

RESEARCH MONOGRAPH . COMPOUND PROFILE

17-alpha-Estradiol

A naturally occurring 17-alpha-epimer of estradiol with approximately 100-fold reduced classical estrogen receptor affinity, topical registration as alfatradiol for androgenetic alopecia, and reproducible male-specific lifespan extension in the NIA Interventions Testing Program, mediated through estrogen receptor alpha signaling in the hypothalamus and liver.

DOCUMENT	KDC-MN-1475
ISSUED	2026-05-13
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Non-feminizing endogenous estradiol stereoisomer with 5-alpha-reductase inhibitory activity and lifespan-extending properties

ABSTRACT

17-alpha-Estradiol (estra-1,3,5(10)-triene-3,17-alpha-diol; CAS 57-91-0; alfatradiol; molecular formula C₁₈H₂₄O₂; molecular weight 272.39 g/mol) is the 17-alpha-stereoisomer of the principal mammalian estrogen 17-beta-estradiol, distinguished solely by the axial (alpha) orientation of the hydroxyl group at carbon 17 of the steroid D-ring. The compound occurs endogenously at low concentrations in mammalian brain and peripheral tissues and has been characterized since the 1950s as a weak estrogen with approximately 100-fold lower binding affinity for the classical nuclear estrogen receptors ER-alpha and ER-beta relative to the 17-beta-epimer [1, 2]. Despite this reduced receptor engagement, 17-alpha-estradiol retains potent estrogen receptor-independent antioxidant activity equivalent to 17-beta-estradiol in lipid peroxidation assays and neuroprotection models [3, 4], inhibits 5-alpha-reductase and aromatase in skin and hair follicle tissue (the basis for its topical registration as alfatradiol in several European jurisdictions for androgenetic alopecia) [5, 6], and has emerged as one of the most robustly validated lifespan-extending compounds in the National Institute on Aging Interventions Testing Program (ITP), a rigorous, multi-site, genetically heterogeneous mouse longevity screening platform.

The ITP demonstrated that dietary 17-alpha-estradiol at 14.4 parts per million (approximately 2 mg/kg/day mouse-equivalent) extended median lifespan by approximately 19 percent in male UM-HET3 mice when initiated at 16 months of age and by approximately 11 percent when initiated at 20 months, with no lifespan extension observed in female mice at any initiation age [7,

8, 9]. The male specificity of the lifespan effect has been replicated across three independent ITP sites (the Jackson Laboratory, the University of Michigan, and the University of Texas Health Science Center) and is among the largest and most reproducible lifespan extensions reported in the ITP, comparable in magnitude to acarbose and exceeded only by rapamycin. The sex-specific pattern has driven substantial mechanistic investigation. Stout et al. (2017) demonstrated that 17-alpha-estradiol alleviates age-related metabolic and inflammatory dysfunction in male mice without inducing feminization, with treated males showing reduced fasting glucose, reduced fasting insulin, reduced glycosylated hemoglobin, reduced visceral adiposity, reduced circulating and adipose tissue pro-inflammatory cytokines, and increased AMP-activated protein kinase activity in visceral adipose tissue [10]. Steyn et al. (2018) established that 17-alpha-estradiol acts through hypothalamic pro-opiomelanocortin (POMC) expressing neurons to reduce feeding behavior, with near-complete loss of the anorectic response in POMC-neuron-ablated mice [11]. Mann et al. (2020) demonstrated through liver-specific and global ER-alpha knockout models that the metabolic health benefits of 17-alpha-estradiol (reductions in fasting insulin, HbA1c, glucose intolerance, and visceral adiposity) are mediated through estrogen receptor alpha, resolving prior uncertainty about whether a non-classical receptor was responsible [12]. Garratt et al. (2017, 2018) reported that males, but not females, metabolize 17-alpha-estradiol into one or more estriol derivatives, and that the sex-specific beneficial effects may depend on a downstream metabolite rather than on the parent compound [13, 14].

The compound has limited human clinical data. A Phase I safety study in eight healthy postmenopausal women demonstrated

tolerability of single rising oral doses (50, 100, and 200 micrograms) with no adverse events, no detectable conversion to 17-beta-estradiol, and no feminizing effects [15]. Topical formulations (alfatradiol 0.025 percent solution, marketed as Ell-Cranell alpha) are registered in Germany, Austria, and several other European jurisdictions for androgenetic alopecia in men and women, with demonstrated stabilization of hair loss through local 5-alpha-reductase inhibition and aromatase induction [5, 6]. No clinical trials of oral 17-alpha-estradiol for longevity, metabolic, or neuroprotective endpoints have been completed or registered in humans as of the monograph revision date.

This monograph reviews the chemistry, stereochemistry, and synthesis of 17-alpha-estradiol; the molecular pharmacology across classical estrogen receptors, non-classical signaling pathways, 5-alpha-reductase inhibition, and antioxidant mechanisms; pharmacokinetics in rodent and limited human contexts; the preclinical evidence base from the ITP and mechanistic studies; the clinical evidence from the Phase I oral safety study and topical alopecia registration; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events and safety signals; and a comparative assessment of five alternative longevity or non-feminizing estrogen candidates against 17-alpha-estradiol on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Alfatradiol (for topical dermatological application).

Common names: 17-alpha-Estradiol, 17alpha-E2, 17aE2, alpha-estradiol, epiestradiol, estra-1,3,5(10)-triene-3,17alpha-diol.

Marketed names: Ell-Cranell alpha (Galderma; Germany, Austria, other European jurisdictions), Pantostin (generic markets). The marketed product is a 0.025 percent topical solution of alfatradiol for androgenetic alopecia.

Chemical Abstracts Service registry number: 57-91-0.

International Union of Pure and Applied Chemistry name: estra-1,3,5(10)-triene-3,17alpha-diol.

PubChem CID: 68570.

DrugBank identifier: DB04575.

1.2 Structural class and chemistry

17-alpha-Estradiol is a C₁₈ estrane steroid, a member of the natural estrogen family characterized by an aromatic A-ring bearing a phenolic hydroxyl at carbon 3 and a secondary hydroxyl at carbon 17 of the D-ring. The compound is the 17-alpha-epimer of 17-beta-estradiol (CAS 50-28-2), the principal endogenous estrogen in mammals. The sole structural difference is the stereochemistry at carbon 17: in 17-beta-estradiol, the hydroxyl is in the equatorial (beta) orientation; in 17-alpha-estradiol, the hydroxyl is in the axial (alpha) orientation. This single stereochemical inversion produces a compound with markedly reduced classical estrogen receptor binding affinity but preserved phenolic ring-dependent antioxidant activity [1, 3].

Molecular formula: C₁₈H₂₄O₂.

Exact mass: 272.1776 g/mol (monoisotopic).

Molecular weight: 272.39 g/mol.

Physical properties: White to off-white crystalline powder. Melting point approximately 220 to 223 degrees Celsius. Sparingly soluble in water; soluble in ethanol, methanol, dimethyl sulfoxide, acetone, and chloroform. The phenolic hydroxyl at carbon 3 confers moderate water solubility at alkaline pH. LogP approximately 4.01, consistent with moderate lipophilicity and capacity for membrane partitioning.

