and inhibited TGF-beta1/Smad3 signaling in hepatic stellate cells [2].

6.7 Subchronic toxicity

The Szabo et al. (2013) study evaluated the dietary safety of cycloastragenol in a 91-day subchronic toxicity study in Sprague-Dawley rats. Animals received cycloastragenol at 0, 40, 80, or 150 mg/kg/day by oral gavage. No treatment-related mortalities occurred. No cardiac effects were identified. No adverse effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, or gross or microscopic pathology were observed. The no-observed-adverse-effect level (NOAEL) was 150 mg/kg/day, the highest dose tested. In a parallel genotoxicity assessment, cycloastragenol was negative in the Ames bacterial reverse mutation assay, the in vitro chromosomal aberration assay in human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay [15].

7. Clinical Evidence Base

7.1 Harley et al. (2011) observational study

The first published human study of TA-65 (Harley et al. 2011, Rejuvenation Research) was an observational cohort study of 114 subjects taking TA-65 for up to 12 months. The study reported significant increases in median telomere length in immune cells and reductions in the percentage of critically short telomeres. Immunological assessments demonstrated reductions in the percentage of senescent (CD8-positive CD28-negative) cytotoxic T cells, consistent with immune rejuvenation. No serious adverse events were reported over the observation period [7].

The study limitations include the observational (non-randomized) design, the absence of a concurrent placebo control group, the proprietary nature of the TA-65 dosing units (which preclude precise pharmacokinetic correlation), and the relatively small sample size.

7.2 Salvador et al. (2016) randomized controlled trial

The Salvador et al. (2016) study, published in Rejuvenation Research, was a randomized, double-blind, placebo-controlled trial of TA-65 in 117 cytomegalovirus-positive subjects aged 53 to 87 years. Subjects were randomized to placebo, low-dose TA-65 (250 U daily), or high-dose TA-65 (1000 U daily) for 12 months [14].

The primary outcome was telomere length change measured by quantitative polymerase chain reaction (qPCR) in peripheral blood leukocytes. Subjects in the low-dose group showed statistically significant telomere lengthening (530 plus or minus 180 base pairs; p equals 0.005) relative to baseline. Subjects in the placebo group showed statistically significant telomere loss (290 plus or minus 100 base pairs; p equals 0.01). The high-dose group showed a trend toward telomere lengthening that did not reach statistical significance.

The paradoxical dose-response (low dose producing a larger effect than high dose) has been attributed to several factors including: possible U-shaped dose-response characteristic of telomerase regulation; potential immunomodulatory feed-

back at higher concentrations; statistical variability in the relatively small per-group sample sizes; and the telomere length measurement methodology (qPCR versus Southern blot or Q-FISH), which introduces analytical variability.

No serious adverse events were reported in any treatment group over the 12-month study period.

7.3 Immunosenescence study

A double-blind, placebo-controlled, randomized clinical trial specifically evaluating the effect of TA-65 on immunosenescent CD8-positive CD28-negative T cells demonstrated significant reductions in this senescent cell population after TA-65 supplementation. The reduction in immunosenescent T cells is consistent with the telomerase reactivation mechanism and with the telomere-lengthening observations in the Harley and Salvador studies [21].

7.4 Systematic review and meta-analysis (2025)

A 2025 systematic review and meta-analysis of TA-65 effects on telomere length, functional outcomes, and inflammation, published in *Cell Biology and Toxicology*, pooled data from available controlled studies and reported modest but statistically significant effects on telomere length maintenance. The review noted the overall favorable safety profile but emphasized the need for larger, longer-duration trials with standardized telomere measurement methodologies and with clinical endpoint assessment beyond biomarker changes [24].

7.5 Limitations of the clinical evidence base

The clinical evidence base for cycloastragenol is limited by several factors. All controlled human studies have used the proprietary TA-65 formulation rather than pure cycloastragenol, making dose-response correlation with the active compound imprecise. Sample sizes have been modest (fewer than 120 subjects per study). The primary outcome in all studies has been telomere length, a surrogate biomarker rather than a hard clinical endpoint such as disease incidence, functional capacity, or mortality. The longest controlled study duration is 12 months, which may be insufficient to detect meaningful effects on aging-related clinical outcomes. No study

has been conducted in a disease-specific population (such as patients with accelerated telomere shortening syndromes or dyskeratosis congenita) where the effect would be most clinically relevant.

