

RESEARCH MONOGRAPH · COMPOUND PROFILE

Epitalon

A 4-residue synthetic peptide developed in St. Petersburg, studied principally for telomerase modulation, pineal function, and circadian rhythm endpoints in a literature dominated by a single research consortium.

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ABSTRACT

Epitalon (also Epithalon, Epithalone; sequence Ala-Glu-Asp-Gly; CAS 307297-39-8; molecular formula C₁₄H₂₂N₄O₉; molecular weight 390.35) is a synthetic tetrapeptide developed at the St. Petersburg Institute of Bioregulation and Gerontology by Vladimir Khavinson and colleagues beginning in the 1980s. The compound was designed as a synthetic analog of an active fragment isolated from a bovine pineal gland extract (the original "Epithalamin" preparation) and is reported to modulate pineal melatonin secretion, support telomerase activity in cultured cell lines, and influence circadian gene expression. The published preclinical record is dominated almost entirely by the Khavinson group and affiliated St. Petersburg laboratories, which is the principal methodological concern in any rigorous review of the literature; independent replication of the most-cited findings (telomerase induction, lifespan extension in rodent models) is sparse. A small number of human studies have been published, primarily uncontrolled or small-sample clinical observation studies in elderly populations, which have been critically reviewed for methodological limitations. Reported activities span pineal function modulation, antioxidant effects, telomere length stabilization in cell culture models, and reduction of age-related pathology markers in animal studies. The compound is not approved by any regulatory authority for human or veterinary use outside of certain Russian clinical contexts where Epithalamin (the parent extract) has historical use. Investigators should approach the literature with awareness of the single-laboratory dominance and the limited independent replication.

Compound identification

Nomenclature and synonyms

The compound is referred to in the literature as Epitalon, Epithalon, or Epithalone, with the spelling variation reflecting transliteration choices from the original Russian-language disclosure. The CAS number is 307297-39-8. The PubChem CID is 219042. The compound is closely related to the parent extract preparation Epithalamin, which is a polypeptide preparation derived from bovine pineal gland that was used clinically in Russia and Soviet-era research; Epitalon is a synthetic single-sequence active fragment of that extract.

A point of nomenclature confusion is the relationship between Epitalon and other Khavinson laboratory peptides. The St. Petersburg Institute of Bioregulation and Gerontology has developed a family of short synthetic peptides marketed as "geroprotectors" and "bioregulators," each derived from organ-specific extracts (thymus, pineal, retina, prostate, vascular). Epitalon (pineal) is one of approximately 20 such peptides in the family. The pharmacology and the supporting literature for each are largely confined to the Khavinson consortium.

Structural chemistry

The amino acid sequence is L-alanine - L-glutamic acid - L-aspartic acid - L-glycine, with a free N-terminal amine and a free C-terminal carboxylate. The molecular formula is $C_{14}H_{22}N_4O_9$; the average molecular weight is 390.35 g/mol; the monoisotopic mass is 390.14 daltons. The peptide has no disulfide bridges, no aromatic residues, and no post-translational modifications. The sequence is highly hydrophilic due to the two acidic residues at positions 2 and 3.

The peptide carries a substantial net negative charge at physiological pH due to the free carboxylates on Glu-2, Asp-3, and the C-terminal Gly-4. The isoelectric point is approximately 3.4. The peptide is an intrinsically disordered random coil in solution; there is no characterized secondary structure.

Physicochemical properties

Epitalon is supplied as a white lyophilized powder. The lot of record (Kodiac biolabs lot 20251204) conforms to this description. Solubility in water and bacteriostatic water is high; concentrations up to 5 mg/mL are routinely prepared without precipitation. The peptide is also soluble in 0.9 percent saline, PBS, and standard biological buffers. Solubility in organic solvents (DMSO, ethanol, acetonitrile) is poor.

The peptide is stable in the lyophilized state at minus 20 degrees Celsius for at least 24 months under standard light protection. Reconstituted solutions in bacteriostatic water are stable for at least 30 days at 2 to 8 degrees Celsius. Freeze-thaw cycles should be avoided.

Discovery and developmental history

Origin in the St. Petersburg Institute

Epitalon emerged from a long-running research program at the St. Petersburg Institute of Bioregulation and Gerontology under the direction of Vladimir Khavinson, beginning in the late 1970s with the isolation of "Epithalamin" from bovine pineal gland extracts. The active polypeptide preparation was characterized in animal models and reported to extend lifespan in rodent populations; the synthetic single-sequence Epitalon was developed in the 1980s and 1990s as a defined chemical entity that could be produced reproducibly.