Stereochemistry: The compound contains five stereocenters (carbons 8, 9, 13, 14, and 17) and is supplied as the single natural stereoisomer with the (8R,9S,13S,14S,17S) absolute configuration. The 17-alpha designation refers to the axial orientation of the C-17 hydroxyl on the alpha face of the steroid skeleton (below the plane of the ring system as conventionally drawn). Investigators should confirm stereochemical identity by optical rotation, chiral high-performance liquid chromatography, or nuclear magnetic resonance comparison against an authenticated reference standard, as contamination with or misidentification as 17-beta-estradiol would fundamentally alter the pharmacological profile of any experiment.

1.3 Synthesis

17-alpha-Estradiol can be prepared by chemical epimerization of 17-beta-estradiol at carbon 17. The classical approach involves Oppenauer oxidation of 17-beta-estradiol to estrone (estra-1,3,5(10)-trien-3-ol-17-one), followed by stereoselective reduction of the 17-ketone under conditions that favor the alpha-alcohol product. Sodium borohydride reduction in methanol at low temperature yields a mixture of the 17-alpha and 17-beta alcohols; the thermodynamically less stable 17-alpha-epimer is the kinetic product under certain conditions and can be enriched by careful control of temperature, solvent, and reaction time [16]. Separation of the two epimers is achieved by fractional crystallization or by chromatography on silica gel. Alternatively, stereoselective reduction using L-Selectride (lithium tri-sec-butylborohydride) or bulky aluminum hydride reagents in tetrahydrofuran provides higher alpha-selectivity by directing hydride delivery from the less hindered alpha-face of the steroid. The product is characterized by nuclear magnetic resonance spectroscopy (the C-17 proton resonance is diagnostic for alpha versus beta configuration), mass spectrometry, and melting point. Industrial synthesis achieves greater than 99 percent stereochemical purity as confirmed by chiral HPLC.

2. Abstract

17-alpha-Estradiol (alfatradiol; CAS 57-91-0) is the 17-alpha-stereoisomer of the principal mammalian estrogen 17-beta-estradiol, characterized by approximately 100-fold reduced affinity for the classical nuclear estrogen receptors ER-alpha and ER-beta relative to the 17-beta-epimer [1, 2]. Despite this reduced classical receptor engagement, the compound has emerged as one of the most robustly validated life-span-extending agents in mammalian studies. The National Institute on Aging Interventions Testing Program (ITP) demonstrated reproducible, multi-site median lifespan extension of approximately 19 percent in male UM-HET3 mice fed 17-alpha-estradiol at 14.4 ppm starting at 16 months of age, with no effect observed in females [7, 8, 9]. This male-specific longevity effect is among the largest in the ITP, exceeded only by rapamycin and comparable to acarbose.

Mechanistic investigation has identified several converging pathways. The metabolic and anti-inflammatory health benefits of 17-alpha-estradiol are mediated through estrogen receptor alpha, as demonstrated by global and tissue-specific ER-alpha knockout models in which fasting insulin, glycosylated hemoglobin, glucose tolerance, and visceral adiposity improvements were abolished [12]. The compound acts centrally through hypothalamic POMC neurons to reduce feeding behavior, contributing to reduced caloric intake and body mass [11]. Peripherally, 17-alpha-estradiol reduces visceral adipose tissue inflammation, increases AMPK activity in adipose tissue, and reduces mTOR complex 1 signaling [10]. The sex-specific metabolism of 17-alpha-estradiol, with males but not females converting the compound to estriol derivatives, may partially explain the sex-specific lifespan effect [13, 14].

Independent of the longevity pharmacology, 17-alpha-estradiol is a potent antioxidant with neuroprotective activity equivalent to 17-beta-estradiol in lipid peroxidation and glutamate excitotoxicity models, operating through the phenolic A-ring hydroxyl in an estrogen receptor-independent mechanism [3, 4]. It inhibits 5-alpha-reductase and induces aromatase in hair follicle tissue, the basis for its topical registration as alfatradiol for androgenetic alopecia in several European countries [5, 6]. The compound does not adversely affect male reproductive parameters including sperm count, motility, morphology, or fertility at lifespan-extending doses in mice [17].

Human clinical data are limited to a Phase I oral safety study in postmenopausal women (single doses of 50 to 200 micrograms; no adverse events, no feminizing effects, no conversion to 17-beta-estradiol) [15] and the topical alopecia registration studies. No clinical trials of oral 17-alpha-estradiol for longevity, metabolic, or neuroprotective endpoints have been completed in humans.

3. Discovery and Development History

3.1 Early identification and characterization

17-alpha-Estradiol was first isolated and characterized as a natural estrogen epimer in the 1930s and 1940s during the structural elucidation of the steroid hormones. The compound was identified in mammalian urine and tissues as a minor metabolite of estradiol metabolism and was recognized early as having substantially reduced uterotrophic (feminizing) activity relative to 17-beta-estradiol [1]. The reduced estrogenic potency was attributed to the altered stereochemistry at carbon 17, which disrupts optimal positioning within the ligand-binding domain of the nuclear estrogen receptors. Throughout the latter half of the twentieth century, 17-alpha-estradiol was used principally as a negative control or weak-estrogen comparator in endocrine pharmacology studies.

3.2 Neuroprotection research

In the 1990s, the Bhatt, Green, and Bhatt-Simpkins laboratories demonstrated that 17-alpha-estradiol retained potent neuroprotective activity in models of glutamate excitotoxicity, oxidative stress, and amyloid-beta toxicity, despite its weak classical estrogen receptor engagement [3, 4]. The neuroprotective activity was shown to depend on the phenolic A-ring hydroxyl group (a structural feature shared by both epimers) and to operate through inhibition of lipid peroxidation and free radical scavenging in an estrogen receptor-independent manner. These findings established 17-alpha-estradiol as a candidate non-feminizing neuroprotective estrogen and prompted investigation in neurodegenerative disease models.

3.3 Topical registration for androgenetic alopecia

Concurrent with the neuroprotection research, 17-alpha-estradiol was developed as a topical treatment for androgenetic alopecia under the pharmaceutical name alfa-tradiol. The mechanism involves local inhibition of 5-alpha-reductase (reducing conversion of testosterone to dihydrotestosterone in the scalp) and induction of aromatase activity in hair follicles [5, 6]. The 0.025 percent topical solution was registered in Germany and other European jurisdictions under the brand name Ell-

Cranell alpha. Clinical studies demonstrated stabilization of hair loss without systemic feminizing effects. This remains the only registered human pharmaceutical application of 17-alpha-estradiol.

3.4 NIA Interventions Testing Program

The pivotal development in the pharmacology of 17-alpha-estradiol was its inclusion in the NIA Interventions Testing Program, a multi-site, genetically heterogeneous mouse longevity study designed to identify compounds that reproducibly extend lifespan under rigorous conditions. The ITP uses the UM-HET3 four-way cross mouse stock, tests compounds at three independent sites simultaneously, and applies pre-specified statistical criteria for significance.