8. Sourcing and Quality Verification

Cycloastragenol is available from multiple categories of sources, each with distinct quality considerations.

Pharmaceutical-grade TA-65: T.A. Sciences markets TA-65 as a dietary supplement in oral capsule form at various dosing units (100 U, 250 U, 1000 U). The formulation is proprietary; the exact cycloastragenol content per capsule is not disclosed on the label. TA-65 represents the most extensively studied formulation of cycloastragenol in human subjects but does not provide the analytical transparency required for quantitative research applications.

Research-grade cycloastragenol: Multiple chemical suppliers provide research-grade cycloastragenol at greater than 98 percent purity by HPLC. Established suppliers include Sigma-Aldrich (catalog number SMB00372), Cayman Chemical, Selleck Chemicals, MedChemExpress, Toronto Research Chemicals, and Santa Cruz Biotechnology. Supply is in milligram to gram quantities. Pricing varies by supplier and purity grade; typical pricing is \$50 to \$300 per 10 milligrams at greater than 98 percent purity at the time of monograph preparation.

Bulk botanical extracts: Chinese manufacturers in Shaanxi province and other regions produce bulk Astragalus root extracts standardized to cycloastragenol content (typically 1 percent, 5 percent, 10 percent, 25 percent, or 50 percent cycloastragenol by weight). These extracts are used in dietary supplement manufacturing and require rigorous analytical verification on receipt.

Quality verification recommendations: Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography with ultraviolet or evaporative light scattering detection (HPLC-UV/ELSD), achieving area-percent purity greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 491.37 for C₃₀H₅₀O₅)
- Nuclear magnetic resonance spectroscopy (¹H-NMR and ¹³C-NMR) for structural confirmation and detection of regioisomeric impurities
- Residual solvent analysis by gas chromatography

- Heavy metal and pesticide residue screening (particularly for botanical-source material)
- Microbial contamination testing for botanical-source material

Third-party analytical verification through independent laboratories is recommended for any investigation where dose-response precision is required. Lot-to-lot variability is observed in botanical-derived preparations, and supplier certificates of analysis should be independently confirmed.

9. Reconstitution and Handling

Cycloastragenol is supplied as a white to off-white powder. The compound has limited aqueous solubility; reconstitution approaches depend on the intended application.

For in vitro studies: Dissolve in dimethyl sulfoxide (DMSO) to prepare a concentrated stock solution at 10 to 50 mM (approximately 4.9 to 24.5 mg/mL). Stock solutions in DMSO are stable at minus 20 degrees Celsius for at least 6 months. Dilute into cell culture medium to achieve final concentrations of 0.1 to 10 micromolar, ensuring that the final DMSO concentration does not exceed 0.1 percent (v/v) to avoid solvent-mediated cytotoxicity. Ethanol may be used as an alternative solvent for cell types sensitive to DMSO.

For in vivo studies (oral gavage): Prepare suspensions in 0.5 percent carboxymethylcellulose sodium (CMC-Na) with 0.1 percent Tween 80 in deionized water. Sonicate briefly to achieve a homogeneous suspension. Prepare fresh daily or store at 2 to 8 degrees Celsius for up to 72 hours. Alternatively, dissolve in corn oil for lipophilic vehicle dosing.

For in vivo studies (intraperitoneal): Dissolve in a mixture of DMSO, polyethylene glycol 400, and saline (typically 10:40:50 v/v/v) to achieve a clear solution at the desired concentration. Ensure the DMSO content of the final injection volume does not exceed 10 percent.

Storage conditions: Store the dry powder at minus 20 degrees Celsius, protected from light and moisture. The compound is hygroscopic and should be stored under desiccant. Under these conditions, the powder is stable for at least 2 years. Avoid repeated freeze-thaw cycles of stock solutions; aliquot into single-use volumes at the time of initial reconstitution.

Light sensitivity: Cycloastragenol is modestly sensitive to ultraviolet light. Amber vials or aluminum foil wrapping is recommended for storage of solutions and for extended incubation experiments.

10. Stack Interactions and Combinations

Cycloastragenol interacts with other compounds through its multi-target pharmacology and its extensive hepatic metabolism. Investigators and formulators should consider the following interaction categories.

