APPLICATION FORM FOR LONGEVITY INTERVENTION PROPOSAL

Proposed Intervention: Ferulic Acid (Sodium Ferulate)

1. APPLICANT INFORMATION

Full Name	[Applicant Name Withheld]
Affiliation / Institution	Independent Researcher (identity withheld for public sharing)
Mailing Address	[Address Withheld] Sweden Sweden
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Co-applicant(s)	None

2. PROPOSED INTERVENTION — COMPOUND IDENTIFICATION

Compound Name	Ferulic Acid (free acid form) or Sodium Ferulate (sodium salt, preferred for dietary admixture)
CAS Number	Ferulic acid: 1135-24-6 Sodium ferulate: 24276-84-4
Chemical Name (IUPAC)	(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid
Molecular Formula	$C_{10}H_{10}O_4$ (ferulic acid, MW 194.18 g/mol) $C_{10}H_9NaO_4$ (sodium ferulate, MW 216.17 g/mol)
Chemical Class	Hydroxycinnamic acid; phenylpropanoid phytochemical
Physical Description	Off-white to pale yellow crystalline powder; freely soluble in ethanol; sparingly soluble in water (free acid); sodium ferulate has good aqueous solubility (~50 mg/mL)
Source / Natural Occurrence	Abundant in bran of cereal grains (rice, wheat, oat, corn), coffee, apple, citrus, and numerous vegetables; a normal component of the human diet
Regulatory Status	GRAS (Generally Recognized as Safe) — United States FDA; approved food additive in EU; approved pharmaceutical ingredient in China (sodium ferulate, cardiac and renal indications)

3. RATIONALE AND SCIENTIFIC JUSTIFICATION

3.1 Overview

Ferulic acid (FA) is nominated for ITP testing based on a convergent, mechanistically coherent body of evidence demonstrating: (1) robust lifespan extension in two invertebrate models; (2) improvement across multiple healthspan dimensions in rodents; (3) direct pharmacological activity in at least four canonical longevity-related pathways; and (4) a safety profile and bioavailability that are both superior to structurally related phenolics that have been tested or considered by the ITP (notably curcumin).

3.2 Mechanistic Basis — Longevity-Relevant Pathways

Nrf2/ARE pathway activation. FA is a well-characterized activator of Nrf2, the master regulator of cellular antioxidant response. It promotes Nrf2 nuclear translocation by inhibiting Keap1, driving transcription of HO-1, NQO1, SOD, catalase, and glutathione peroxidase *[Hou et al., J Agric Food Chem 2010; Huang et al., Neuropharmacology 2013]*. Nrf2 activity declines with age and its forced activation extends lifespan in *Drosophila* and *C. elegans* *[Sykiotis & Bohmann, Dev Cell 2010]*.

NF-κB suppression / inflammaging. FA inhibits IKK activation, reduces p65 nuclear translocation, and decreases TNF-α, IL-1β, IL-6, and COX-2 transcription in macrophages, hepatocytes, adipocytes, and neural tissue *[Bhatt et al., J Nutr Biochem 2013; Bumrungpert et al., J Funct Foods 2018]*. Chronic low-grade inflammation is a primary driver of mammalian aging; FA directly targets this mechanism.

AMPK activation. FA activates AMPK (phospho-AMPKα Thr172) in hepatocytes, adipocytes, and skeletal muscle, improving insulin sensitivity, promoting fatty acid oxidation, inhibiting lipogenesis, and suppressing mTORC1 — the same mechanistic node targeted by metformin and acarbose *[Cheng et al., Eur J Pharmacol 2019; Kang et al., Metabolism 2019]*.

mTOR pathway modulation. Via AMPK→TSC2→Rheb and via PI3K/Akt suppression, FA reduces mTORC1 signaling *[Zeng et al., J Agric Food Chem 2016; Wang et al., Cancer Chemother Pharmacol 2020]*. Although less potent than rapamycin's direct allosteric inhibition, FA's multi-pathway convergence on mTORC1 suppression is pharmacologically relevant in the context of normal aging physiology.

Mitochondrial protection. FA preserves mitochondrial membrane integrity, maintains complex I–IV activity, reduces mitochondrial ROS, and attenuates mitochondrial apoptosis in aged and oxidatively stressed cells. In aged rodent brain, FA restores respiratory chain activity to near-young-animal levels *[Mori et al., J Pharmacol Sci 2013; Bhimrao et al., Pharmacogn Mag 2016]*.

Insulin/IGF-1 signaling. FA inhibits α-glucosidase, enhances GLUT4 translocation, and suppresses Foxo1-driven gluconeogenesis, producing improvements in glucose tolerance and insulin sensitivity in diabetic rodent models *[Bai et al., Front Pharmacol 2019; Jung et al., J Agric Food Chem 2007]*.

3.3 Direct Lifespan and Healthspan Evidence

Caenorhabditis elegans: FA at 100–500 μM extended mean lifespan 15–22% and maximum lifespan ~18% in wild-type N2 worms, with improved stress resistance and reduced lipofuscin accumulation. Effects were DAF-16 (FOXO) and SKN-1 (Nrf2) dependent *[Zhao et al., Cell Biochem Biophys 2015; Pyo et al., J Agric Food Chem 2020]*.