Strong et al. (2016) reported the first ITP result: 17-alpha-estradiol at 14.4 ppm in diet extended median lifespan by approximately 12 percent in male mice initiated at 10 months of age, with no effect in females [7]. Harrison et al. (2014) had previously reported suggestive male-specific effects in a smaller cohort [8]. The 2021 Harrison et al. publication confirmed and extended the finding: 17-alpha-estradiol initiated at 16 months of age extended male median lifespan by approximately 19 percent, and initiation at 20 months still produced approximately 11 percent extension, demonstrating efficacy even with late-life treatment [9]. Female mice showed no benefit at any age of initiation.

3.5 Mechanistic characterization

The period from 2017 to the present has seen intensive mechanistic characterization. The Stout laboratory at the University of Oklahoma Health Sciences Center and collaborators have published a series of studies establishing: the metabolic and anti-inflammatory phenotype in treated male mice [10]; the hypothalamic POMC neuron dependence of the anorectic response [11]; the requirement for estrogen receptor alpha [12]; the sex-specific metabolism to estriol derivatives [13, 14]; the absence of adverse effects on male reproductive parameters [17]; and the role of hepatic ER-beta in mediating some liver-specific metabolic benefits [18]. These studies collectively establish 17-alpha-estradiol as an ER-alpha-dependent, centrally and peripherally acting metabolic modulator with a sex-specific pharmacological profile.

4. Mechanism of Action

17-alpha-Estradiol is a multi-mechanism compound whose pharmacological actions span classical estrogen receptor signaling, non-classical estrogen signaling, receptor-independent antioxidant activity, and enzymatic inhibition. The relative contributions of each mechanism vary by tissue, dose, and route of administration.

4.1 Classical estrogen receptor binding

17-alpha-Estradiol binds to estrogen receptor alpha (ER-alpha) and estrogen receptor beta (ER-beta) with approximately 100-fold lower affinity than 17-beta-estradiol [1, 2]. The reduced affinity reflects the disrupted positioning of the C-17 hydroxyl within the receptor ligand-binding domain. Despite this reduced affinity, the compound retains measurable ER-alpha agonist activity at sufficient concentrations, and the metabolic health benefits in male mice have been demonstrated to require functional ER-alpha through global and liver-specific knockout studies [12]. In ER-alpha knockout male mice treated with 17-alpha-estradiol, the improvements in fasting insulin, glycosylated hemoglobin, glucose tolerance, and visceral adiposity observed in wild-type treated males were abolished. This establishes that the low-affinity ER-alpha engagement, while weak relative to 17-beta-estradiol, is biologically sufficient at the concentrations achieved in vivo during chronic dietary administration.

4.2 Hypothalamic signaling through POMC neurons

17-alpha-Estradiol reduces food intake in male mice through activation of hypothalamic anorexigenic pathways. Steyn et al. (2018) demonstrated that the compound increases pro-opiomelanocortin (POMC) expression in the arcuate nucleus of the hypothalamus, and that mice with near-complete loss of arcuate POMC transcription (through Cre-mediated POMC neuron ablation) fail to reduce food intake in response to 17-alpha-estradiol treatment [11]. The POMC neuron dependence of the anorectic response establishes a central mechanism for the caloric restriction-like metabolic phenotype observed in treated male mice. Notably, some peripheral

metabolic markers (fasting glucose, insulin sensitivity) were still improved in POMC-ablated mice, suggesting that 17-alpha-estradiol has both central and peripheral actions that can operate cooperatively or independently [11].

4.3 Peripheral metabolic and anti-inflammatory effects

In male mice, chronic 17-alpha-estradiol treatment produces a constellation of metabolic improvements: reduced fasting glucose, reduced fasting insulin, reduced glycosylated hemoglobin, improved glucose tolerance, reduced visceral adiposity, reduced body mass (approximately 20 percent reduction), and reduced circulating pro-inflammatory cytokines [10]. At the tissue level, 17-alpha-estradiol increases AMP-activated protein kinase alpha (AMPK-alpha) activity and reduces mammalian target of rapamycin complex 1 (mTORC1) signaling in visceral adipose tissue, but not in liver or skeletal muscle [10]. The AMPK activation and mTORC1 suppression in adipose tissue are consistent with improved metabolic efficiency and reduced anabolic signaling, a profile shared with caloric restriction and with other ITP-validated longevity interventions including rapamycin and acarbose.

Visceral adipose tissue inflammation is substantially reduced, with lower tissue concentrations of tumor necrosis factor alpha, interleukin-6, and monocyte chemoattractant protein-1 in treated males [10]. Hypothalamic neuroinflammation (astrogliosis and microgliosis) is also reduced in 17-alpha-estradiol-treated male mice, with the anti-neuroinflammatory effect demonstrating the same sex specificity as the lifespan extension [19].

4.4 Antioxidant and neuroprotective activity

17-alpha-Estradiol is a potent inhibitor of lipid peroxidation with efficacy equivalent to 17-beta-estradiol in cell-free, cellular, and tissue models of oxidative damage [3, 4]. The antioxidant mechanism depends on the phenolic hydroxyl at carbon 3 of the A-ring, which functions as a chain-breaking radical scavenger in lipid membranes. This activity is entirely estrogen receptor-independent, as demonstrated by preservation of the antioxidant effect in the presence of the estrogen receptor antagonist ICI-182,780 and in ER-alpha and ER-beta knockout systems [4].

The neuroprotective activity has been demonstrated in multiple in vitro models: glutamate excitotoxicity in primary cortical neurons, hydrogen peroxide-induced oxidative death in SK-N-SH human neuroblastoma cells, and amyloid-beta peptide-

induced toxicity in hippocampal cultures [3, 4, 20]. In vivo, 17-alpha-estradiol at 5 to 10 micrograms per kilogram is neuroprotective in male and female rats in a model of early brain injury with equivalent efficacy to 17-beta-estradiol, without inducing uterine weight gain or serum estradiol elevation [20]. The neuroprotective profile, combined with the absence of feminizing effects, has prompted characterization of 17-alpha-estradiol as a candidate neuroSERM (selective estrogen receptor modulator for neurological applications) [21].

4.5 5-alpha-reductase inhibition and aromatase induction

In skin and hair follicle tissue, 17-alpha-estradiol inhibits 5-alpha-reductase, the enzyme that converts testosterone to the more potent androgen dihydrotestosterone (DHT). It additionally inhibits 17-beta-hydroxysteroid dehydrogenase, reducing the conversion of androstenedione to testosterone, and induces aromatase activity, accelerating the conversion of testosterone to estradiol [5, 6]. The net effect is a local reduction in androgenic signaling in the hair follicle, the pharmacological basis for the topical alopecia indication. These enzymatic effects are tissue-specific and are not observed systemically at topical application doses.

4.6 Sex-specific metabolism

Garratt et al. (2017, 2018) reported that male mice, but not female mice, metabolize 17-alpha-estradiol into one or more estriol derivatives [13, 14]. This sex-specific biotransformation raises the possibility that the lifespan-extending activity resides in a downstream metabolite rather than in 17-alpha-estradiol itself, and that the failure of lifespan extension in females reflects the absence of the active metabolite rather than a sex-specific target tissue difference. The identity and pharmacology of the putative active estriol derivative have not been fully characterized.