Astragaloside IV: The parent glycoside and the aglycone cycloastragenol share the same target pharmacology. Co-administration produces additive or synergistic telomerase activation and telomere elongation, as demonstrated in human mesenchymal stromal cells where the combination produced greater effects than either agent alone [11]. The combination is pharmacologically rational and is present in some commercial Astragalus extract formulations.

CYP3A4 inhibitors and inducers: Given the lipophilic triterpenoid structure and the probable CYP3A4-mediated metabolism, concurrent administration of strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, grapefruit juice) may increase cycloastragenol exposure and prolong elimination. Conversely, CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) may reduce systemic exposure and attenuate biological effects. Formal drug-drug interaction studies have not been conducted; the interaction is predicted from metabolic profiling data [4, 23].

Other telomerase activators: Co-administration with other small-molecule or nutraceutical telomerase activators (resveratrol, epigallocatechin gallate, genistein) would be expected to produce additive effects on hTERT expression and telomerase activity. The safety of combinations has not been formally evaluated; additive effects on telomerase raise the same theoretical oncogenesis concerns as high-dose monotherapy.

Antioxidant compounds: The Nrf2-activating mechanism of cycloastragenol is shared with other Nrf2 activators including sulforaphane, curcumin, and bardoxolone methyl. Concurrent administration may produce additive antioxidant pathway induction; whether this translates to additive cytoprotection or to potential Nrf2 pathway over-activation (which has been associated with adverse effects in some contexts) has not been investigated.

Immunosuppressants: Given the immunomodulatory effects of cycloastragenol (enhanced T-cell function, reduced immunosenescence, increased natural killer cell activity), concurrent use with immunosuppressive agents (calcineurin inhibitors, mTOR inhibitors, corticosteroids) may produce pharmacodynamic antagonism. Organ transplant recipients and individuals on immunosuppressive therapy should consider this potential interaction.

Chemotherapeutic agents: The telomerase-activating mechanism theoretically opposes the therapeutic strategy of telomerase inhibition in oncology (imetelstat). Concurrent use of cycloastragenol with telomerase inhibitors would be pharmacodynamically contradictory and is not recommended. The interaction with conventional cytotoxic chemotherapy has not been characterized.

Cardiovascular medications: The cardioprotective autophagy-promoting mechanism of cycloastragenol operates through AKT1-mTOR pathway inhibition, a pathway also targeted by mTOR inhibitors (everolimus, sirolimus) used in cardiology and oncology. Additive mTOR inhibition could amplify autophagy beyond physiologically beneficial levels; the interaction has not been characterized in combination pharmacology studies.

11. Adverse Events and Safety Signal

11.1 Preclinical safety

The 91-day subchronic toxicity study in Sprague-Dawley rats at doses of 40, 80, and 150 mg/kg/day by oral gavage produced no treatment-related adverse findings across all endpoints: mortality, clinical signs, body weight, food consumption, ophthalmoscopy, clinical chemistry, hematology, urinalysis, organ weights, and gross and microscopic pathology. The NOAEL was 150 mg/kg/day, the highest dose tested [15].

Genotoxicity testing was uniformly negative: Ames assay (Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and E. coli WP2 uvrA, with and without metabolic activation), in vitro chromosomal aberration assay in human peripheral blood lymphocytes, and in vivo mouse bone marrow micronucleus assay [15].

No evidence of carcinogenicity promotion was observed in the subchronic study or in any published preclinical investigation. The telomerase-activating mechanism raises a theoretical concern regarding oncogene-mediated cancer promotion, since telomerase reactivation is a hallmark of approximately 85 percent of human cancers. However, the mechanistic distinction between pathological telomerase reactivation (which occurs in the context of oncogenic transformation with disrupted cell-cycle checkpoints) and pharmacological telomerase activation in normal somatic cells (which retain intact checkpoint function) suggests that the cancer risk of cycloastragenol at pharmacologically relevant doses is low. The Blasco laboratory demonstrated in a mouse model (de Jesus et al. 2012) that TA-65 treatment elongated short telomeres and increased health span of adult and old mice without increasing cancer incidence [25].

11.2 Clinical adverse events

Clinical studies of TA-65 supplementation over 12 months have reported no serious adverse events. The principal dose-dependent adverse effect is mild gastrointestinal discomfort (nausea, abdominal discomfort, loose stools), particularly when

taken on an empty stomach. The gastrointestinal effect is consistent with the saponin-like properties of the triterpenoid scaffold and is mitigated by administration with food [7, 14].