The Khavinson laboratory has authored or co-authored the great majority of the peer-reviewed Epitalon literature. The consortium's publications in Russian-language journals are extensive; English-language translations and original English-language publications are fewer but include several reviews in the journal *Neuroendocrinology Letters* and in the gerontology literature.

Independent replication and clinical translation

Independent replication of the most-cited Khavinson group findings (telomerase induction in cell culture, lifespan extension in mice and rats, normalization of melatonin secretion in elderly subjects) has been limited. A 2003 paper by Anisimov and colleagues from the same St. Petersburg consortium reported lifespan extension in CBA mice. Independent groups outside the consortium have not extensively replicated these findings. A small number of uncontrolled clinical observation studies in Russia have reported effects on cardiovascular and ophthalmologic endpoints; these are not Phase 2 or Phase 3 trials in the Western regulatory sense.

There is no FDA-approved IND for Epitalon in any indication. The compound is not a regulated drug substance in the United States, the European Union, or Japan. Epithalamin (the parent extract) had clinical use in Russia in earlier decades but does not have current Western regulatory approval.

Mechanism of action

Telomerase modulation

The most-cited mechanistic claim is that Epitalon induces telomerase activity in cultured human somatic cells, particularly fibroblasts and lymphocytes. The reported mechanism involves transcriptional upregulation of the TERT (telomerase reverse transcriptase) gene, possibly through binding interactions with chromatin or through modulation of upstream transcription factors. The supporting evidence is primarily from in vitro cell culture work in the Khavinson consortium publications. Independent replication in non-affiliated laboratories is sparse, and the magnitude of telomerase induction reported is often at the lower end of detectable effects.

Investigators should treat the telomerase claim as an interesting hypothesis with limited independent support rather than as established pharmacology. The compound is sometimes marketed in research-grade vendor literature with claims of telomere lengthening and anti-aging effects; these claims substantially exceed what the published literature can support.

Pineal function and melatonin

Several Khavinson group publications report that Epitalon normalizes the circadian melatonin rhythm in elderly subjects with reduced or disrupted melatonin secretion. The mechanism is reported to involve direct effects on pineal pinealocytes that increase melatonin synthesis or release. The supporting evidence includes both rodent studies and small uncontrolled clinical observation series in elderly humans. Independent replication is limited.

Circadian gene expression

Reported effects on circadian gene expression include modulation of clock gene expression (Bmal1, Per1, Cry1) in peripheral tissues, with downstream effects on metabolic and antioxidant gene programs. The supporting evidence is principally from the Khavinson consortium and has not been extensively replicated.

Antioxidant and anti-inflammatory effects

Reported antioxidant effects include reduced lipid peroxidation, reduced reactive oxygen species production, and elevated glutathione concentrations in tissues from animals administered Epitalon. The mechanism is reported to involve transcriptional upregulation of antioxidant defense genes. Anti-inflammatory effects (reduced pro-inflammatory cytokine production, attenuated NF-kappa-B activation) have been reported in similar models.

Limits of the mechanistic model

The mechanistic literature is dominated by a single research group with limited independent replication. The proposed mechanisms (telomerase induction, pineal modulation, circadian gene expression, antioxidant defense) are each individually plausible but the totality of the claim space exceeds what the published evidence rigorously supports. Investigators should treat Epitalon as an interesting research tool with documented short-term safety in cell culture and rodent models but with limited and consortium-dominated mechanistic evidence.

Pharmacokinetics

Routes of administration

Subcutaneous, intramuscular, intranasal, and oral administration have been used in published preclinical work. Oral bioavailability is highly variable in the published reports; the small size of the peptide and the absence of unnatural amino acids make it a candidate for substantial degradation in gastric fluid. Intranasal administration is reported in some publications as an alternative route that bypasses first-pass degradation. Most pharmacology studies use parenteral routes (subcutaneous or intramuscular) for predictable absorption.

Plasma half-life

The plasma half-life is short, on the order of minutes, due to rapid peptidase clearance of the small all-L tetrapeptide. The published pharmacokinetic data are limited; tissue distribution and persistence are not well characterized. The reported biological effects often exceed the duration that the plasma half-life would predict, suggesting either persistent metabolite activity, transcriptional effects that outlast the parent compound, or aspects of the pharmacodynamics that are not captured by plasma pharmacokinetics.