5. Pharmacokinetics and Routes of Administration

5.1 Rodent pharmacokinetics

17- α -Estradiol is orally bioavailable in mice and rats. In the ITP studies, the compound was administered in the diet at 14.4 parts per million, corresponding to an estimated daily intake of approximately 2 mg/kg in adult male mice [7]. The compound is absorbed from the gastrointestinal tract and distributed systemically. Plasma concentrations after dietary administration have not been reported in published ITP studies, but the metabolic and inflammatory endpoints confirm systemic exposure sufficient for ER- α engagement in liver, hypothalamus, and adipose tissue.

The compound undergoes hepatic metabolism. As noted in Section 4.6, males convert 17- α -estradiol to estriol derivatives through pathways that females do not utilize [13, 14]. The specific cytochrome P450 isoforms and conjugation enzymes involved in 17- α -estradiol metabolism have not been fully characterized in published literature, but by analogy to 17- β -estradiol metabolism, the principal hepatic transformations are expected to include 2-hydroxylation (CYP1A2, CYP3A4), 4-hydroxylation (CYP1B1), 16- α -hydroxylation, and subsequent conjugation by UDP-glucuronosyltransferases, sulfotransferases, and catechol-O-methyltransferase. The moderate lipophilicity (LogP approximately 4.0) predicts substantial tissue partitioning and central nervous system penetration.

5.2 Human pharmacokinetics

Published human pharmacokinetic data for oral 17- α -estradiol are limited to the Phase I safety study by Moos et al. (2009), which characterized single oral doses of 50, 100, and 200 micrograms in eight healthy postmenopausal women [15]. The compound was absorbed and cleared without detectable conversion to 17- β -estradiol. Detailed pharmacokinetic parameters (time to peak concentration, area under the curve, elimination half-life) from this study have not been published in full in the peer-reviewed literature.

For topical alfatradiol (0.025 percent solution), systemic absorption is minimal. The compound acts locally in the scalp and hair follicle compartment with negligible systemic exposure, as confirmed by the absence of changes in serum estradiol, gonadotropins, or endometrial thickness in topical application studies [5].

5.3 Routes of administration

Dietary (rodent research): 14.4 ppm in chow is the standard ITP formulation, corresponding to approximately 2 mg/kg/day. This is the route for all published lifespan and metabolic studies.

Oral (human, investigational): Single doses of 50 to 200 micrograms were studied in the Phase I trial [15]. No repeated-dose oral human studies have been published.

Topical (human, registered): 0.025 percent solution (alfatradiol) applied to the scalp once daily for androgenetic alopecia [5, 6].

Subcutaneous and intraperitoneal (rodent research): Used in neuroprotection studies at doses of 5 to 100 micrograms per kilogram [20]. These routes provide direct systemic exposure without first-pass hepatic metabolism.

6. Preclinical Pharmacology

6.1 NIA Interventions Testing Program lifespan studies

The ITP is a multi-site, genetically heterogeneous mouse longevity study operated under the National Institute on Aging. Compounds are administered in the diet to male and female UM-HET3 mice (the four-way cross of (BALB/cByJ x C57BL/6J)F1 females mated with (C3H/HeJ x DBA/2J)F1 males), and lifespan is the primary endpoint. Three independent sites (the Jackson Laboratory, the University of Michigan, and the University of Texas Health Science Center at San Antonio) test each compound simultaneously to ensure reproducibility.

17-alpha-Estradiol at 14.4 ppm has been tested in multiple ITP cohorts:

The Strong et al. (2016) report documented approximately 12 percent median lifespan extension in males initiated at 10 months of age ($p < 0.01$ by log-rank test), with no effect in females [7]. The Harrison et al. (2021) report documented approximately 19 percent median lifespan extension in males initiated at 16 months (the largest cohort), and approximately 11 percent extension with initiation at 20 months [9]. Both late-life initiation results were statistically significant across all three sites. Female mice showed no benefit at any initiation age.

The magnitude of the male lifespan extension places 17-alpha-estradiol among the top ITP compounds, comparable to acarbose (approximately 22 percent male median extension at 1000 ppm) and exceeded only by rapamycin (approximately 23 percent male median extension at 42 ppm initiated at 20 months) [7, 9].

6.2 Metabolic phenotyping

Stout et al. (2017) conducted comprehensive metabolic phenotyping of 17-alpha-estradiol-treated male mice [10]. Key findings:

Treated males showed approximately 20 percent reduction in body mass relative to controls, with disproportionate reduction in visceral adiposity. Fasting glucose was reduced by approximately 25 percent. Fasting insulin was reduced by approximately 50 percent. Glycosylated hemoglobin was significantly reduced. Glucose tolerance (by intraperitoneal glucose tolerance test) was significantly improved.

Circulating interleukin-6 and tumor necrosis factor alpha were reduced. Visceral adipose tissue showed reduced macrophage infiltration, reduced crown-like structure density, and reduced pro-inflammatory gene expression. AMPK-alpha phosphorylation was increased and mTORC1 substrate phosphorylation was decreased in visceral adipose tissue. Seminal vesicle weight, preputial gland weight, and testes weight were unchanged, confirming the absence of feminizing or anti-androgenic effects in reproductive tissues [10].

6.3 Hypothalamic and neuroendocrine effects

Steyn et al. (2018) demonstrated that 17-alpha-estradiol activates hypothalamic POMC neurons and reduces food intake in male mice on both standard and high-fat diets [11]. POMC-neuron-ablated mice failed to reduce food intake but retained some peripheral metabolic improvements, indicating dual central and peripheral mechanisms.

Subsequent studies demonstrated reduced hypothalamic astrogliosis and microgliosis in treated male mice, with the neuroinflammatory improvement showing the same sex specificity as the lifespan extension [19]. Single-nucleus transcriptomic sequencing of the hypothalamus in 17-alpha-estradiol-treated male mice revealed altered endocrine signaling pathways, including modulation of gonadotropin-releasing hormone, corticotropin-releasing hormone, and growth hormone-releasing hormone neuronal populations [22].

6.4 Reproductive safety

Garratt et al. (2023) evaluated the effects of chronic 17-alpha-estradiol treatment on male reproductive parameters [17]. At the standard ITP dose of 14.4 ppm, treated males showed no adverse effects on testes mass, seminiferous tubule morphology, sperm quantity, sperm morphology, sperm membrane integrity, or any measured motility parameter. Chronic treatment did not alter plasma 17-beta-estradiol, estrone, follicle-stimulating hormone, or luteinizing hormone concentrations. Plasma testosterone was mildly increased. Treated males retained normal fertility, successfully impregnating female mice and generating viable embryos. These findings are significant because they demonstrate that the lifespan extension does not operate through a reproduction-longevity trade-off mechanism [17].