No clinically significant changes in hepatic function tests, renal function tests, hematological parameters, or cardiovascular parameters (blood pressure, heart rate, electrocardiogram) have been reported in controlled studies.

11.3 Populations requiring caution

Individuals with active malignancy or a history of cancer should exercise caution with telomerase activators, given the theoretical potential for telomerase activation to support the replicative immortality of cancer cells. While preclinical data have not demonstrated increased cancer risk, and the de Jesus et al. (2012) mouse study showed no cancer incidence increase, clinical experience in cancer populations is absent.

Pregnant and lactating individuals should avoid cycloastragenol supplementation owing to the absence of reproductive toxicology data. The subchronic toxicity study did not include fertility, embryo-fetal development, or peri-postnatal development assessments [15].

Individuals on immunosuppressive therapy should consider the immunomodulatory effects of cycloastragenol, which may oppose the intended immunosuppression.

11.4 Long-term safety

Data on long-term safety (beyond 12 months) of cycloastragenol supplementation in humans are limited to uncontrolled observational reports. The long-term consequences of chronic telomerase activation in somatic cells, including the theoretical concerns regarding cancer promotion and the potential effects on stem cell exhaustion, tissue homeostasis, and epigenetic regulation, are incompletely understood and warrant continued investigation.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five telomerase-modulating or Astragalus-derived compounds against cycloastragenol, evaluated against five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile, and overall validation. The comparators were selected as compounds that share the telomerase-activating mechanism, the Astragalus-derived origin, or the anti-aging research positioning of cycloastragenol.

12.1 Astragaloside IV

Mechanism: Cycloartane-type triterpenoid saponin; the glycosylated precursor of cycloastragenol. Activates telomerase through the same hTERT transcriptional mechanism as cycloastragenol, with additional cardiovascular and immunomodulatory activities attributed to the parent glycoside [11, 16].

Relationship to cycloastragenol: Astragaloside IV is the direct biosynthetic precursor; hydrolysis of the sugar moieties yields cycloastragenol. The two compounds share the same aglycone core and the same fundamental mechanism of telomerase activation.

Novelty: Low. The telomerase-activating mechanism is shared with cycloastragenol; the compound is well established in the Astragalus pharmacological literature.

Effect size: Moderate in vitro telomerase activation, but substantially lower oral bioavailability (2.2 percent versus 25.7 percent for cycloastragenol) limits in vivo potency at equivalent oral doses. In human mesenchymal stromal cells, astragaloside IV produces lower telomerase activation than cycloastragenol at equimolar concentrations, though the combination produces synergistic effects [5, 11].

Promising potential: Moderate. Astragaloside IV is extensively studied in cardiovascular and immunological contexts with a large preclinical literature and some clinical evidence in heart failure and diabetic nephropathy. The compound is com-

mercially available as a standardized extract and as a dietary supplement ingredient.

Side-effect profile: Favorable. Preclinical and clinical evidence indicate good tolerability at studied doses. The principal limitation is the very low oral bioavailability, which necessitates higher doses to achieve systemic effects.

Overall validation: Moderate. The compound has a substantially larger preclinical literature than cycloastragenol in cardiovascular and immunological applications, but a less developed telomerase-specific evidence base.

Comparison to cycloastragenol: Cycloastragenol has approximately 12-fold higher oral bioavailability, higher in vitro telomerase activation potency, and a more developed clinical evidence base for telomere endpoints (through the TA-65 studies). Astragaloside IV has a larger cardiovascular and immunological literature. The combination of the two compounds produces synergistic telomerase effects, suggesting complementary rather than competitive positioning.

12.2 Epigallocatechin gallate (EGCG)

Mechanism: Polyphenolic catechin from green tea (*Camellia sinensis*). EGCG has been reported to activate telomerase in some cell types and to inhibit telomerase in cancer cell lines, suggesting cell-type-dependent and concentration-dependent effects. The primary mechanism relevant to telomere biology is antioxidant-mediated reduction of telomeric oxidative damage rather than direct enzymatic activation of telomerase [26].

Novelty: Low. EGCG is among the most extensively studied dietary polyphenols with a literature spanning thousands of publications.

Effect size: Small to moderate on telomere-related endpoints. The effects on telomere length and telomerase activity are inconsistent across studies and cell types, with some reports showing activation and others showing inhibition depending on concentration and cellular context. Effect sizes on antioxidant endpoints are well characterized and moderate.