Metabolism and excretion

Epitalon is rapidly hydrolyzed by serum and tissue peptidases. Major metabolites include the constituent free amino acids and shorter di- and tri-peptides; biological activity of the metabolites is not well characterized. Renal excretion of intact peptide and short fragments is the primary clearance route. The compound is not a known inducer or inhibitor of major CYP isoforms.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 1 to 100 micrograms per kilogram subcutaneously, with the majority of studies clustering around 0.5 to 10 micrograms per kilogram daily for chronic administration over weeks to months. Allometric scaling places the equivalent human exposure in the range of 0.07 to 14 micrograms per kilogram per dose, or approximately 5 to 1000 micrograms per dose for a 70 kg subject.

The dose range commonly cited in research-grade vendor literature (5 to 10 milligrams per research subject per cycle, with cycles of 10 to 20 days repeated 2 to 4 times per year) is at or above the upper end of the allometrically scaled range. The cycle-based dosing reflects the Khavinson consortium's traditional protocol design, in which Epitalon is administered for short courses interspersed with extended washouts. Investigators should treat the published research-grade dose ranges as approximate guidance.

Sourcing and quality verification

Synthesis route

Epitalon is produced by solid-phase peptide synthesis using Fmoc chemistry. The 4-residue length and the absence of unnatural amino acids make the synthesis straightforward. The principal synthetic concerns are correct stereochemistry of the L-amino acids (no D-amino acid contamination from racemization), correct cleavage of the protecting groups (deprotection failures produce inactive contaminants), and adequate desalting to remove TFA counterions.

The lot of record (Kodiak biolabs lot 20251204) was synthesized by the supplier of record and shipped in lyophilized acetate salt form. The vendor analytical report records 99.3 percent purity by HPLC (vendor COA value) with a supplementary HPLC report at 98.27 percent.

Common adulterants and impurities

The research-grade Epitalon supply chain has documented patterns of substandard product. Reported issues include:

1. Substitution of related Khavinson laboratory peptides (Vilon, Livagen, others) for Epitalon, on the assumption that the buyer cannot distinguish them. Mass spectrometry resolves this readily; the peptides have different molecular weights and retention times.
2. Deletion sequences from incomplete coupling, primarily producing tripeptide impurities of related sequence. Mass spectrometry and HPLC distinguish these.
3. Racemization at the central glutamate or aspartate during prolonged synthesis at elevated temperature. Chiral HPLC is required to detect this; standard reversed-phase HPLC does not separate the L/D variants reliably.
4. Excess acetate or trifluoroacetate counterions inflating apparent mass by 10 to 15 percent (proportionally large because the parent peptide is small).
5. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC and mass spectrometry on every batch is essential. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 215 nm and 280 nm, is the standard purity assay. Identity confirmation by LC-MS yields a protonated molecular ion (M+H) at 391.1 m/z. Mass spectrometry is essential for distinguishing Epitalon from related Khavinson laboratory peptides of similar size.

Reconstitution and handling

Solvent system

Epitalon dissolves readily in water, bacteriostatic water, and 0.9 percent saline. The standard reconstitution protocol uses bacteriostatic water for any solution intended for storage beyond a single use. For acute experiments, sterile water for injection or PBS works. DMSO is not the appropriate vehicle.

Reconstitution protocol

A 20 mg vial reconstituted in 2 mL produces a 10 mg/mL solution; in 4 mL produces a 5 mg/mL solution. Allow the vial to rest at room temperature for 60 to 90 seconds, then gently swirl until the powder fully dissolves. The peptide is highly soluble; full dissolution is typically complete within 60 seconds.

Storage stability

Lyophilized Epitalon: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted solutions: stable at 2 to 8 degrees Celsius for at least 30 days. Aliquot working solutions to avoid freeze-thaw cycles.

Stack interaction considerations

Epitalon is occasionally combined with melatonin in research-grade protocols on the rationale that the two compounds act on overlapping pineal pathways. The mechanistic case for synergy is plausible but not formally established. Combination with other Khavinson laboratory peptides (Vilon, Livagen) is reported in the consortium's own literature; the supporting evidence for clinical or preclinical synergy is dominated by the same consortium and should be evaluated with the same methodological caveats.

Epitalon is not commonly stacked with the GHS family (Ipamorelin, CJC-1295), the regenerative peptide family (BPC-157, TB-500), or the metabolic compounds (5-Amino-1MQ, NAD+). The pharmacological domains are sufficiently distinct that no specific interaction has been documented.

Pharmacokinetic interactions with CYP-substrate compounds are not expected. Epitalon has no documented receptor-level interactions with conventional small-molecule pharmacotherapy.

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