6.5 Neuroprotection

In vivo neuroprotection by 17-alpha-estradiol has been demonstrated at 5 to 10 micrograms per kilogram in rat models of subarachnoid hemorrhage-induced early brain injury, with effects equivalent to 17-beta-estradiol in reducing cerebral edema, blood-brain barrier disruption, and neuronal apoptosis [20]. The neuroprotective effect was observed in both male and female rats and was not blocked by estrogen receptor antagonism, confirming the receptor-independent (antioxidant) mechanism in the acute neuroprotection context. Chronic neuroprotection in aging models (as distinct from acute injury) has not been directly tested, but the reduced hypothalamic neuroinflammation in ITP-dose-treated male mice suggests a chronic neuroprotective contribution [19].

7. Clinical Evidence Base

7.1 Phase I oral safety study

The Phase I study by Moos, Bhatt, and colleagues evaluated single rising oral doses of 17-alpha-estradiol (designated MX-4509) at 50, 100, and 200 micrograms in eight healthy postmenopausal women with a washout period of seven days between doses [15]. All doses were well tolerated. No adverse events were reported. All biochemistry, hematology, urinalysis, vital signs, and electrocardiogram measurements remained within normal ranges. Critically, no detectable conversion of 17-alpha-estradiol to 17-beta-estradiol was observed, and no changes in serum estradiol levels were measured. Uterine effects (endometrial thickness) were not assessed in this single-dose study. The study established preliminary safety for oral administration but did not evaluate repeated dosing, dose-response pharmacodynamics, or efficacy endpoints.

7.2 Topical alfatradiol for androgenetic alopecia

The principal clinical evidence for 17-alpha-estradiol in humans comes from the topical alopecia indication. The topical 0.025 percent alfatradiol solution (Ell-Cranell alpha) has been evaluated in several clinical studies:

A randomized, controlled, double-blind study by Orfanos et al. (1980) in androgenetic alopecia demonstrated that topical 17-alpha-estradiol reduced hair loss compared to placebo [23]. The mechanism involves local inhibition of 5-alpha-reductase in the hair follicle, reducing DHT-mediated follicular miniaturization.

Kim et al. (2012) conducted a single-center, open-label, non-comparative Phase IV study of Ell-Cranell alpha 0.025 percent solution in female pattern hair loss [5]. Hair counts and hair diameter increased significantly from baseline to 4 and 8 months ($p < 0.0001$). The treatment was well tolerated over the 8-month period with no significant adverse events.

Blume-Peytavi et al. (2007) compared topical alfatradiol to topical finasteride in a retrospective study of 119 postmenopausal women with female pattern hair loss, with both treatments showing comparable efficacy in stabilizing hair loss [6].

The topical formulation has demonstrated safety over extended treatment periods (up to 12 months in published studies) with no systemic hormonal effects, consistent with the negligible systemic absorption of the topical application.

7.3 Absence of clinical longevity or metabolic trials

No clinical trials of oral 17-alpha-estradiol for longevity, metabolic, neuroprotective, or anti-inflammatory endpoints have been registered, initiated, or completed in humans as of the monograph revision date. The translational gap between the robust rodent longevity data and human clinical evaluation remains the principal limitation of the compound's clinical evidence base. Factors contributing to this gap include the absence of a clear commercial development pathway for a non-patentable steroid epimer, the difficulty of designing a lifespan endpoint trial in humans, and uncertainty about whether the male-specific rodent effect would translate to human physiology.

8. Sourcing and Quality Verification

17- α -Estradiol is available from multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Tocris, MedChemExpress, Selleckchem, Toronto Research Chemicals, others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the free steroid. Pricing is moderate, in the range of \$30 to \$150 per gram of research-grade material at the time of monograph preparation.

Pharmaceutical-grade topical alfatradiol (Ell-Cranell alpha 0.025 percent solution) is available by prescription or over the counter in Germany and other European jurisdictions where it is registered for androgenetic alopecia.

Investigators should confirm compound identity and stereochemical purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (273.185 for the protonated molecule $[M+H]^+$, or 272.178 monoisotopic for the neutral compound)
- Chiral HPLC or nuclear magnetic resonance confirmation that the material is 17- α -estradiol and not 17- β -estradiol, as the two epimers have identical molecular weight and similar chromatographic behavior on achiral columns. The C-17 proton chemical shift in 1H NMR ($CDCl_3$) is diagnostic: approximately 3.53 ppm for the 17- α -epimer versus approximately 3.73 ppm for the 17- β -epimer
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis if the synthesis route is not specified by the vendor

The critical quality consideration for 17- α -estradiol research is confirmation of stereochemical identity. Contamination with even small percentages of 17- β -estradiol would introduce classical estrogenic activity that could confound mechanistic interpretation. Third-party analytical laboratories (Janoshik Analytical, others) provide independent confirmation of vendor certificates of analysis.

9. Reconstitution and Handling

17-alpha-Estradiol is a crystalline solid at room temperature with limited aqueous solubility. For research applications:

In vitro stock solutions: Dissolve in dimethyl sulfoxide (DMSO) at 10 to 100 mM for cell culture experiments; final DMSO concentration in assay medium should not exceed 0.1 percent. Alternatively, dissolve in ethanol at 10 to 50 mM. Aqueous solubility can be improved by cyclodextrin complexation (2-hydroxypropyl-beta-cyclodextrin at equimolar or 2-fold excess).

In vivo formulations: For rodent studies, the compound is typically administered in the diet (mixed into chow at 14.4 ppm for ITP-standard dosing) or dissolved in sesame oil or corn oil for subcutaneous or intraperitoneal injection. For oral gavage, suspension in 0.5 percent carboxymethylcellulose with 0.1 percent Tween-80 is standard.

Storage: Store the solid at minus 20 degrees Celsius, protected from light and moisture, under inert gas (nitrogen or argon) if long-term storage is intended. The compound is stable at room temperature for months in dry conditions but may undergo slow oxidation of the phenolic ring on prolonged storage in air. Stock solutions in DMSO are stable at minus 20 degrees Celsius for at least 6 months; ethanol stock solutions should be used within 3 months. Aqueous solutions should be prepared fresh or used within 24 hours.

Light sensitivity: The compound is modestly light-sensitive owing to the aromatic A-ring. Amber vials or foil wrapping is recommended for stock solutions.

Aliquoting: Single-use aliquots are recommended to avoid repeated freeze-thaw cycles. The compound tolerates at least 3 freeze-thaw cycles without measurable degradation, but single-use aliquoting is best practice.

10. Stack Interaction Considerations

Investigators combining 17-alpha-estradiol with other research compounds should consider:

Estrogen receptor ligands: Concurrent administration with 17-beta-estradiol, estrone, estriol, selective estrogen receptor modulators (tamoxifen, raloxifene), or selective estrogen receptor degraders (fulvestrant) produces competitive or additive effects at ER-alpha and ER-beta. The combination of 17-alpha-estradiol with fulvestrant or ICI-182,780 would be expected to block the ER-alpha-mediated metabolic benefits while preserving the antioxidant and 5-alpha-reductase inhibitory effects. This dissociation has been used experimentally to separate ER-dependent from ER-independent mechanisms [4, 12].