Promising potential: Moderate for general antioxidant and anti-inflammatory applications; low as a specific telomerase activator owing to the inconsistent and bidirectional effects on telomerase activity.

Side-effect profile: Generally favorable at dietary intake levels. Hepatotoxicity has been reported at high supplemental doses (greater than 800 mg/day), particularly in fasting conditions and with concentrated extract formulations. This safety signal has led to regulatory advisories in some jurisdictions [26].

Overall validation: High for antioxidant and general health applications based on extensive epidemiological and interventional literature; low for telomerase-specific applications.

Comparison to cycloastragenol: Cycloastragenol has a more specific and consistent telomerase-activating mechanism, with direct transcriptional upregulation of hTERT rather than the indirect and inconsistent effects of EGCG. EGCG has a vastly larger general research literature and broader commercial availability. The two compounds operate through different primary mechanisms and could theoretically be combined for complementary antioxidant (EGCG) and telomerase-activating (cycloastragenol) effects.

12.3 Resveratrol

Mechanism: Stilbenoid polyphenol from grape skin and red wine. Activates SIRT1 (sirtuin 1), a NAD-dependent deacetylase implicated in longevity and cellular stress resistance. The telomere-relevant mechanism is SIRT1-mediated deacetylation of hTERT, which promotes nuclear localization and enzymatic activity of the telomerase catalytic subunit. Resveratrol does not directly activate hTERT transcription in the manner of cycloastragenol [27].

Novelty: Low. Resveratrol is the prototypical dietary SIRT1 activator with an extensive literature spanning over 10,000 publications.

Effect size: The effect on telomerase activity is modest and indirect; the primary anti-aging mechanism is through SIRT1-mediated pathways including mitochondrial biogenesis, autophagy, and anti-inflammatory signaling rather than direct telomere elongation. Clinical trials of resveratrol for aging-related endpoints have produced mixed results with generally small effect sizes.

Promising potential: Moderate. Despite the enormous research literature, resveratrol has not achieved regulatory approval for any clinical indication and has been limited by poor oral bioavailability (less than 1 percent in some reports), rapid metabolism, and inconsistent clinical results. Several clinical development programs have been discontinued.

Side-effect profile: Favorable at moderate dietary supplement doses (150 to 500 mg/day). Gastrointestinal effects (nausea, diarrhea) at higher doses. Potential drug interactions through CYP enzyme modulation. No serious safety signals at commonly studied doses.

Overall validation: Moderate. The preclinical evidence is extensive; the clinical evidence has been disappointing relative to preclinical promise, largely owing to pharmacokinetic limitations.

Comparison to cycloastragenol: Cycloastragenol has a more direct and potent telomerase-activating mechanism (hTERT transcriptional upregulation versus post-translational SIRT1-mediated deacetylation). Cycloastragenol has superior oral bioavailability (approximately 25.7 percent versus less than 1 percent for resveratrol). Resveratrol has a vastly larger literature and broader commercial and scientific recognition. The two compounds operate through complementary mechanisms (CREB/NRF2-mediated hTERT transcription for cycloastragenol versus SIRT1-mediated hTERT post-translational modification for resveratrol) and could theoretically be combined.

12.4 TA-65 (proprietary formulation)

Mechanism: TA-65 is a proprietary purified extract of *Astragalus membranaceus* root enriched for cycloastragenol. The mechanism is identical to cycloastragenol; TA-65 is included as a comparator because it is the formulated product rather than the pure compound and has a distinct evidence base.

Novelty: Low as a distinct mechanism; the formulation represents a delivery vehicle for cycloastragenol rather than a novel chemical entity.

Effect size: The clinical evidence for TA-65 is the most developed of any telomerase activator, with two controlled human studies demonstrating telomere lengthening and immunosenescence reversal. Effect sizes are modest: 530 plus or minus 180 base pairs of telomere lengthening at 12 months (low-dose group, Salvador et al. 2016), which represents approximately 5 to 10 percent of age-related telomere attrition per year [7, 14].

Promising potential: Moderate. The product is commercially successful as a premium dietary supplement. Clinical development beyond the existing biomarker studies would require investment in disease-endpoint trials.

Side-effect profile: Favorable. No serious adverse events in controlled studies of up to 12 months duration [7, 14].