Other ITP-validated longevity compounds: The combination of 17-alpha-estradiol with rapamycin, acarbose, or canagliflozin has not been studied in published ITP cohorts. The metabolic mechanisms are partially overlapping (all reduce mTORC1 signaling or improve insulin sensitivity) and partially orthogonal (rapamycin acts through direct mTOR inhibition, acarbose through carbohydrate absorption delay, canagliflozin through renal glucose excretion). Additive or synergistic lifespan effects are plausible but undemonstrated.

5-alpha-reductase inhibitors: Concurrent use with finasteride or dutasteride produces additive inhibition of DHT synthesis. The combination has been used in topical alopecia research but systemic co-administration has not been characterized.

Aromatase inhibitors: Concurrent administration with anastrozole, letrozole, or exemestane would oppose the aromatase-inducing activity of 17-alpha-estradiol and could reduce the local estrogenic milieu in target tissues. The pharmacological interaction is antagonistic at the enzymatic level.

CYP enzyme interactions: By analogy to 17-beta-estradiol, 17-alpha-estradiol may undergo metabolism by CYP1A2, CYP3A4, and CYP1B1. Strong inhibitors of these enzymes (fluvoxamine for CYP1A2; ketoconazole, itraconazole for CYP3A4)

may increase 17-alpha-estradiol exposure. Strong inducers (rifampin, carbamazepine, phenobarbital) may decrease exposure. These interactions are predicted by analogy and have not been directly characterized for 17-alpha-estradiol.

Caloric restriction and intermittent fasting: The 17-alpha-estradiol metabolic phenotype resembles caloric restriction (reduced body mass, improved insulin sensitivity, AMPK activation, mTORC1 suppression). Concurrent caloric restriction and 17-alpha-estradiol treatment may produce additive metabolic effects but could also produce excessive weight loss or hypoglycemia. This combination has not been formally studied.

11. Adverse Events and Safety

11.1 Rodent safety profile

At the ITP-standard dose of 14.4 ppm in diet (approximately 2 mg/kg/day), 17-alpha-estradiol has been administered chronically (from 10, 16, or 20 months of age until natural death) to thousands of UM-HET3 mice across the three ITP sites. The safety profile in male mice is notable for: approximately 20 percent reduction in body mass (which is an intended pharmacological effect rather than an adverse event in the longevity context); no feminizing effects (no gynecomastia, no reduction in testes weight, no increase in seminal vesicle or preputial gland weight); no adverse effects on fertility, sperm parameters, or gonadotropin levels [10, 17]; no increase in tumor incidence reported in published ITP analyses; and no excess mortality at any time point.

In female mice, 17-alpha-estradiol at 14.4 ppm produced no lifespan extension and no reported adverse effects. The compound appears biologically inert with respect to lifespan and metabolic endpoints in female mice at this dose, consistent with the sex-specific metabolic activation hypothesis [13, 14].

11.2 Human safety (oral)

The Phase I study in eight postmenopausal women reported no adverse events at single oral doses of 50 to 200 micrograms [15]. All clinical chemistry, hematology, and vital sign parameters remained normal. No feminizing effects were observed (no change in serum estradiol, no uterine effects assessed). The study is limited by its single-dose design, small sample size, and absence of repeated-dose data.

11.3 Human safety (topical)

Topical alfatradiol 0.025 percent solution has been well tolerated in studies extending up to 12 months [5, 6, 23]. Reported adverse events are confined to occasional mild local irritation at the application site. No systemic hormonal effects, no changes in serum estradiol or gonadotropins, and no feminizing effects have been reported with topical use.

11.4 Theoretical safety considerations

Long-term oral administration of 17-alpha-estradiol in humans has not been studied, and several theoretical safety considerations merit attention:

The compound retains weak ER-alpha agonist activity, and chronic oral dosing at higher concentrations than the Phase I study could potentially produce estrogen-responsive tissue effects (endometrial stimulation, breast tissue proliferation) in susceptible individuals. The magnitude of this risk is predicted to be substantially lower than with 17-beta-estradiol given the approximately 100-fold reduction in receptor affinity, but it has not been excluded by clinical data.

The sex-specific metabolism to estriol derivatives in rodents raises uncertainty about whether the same metabolic pathway operates in humans and whether the resulting metabolites have their own safety profile.

The body mass reduction observed in male mice (approximately 20 percent) could be excessive in lean individuals; dose-response characterization in humans would be necessary to establish a safe and effective oral dose.

11.5 Pregnancy and lactation

17-alpha-Estradiol is an endogenous steroid present at low concentrations in mammalian tissues. Exogenous administration during pregnancy has not been studied. Given the compound's weak estrogenic activity and its role as a steroid hormone epimer, use during pregnancy or lactation is not recommended in the absence of safety data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five compounds against 17-alpha-estradiol, evaluated against five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The five comparators were selected to span the non-feminizing estrogen, longevity intervention, and neuroprotective estrogen spaces that define the pharmacological positioning of 17-alpha-estradiol.

12.1 Rapamycin (Sirolimus)

Mechanism: Allosteric inhibitor of mechanistic target of rapamycin complex 1 (mTORC1). Rapamycin binds FKBP12 and the resulting complex inhibits mTORC1 kinase activity, reducing protein synthesis, cellular growth, and proliferative signaling.

Longevity evidence: Rapamycin is the most extensively validated lifespan-extending compound in the ITP. It extends median lifespan in both male and female UM-HET3 mice at multiple doses and ages of initiation. At 42 ppm initiated at 20 months, male median lifespan extension is approximately 23 percent and female median extension is approximately 26 percent [24, 25]. The compound extends lifespan even when initiated at 600 days of age.

Novelty: Moderate. The mTOR pathway is a well-characterized longevity target validated across yeast, worms, flies, and mice. Rapamycin was the first compound to reproducibly extend mammalian lifespan in the ITP and remains the benchmark.

Effect size: Large. The lifespan extension is among the largest reported in any mammalian pharmacological intervention and is effective in both sexes, unlike 17-alpha-estradiol.

Promising potential: High. Rapamycin is FDA-approved as an immunosuppressant for organ transplant. Multiple clinical trials of rapamycin analogs (rapalogs) for aging-related indications are ongoing. The PEARL trial evaluated everolimus for

immune function in elderly subjects [26].

Side-effect profile: Significant. Chronic rapamycin produces immunosuppression, impaired wound healing, glucose intolerance (paradoxically, despite improving longevity), hyperlipidemia, thrombocytopenia, and mucositis. The immunosuppressive effects are the principal limitation for human longevity application. Intermittent dosing regimens are under investigation to mitigate side effects while preserving longevity benefits.

Overall validation: Very high. Rapamycin is the most validated pharmacological longevity intervention in mammals and the standard against which other compounds are compared.

Comparison to 17-alpha-estradiol: Rapamycin produces larger lifespan extension in both sexes, whereas 17-alpha-estradiol is effective only in males. Rapamycin has a more challenging side-effect profile (immunosuppression, metabolic effects) compared to the benign profile of 17-alpha-estradiol. The two compounds share mTORC1 pathway modulation but through different mechanisms (direct inhibition versus upstream AMPK activation). The combination has not been tested. For male-specific applications where immunosuppression is unacceptable, 17-alpha-estradiol offers a substantially more favorable safety profile at the cost of smaller effect size.

12.2 Acarbose

Mechanism: Alpha-glucosidase inhibitor. Acarbose competitively inhibits brush border alpha-glucosidases in the small intestine, delaying carbohydrate digestion and blunting postprandial glucose excursions.

Longevity evidence: Acarbose at 1000 ppm in diet extended median lifespan by approximately 22 percent in male UM-HET3 mice and approximately 5 percent in female mice in the ITP [27]. The male specificity of the large effect size parallels 17-alpha-estradiol, though the female effect is small rather than absent.

Novelty: Low. Alpha-glucosidase inhibition is a well-established diabetes pharmacology; the longevity application is the novel element.

Effect size: Large in males, modest in females.

Promising potential: Moderate. Acarbose is FDA-approved for type 2 diabetes. The longevity indication is not under clinical development, but the established safety record supports off-label investigation.

Side-effect profile: Gastrointestinal: flatulence, bloating, diarrhea from undigested carbohydrate reaching the colon. Effects are dose-dependent and generally manageable. No immunosuppression or metabolic toxicity.

Overall validation: High. Multi-site ITP replication, established human safety database, clear mechanism.

Comparison to 17-alpha-estradiol: Both compounds show male-biased lifespan extension in the ITP, with acarbose showing a marginally larger effect in males and a small female effect. Acarbose acts through carbohydrate metabolism modification, while 17-alpha-estradiol acts through ER-alpha-mediated metabolic reprogramming and hypothalamic appetite regulation. The mechanisms are largely non-overlapping. Acarbose has a more established human safety database; 17-alpha-estradiol has a cleaner side-effect profile (no gastrointestinal effects in rodent studies).

12.3 Canagliflozin

Mechanism: Sodium-glucose cotransporter 2 (SGLT2) inhibitor. Canagliflozin blocks renal glucose reabsorption in the proximal tubule, producing glycosuria and caloric loss.

Longevity evidence: Canagliflozin at 180 ppm in diet extended median lifespan by approximately 14 percent in male UM-HET3 mice in the ITP, with no significant effect in females [28]. The male-specific pattern matches 17-alpha-estradiol and acarbose.

Novelty: Low to moderate. SGLT2 inhibition is an established diabetes and heart failure pharmacology; the longevity application is novel.

Effect size: Moderate in males, absent in females.

Promising potential: Moderate to high. Canagliflozin is FDA-approved for type 2 diabetes and heart failure with reduced ejection fraction. Cardiovascular outcome trials (CANVAS, CREDENCE) demonstrated reduced cardiovascular events and renal protection.

Side-effect profile: Genital mycotic infections, volume depletion, diabetic ketoacidosis (rare), lower extremity amputations (signal in CANVAS, not replicated). Generally well tolerated in human clinical use.

Overall validation: Moderate to high for longevity (single ITP cohort), very high for human metabolic and cardiovascular endpoints.

Comparison to 17-alpha-estradiol: Both compounds extend male but not female lifespan in the ITP, with 17-alpha-estradiol showing a larger effect (19 percent versus 14 percent). Canagliflozin has a vastly larger human clinical evidence base. The mechanisms are complementary (renal glucose excretion versus hypothalamic appetite regulation and ER-alpha-mediated metabolic reprogramming).

12.4 17-beta-Estradiol

Mechanism: Primary endogenous estrogen. Full agonist at ER-alpha and ER-beta with high binding affinity (approximately 100-fold greater than 17-alpha-estradiol). Mediates the full spectrum of estrogenic effects including reproductive, metabolic, cardiovascular, skeletal, and neuroprotective functions.

Longevity evidence: Endogenous 17-beta-estradiol is associated with the female survival advantage in mammals. Exogenous 17-beta-estradiol has not been tested in the ITP. Observational and interventional data in postmenopausal women (Women's Health Initiative, Danish Osteoporosis Prevention Study) suggest complex effects on longevity that depend on timing of initiation, formulation, and progestogen co-administration [29].

Novelty: None. 17-beta-estradiol is the canonical estrogen.

Effect size: Large for intended estrogenic effects (bone density, vasomotor symptom control, cardiovascular protection in early menopause). Not characterized for lifespan extension in the ITP paradigm.

Promising potential: Not applicable for longevity. Established for hormone replacement therapy.

Side-effect profile: Significant feminizing effects (breast development, fat redistribution, endometrial stimulation requiring progestogen opposition in women with intact uterus). Increased risk of venous thromboembolism, stroke, and hormone-receptor-positive breast cancer with prolonged oral use [29].

Overall validation: Very high for estrogenic indications. Not validated for lifespan extension.

Comparison to 17-alpha-estradiol: 17-beta-estradiol has approximately 100-fold greater ER affinity and full feminizing activity, making it unsuitable for male longevity applications. 17-alpha-estradiol achieves ER-alpha-mediated metabolic benefits at the low end of the ER-alpha dose-response curve, without feminization. The two compounds share the phenolic A-ring antioxidant mechanism. For neuroprotection, both are effective, but 17-alpha-estradiol is preferred where feminizing effects are unacceptable.

12.5 Estetrol (E4)

Mechanism: Natural fetal estrogen (produced by the fetal liver during human pregnancy). Estetrol is a weak ER-alpha and ER-beta agonist with a distinct pharmacological profile: it acts as a full agonist in some tissues (endometrium, bone) and as a partial agonist or antagonist in others (breast), earning the designation "native estrogen with selective action in tissues" (NEST) [30].

Longevity evidence: Estetrol has not been tested in the ITP or in any mammalian longevity paradigm. The compound has no published lifespan data.

Novelty: High for the NEST concept. Moderate as an estrogen.

Effect size: Not characterized for longevity. Effective for contraception (approved as Nextstellis in combination with drospirenone) and under investigation for menopausal vasomotor symptoms.

Promising potential: Moderate to high for reproductive and menopausal indications. Unknown for longevity.

Side-effect profile: Favorable relative to ethinyl estradiol for contraception (reduced impact on hemostasis, lipids, and liver parameters). Breast tissue effects are reduced relative to 17-beta-estradiol in preclinical models [30].

Overall validation: Moderate (recently approved for contraception, limited data outside reproductive indications).

Comparison to 17-alpha-estradiol: Estetrol and 17-alpha-estradiol are both weak estrogens with reduced feminizing profiles relative to 17-beta-estradiol, but through different mechanisms (tissue-selective agonism versus globally reduced

affinity). Estetrol has no longevity data. 17-alpha-estradiol has robust ITP longevity validation. Estetrol has more advanced clinical development for reproductive indications. The two compounds are not directly competitive; they occupy different pharmacological niches.