Overall validation: Moderate. The controlled clinical evidence is the strongest of any telomerase activator, though limited by small sample sizes, biomarker-only endpoints, and proprietary formulation that limits pharmacokinetic precision.

Comparison to cycloastragenol: TA-65 is a formulated product of cycloastragenol; the comparison is therefore between the pure compound and its principal commercial delivery vehicle. Research-grade cycloastragenol offers analytical precision and dose-response control; TA-65 offers the most developed clinical evidence base and regulatory positioning as a marketed supplement.

12.5 Danazol

Mechanism: Synthetic androgen and anti-gonadotropin. Danazol upregulates hTERT transcription through a mechanism involving estrogen and androgen receptor signaling, producing telomerase activation and telomere elongation in hematopoietic stem cells. The compound is the only telomerase activator with demonstrated efficacy in a human disease characterized by accelerated telomere shortening: telomere biology disorders including dyskeratosis congenita and aplastic anemia [28].

Novelty: Moderate. The repurposing of a long-established synthetic androgen as a telomerase activator represents a novel application of a well-characterized compound.

Effect size: In the Townsley et al. (2016) Phase 1/2 clinical trial in 27 patients with telomere biology disorders, danazol at 800 mg daily for 24 months produced telomere elongation in peripheral blood leukocytes in 11 of 12 evaluable patients, with a mean increase of 386 plus or minus 178 base pairs at 24 months. This is the largest and most consistent telomere elongation effect demonstrated in a human clinical trial for any telomerase activator [28].

Promising potential: Moderate to high for telomere biology disorders; low for general anti-aging applications owing to the androgen-related side-effect profile.

Side-effect profile: Substantial. Danazol is a synthetic androgen with dose-dependent virilizing effects (acne, hirsutism, voice deepening), hepatotoxicity (elevated aminotransferases, rare hepatic adenoma and peliosis hepatis), lipid profile

disturbance (decreased HDL, increased LDL), and weight gain. These side effects limit the compound to disease-specific applications where the telomere phenotype is severe and the benefit-risk balance is favorable [28].

Overall validation: Moderate to high for telomere biology disorders based on the Townsley et al. clinical trial; low for general population applications.

Comparison to cycloastragenol: Danazol has the strongest clinical evidence for telomere elongation in a disease population and the largest effect size on telomere length in a controlled human trial. Cycloastragenol has a vastly superior safety profile and is suitable for long-term supplementation in healthy populations where danazol is not. The two compounds operate through different upstream mechanisms (androgen/estrogen receptor signaling for danazol versus CREB/NRF2 signaling for cycloastragenol) converging on hTERT transcriptional activation. Cycloastragenol is positioned for general anti-aging and health-maintenance applications; danazol is positioned for treatment of telomere biology disorders.

12.6 Comparator summary

The five comparators occupy distinct positions in the telomerase biology and anti-aging pharmacology landscape. **Astragaloside IV** is the direct biosynthetic precursor with complementary but lower-potency telomerase activation and substantially lower bioavailability. **EGCG** is a broadly studied antioxidant polyphenol with inconsistent telomerase effects. **Resveratrol** is the prototypical SIRT1 activator with indirect telomerase-relevant mechanisms and poor bioavailability. **TA-65** is the proprietary formulated product of cycloastragenol with the most developed clinical evidence base. **Danazol** is the only telomerase activator with clinical evidence in telomere biology disorders but carries an androgen-related side-effect profile that limits it to disease-specific applications.

Cycloastragenol occupies a distinctive position as the most potent and specific small-molecule telomerase activator with a favorable safety profile suitable for long-term supplementation. Its advantages include direct hTERT transcriptional activation through a characterized CREB/NRF2 mechanism; superior oral bioavailability relative to its precursor astragaloside IV; a multi-target pharmacology spanning anti-inflammatory, neuroprotective, cardioprotective, and antioxidant activities; clinical evidence from controlled human trials (via TA-65) demonstrating telomere lengthening; and a preclinical safety profile supporting chronic administration at high doses without organ toxicity, genotoxicity, or carcinogenicity pro-

motion. The principal limitations are the modest effect sizes on telomere length in clinical studies, the biomarker-only (rather than clinical-endpoint) nature of the human evidence, the extensive first-pass hepatic metabolism limiting systemic exposure, and the absence of disease-specific clinical trials comparable to the danazol telomere biology disorder study.

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