12.6 Comparator summary

The five comparators span the longevity intervention and non-feminizing estrogen spaces. **Rapamycin** is the gold standard for mammalian lifespan extension with the largest effect size in both sexes but carries significant immunosuppressive side effects. **Acarbose** produces male-biased lifespan extension comparable to 17-alpha-estradiol with an established human safety record but gastrointestinal side effects. **Canagliflozin** shows male-specific lifespan extension of smaller magnitude than 17-alpha-estradiol with a large human cardiovascular evidence base. **17-beta-Estradiol** is the canonical estrogen with no longevity validation and full feminizing activity. **Estetrol** is a tissue-selective estrogen with no longevity data but a favorable safety profile.

17-alpha-Estradiol occupies a unique position: it is the only compound in this panel with both robust ITP longevity validation and an absence of feminizing effects, the only compound whose mechanism integrates ER-alpha-mediated metabolic reprogramming with receptor-independent antioxidant neuroprotection, and the only compound with demonstrated preservation of male reproductive parameters at lifespan-extending doses. Its principal limitations are the male specificity of the longevity effect, the absence of human longevity clinical data, and the incomplete characterization of the sex-specific metabolism that may underlie the male-specific efficacy.

13. References

1. Kuiper GG, Carlsson B, Grandien K, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology*. 1997;138(3):863-870.
2. Korenman SG. Comparative binding affinity of estrogens and its relation to estrogenic potency. *Steroids*. 1969;13(2):163-177.
3. Green PS, Gordon K, Bhatt DK, et al. Neuroprotective effects of estrogens: potential mechanisms of action. *Int J Dev Neurosci*. 1997;15(4-5):551-557.
4. Behl C, Skutella T, Lezoualc'h F, et al. Neuroprotection against oxidative stress by estrogens: structure-activity relationship. *Mol Pharmacol*. 1997;51(4):535-541.
5. Kim WB, Shelley AJ, Novice K, et al. The efficacy and safety of 17alpha-estradiol (Ell-Cranell alpha 0.025%) solution on female pattern hair loss: single center, open-label, non-comparative, Phase IV study. *Ann Dermatol*. 2012;24(3):295-305.
6. Blume-Peytavi U, Kunte C, Gass S, Mandt N. Comparison of the efficacy and safety of topical minoxidil and topical alfatradiol in the treatment of androgenetic alopecia in women. *J Dtsch Dermatol Ges*. 2007;5(5):391-395.
7. Strong R, Miller RA, Antebi A, et al. Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an alpha-glucosidase inhibitor, or a Nrf2-inducer. *Aging Cell*. 2016;15(5):872-884.
8. Harrison DE, Strong R, Allison DB, et al. Acarbose, 17-alpha-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell*. 2014;13(2):273-282.
9. Harrison DE, Strong R, Reifsnyder P, et al. 17-alpha-estradiol late in life extends lifespan in aging UM-HET3 male mice; nicotinamide riboside and three other drugs do not affect lifespan in either sex. *Aging Cell*. 2021;20(5):e13328.
10. Stout MB, Steyn FJ, Jurczak MJ, et al. 17-alpha-estradiol alleviates age-related metabolic and inflammatory dysfunction in male mice without inducing feminization. *J Gerontol A Biol Sci Med Sci*. 2017;72(1):3-15.

11. Steyn FJ, Ngo ST, Chen VP, et al. 17-alpha-estradiol acts through hypothalamic pro-opiomelanocortin expressing neurons to reduce feeding behavior. *Aging Cell*. 2018;17(1):e12703.
12. Mann SN, Hadad N, Nelson Holte M, et al. Health benefits attributed to 17-alpha-estradiol, a lifespan-extending compound, are mediated through estrogen receptor alpha. *eLife*. 2020;9:e59616.
13. Garratt M, Bower B, Garcia GG, Miller RA. Sex differences in lifespan extension with acarbose and 17-alpha-estradiol: gonadal hormones underlie male-specific improvements in glucose tolerance and mTORC2 signaling. *Aging Cell*. 2017;16(6):1256-1266.
14. Garratt M, Lagerborg KA, Tsai YM, et al. Male lifespan extension with 17-alpha-estradiol is linked to a sex-specific metabolomic response modulated by gonadal hormones in mice. *Aging Cell*. 2018;17(4):e12786.
15. Moos WH, Dykens JA, Nohynek D, et al. Review of the effects of 17-alpha-estradiol in humans: a less feminizing estrogen with neuroprotective potential. *Drug Dev Res*. 2009;70(1):1-21.
16. Fieser LF, Fieser M. *Steroids*. Reinhold Publishing; 1959.
17. Garratt M, Stout MB, Hurst KA, et al. 17-alpha-estradiol does not adversely affect sperm parameters or fertility in male mice: implications for reproduction-longevity trade-offs. *GeroScience*. 2023;45(2):1165-1176.
18. Shen Z, Ye C, McCain K, et al. Metabolic benefits of 17-alpha-estradiol in liver are partially mediated by ERbeta in male mice. *Sci Rep*. 2023;13(1):9841.
19. Stout MB, Tchkonina T, Kirkland JL, et al. 17-alpha-estradiol has sex-specific effects on neuroinflammation that are partly reversed by gonadectomy. *J Gerontol A Biol Sci Med Sci*. 2022;77(1):66-74.
20. Perez-Alvarez MJ, Maza MC, Anton M, et al. 17-alpha-estradiol is neuroprotective in male and female rats in a model of early brain injury. *Exp Neurol*. 2015;210(1):41-50.
21. Toran-Allerand CD. 17-alpha-estradiol: a candidate neuroSERM and non-feminizing estrogen for postmenopausal neuronal complications. *Front Neuroendocrinol*. 2015;36:150-163.

22. Yu K, He Y, Hyseni I, et al. The effects of 17-alpha-estradiol treatment on endocrine system revealed by single-nucleus transcriptomic sequencing of hypothalamus. *eLife*. 2025;14:e100346.
23. Orfanos CE, Vogels L. Local therapy of androgenetic alopecia with 17-alpha-estradiol: a controlled, randomized double-blind study. *Dermatologica*. 1980;161(2):124-132.
24. Miller RA, Harrison DE, Astle CM, et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci*. 2011;66(2):191-201.
25. Harrison DE, Strong R, Sharp ZD, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature*. 2009;460(7253):392-395.
26. Mannick JB, Del Giudice G, Sabber M, et al. mTOR inhibition improves immune function in the elderly. *Sci Transl Med*. 2014;6(268):268ra179.
27. Harrison DE, Strong R, Alavez S, et al. Acarbose improves health and lifespan in aging HET3 mice. *Aging Cell*. 2019;18(2):e12898.
28. Miller RA, Harrison DE, Allison DB, et al. Canagliflozin extends life span in genetically heterogeneous male but not female mice. *JCI Insight*. 2020;5(21):e140019.
29. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
30. Visser M, Foidart JM, Coelingh Bennink HJT. In vitro effects of estetrol on receptor binding, drug targets, and human liver cell metabolism. *Climacteric*. 2008;11(Suppl 1):64-68.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. 17-alpha-Estradiol is not approved by the United States Food and Drug Administration for any indication. The compound is regis-

tered as alfatradiol for topical use in androgenetic alopecia in Germany and several other European jurisdictions. Investigators should consult their local regulatory authority before any human research application.