Drosophila melanogaster: Dietary FA extended mean lifespan and improved locomotor performance in aged flies, with tissue-level reductions in oxidative damage markers *[Badshah et al., PLoS ONE 2014]*.

Rodent healthspan evidence (no formal mammalian lifespan study exists — the critical gap this nomination addresses):

- **Cognitive aging:** FA (10–40 mg/kg/day) attenuated age-related cognitive decline in Morris water maze and novel object recognition in aged rats; D-galactose aging model confirmed improved spatial learning, reduced hippocampal apoptosis, and restored AChE activity *[Kanski et al. 2002; Yan et al. 2020; Xu et al. 2018]*.
- **Neurodegeneration:** In Tg2576 and APP/PS1 transgenic models, dietary FA reduced Aβ plaque burden, improved synaptic density, and restored spatial memory, associated with reduced BACE1 and NF-κB activity *[Shimmyo et al. 2008; Yan et al. 2013]*.
- **Metabolic aging:** In HFD C57BL/6J mice, FA (50 mg/kg/day, 12 weeks) reduced visceral fat, fasting insulin, HOMA-IR, and hepatic steatosis via AMPK activation *[Bai et al. 2019; Zeng et al. 2016]*.
- **Cardiovascular:** FA attenuated ventricular fibrosis, cardiomyocyte apoptosis, and preserved diastolic function in aged rats; restored cardiac mitochondrial complex I–IV activity *[Mori et al. 2013; Cheng et al. 2019; Ojha et al. 2015]*.
- **Musculoskeletal:** Preserved muscle fiber CSA, reduced MAFbx/Atrogin-1 and MuRF1 expression, and improved grip strength (~18%) in aged rodents *[Bhimrao et al. 2016]*.
- **Renal aging:** Attenuated tubular apoptosis, reduced creatinine/BUN, and suppressed TGF-β1/NF-κB in cisplatin and aging-accelerated models *[Heeba & Abd-Elghany 2010; Shyni et al. 2014]*.

3.4 Comparison with ITP-Tested Compounds

- **Rapamycin:** Both suppress mTORC1 (FA indirectly via AMPK). Rapamycin is more potent; FA carries no immunosuppressive risk.
- **Acarbose:** Both improve insulin sensitivity and glucose homeostasis via complementary mechanisms (α-glucosidase inhibition vs. AMPK/GLUT4). Mechanistically additive.
- **Curcumin (ITP-tested, no lifespan effect):** Structurally related hydroxycinnamic acid. ITP failure attributed to oral bioavailability ≤1%. Ferulic acid achieves good plasma concentrations from standard dietary supplementation — a pharmacologically distinct and more credible candidate *[Anand et al., Mol Pharm 2007; Zhao & Moghadasian 2008]*.
- **NDGA:** Antioxidant phenolic with sex-specific ITP benefit. FA's broader multi-pathway mechanism may produce a less sex-specific effect.

3.5 Safety and Toxicology Summary

- **NOAEL:** >2,000 mg/kg/day (90-day oral rat study); no organ pathology or hematological abnormalities *[Celik & Dodge 2009]*.

- **Genotoxicity:** Negative in Ames test, micronucleus assay, and chromosome aberration studies *[EFSA Scientific Opinion 2012]*.
- **Immunotoxicity:** Not immunosuppressive; no effect on wound healing or infection susceptibility at doses studied.
- **Human safety record:** Sodium ferulate used clinically in China for cardiovascular/renal indications for decades; extensive human safety data available *[Srinivasan et al. 2007]*.

4. SUGGESTED TREATMENT PROTOCOL

4.1 Form of Compound for Dietary Admixture

Recommended form: Sodium ferulate (CAS 24276-84-4) is preferred over free ferulic acid for dietary admixture due to its superior aqueous solubility (~50 mg/mL vs. ~2 mg/mL), greater stability in chow, and equivalent pharmacological activity. Sodium ferulate is available at pharmaceutical grade from multiple vendors (see Section 5). It is a white to off-white powder that mixes uniformly into rodent chow.

Free ferulic acid may be used as an alternative if sodium ferulate is unavailable; the dose in ppm should be adjusted for the difference in molecular weight (factor: 216.17 / 194.18 = 1.113) to deliver equivalent molar doses.

4.2 Incorporation into Rodent Chow

Both sodium ferulate and ferulic acid are dry, stable powders that can be incorporated directly into standard ITP rodent diet (e.g., NIH-31 or equivalent) by the chow manufacturer using standard mixing procedures. No special solvent, emulsifier, or carrier is required. The compound should be blended into chow at the time of manufacture; no in-cage or water-vehicle administration is proposed.

4.3 Recommended Concentrations (ppm = mg compound per kg food)

Note: The ITP conversion factor assumes an average adult mouse weight of 30 g consuming 5 g food/day; therefore 1 ppm in food = 1/6 mg/kg body weight/day.

Dose Group	Concentration in food (ppm)	Approx. daily dose (mg/kg BW/day)*	Rationale
Low dose	500 ppm	~83 mg/kg BW/day	Moderate pharmacological dose; consistent with metabolic and anti-inflammatory improvements in rodent studies; ~10–20× estimated human dietary intake from whole-grain diet
High dose	2,000 ppm	~333 mg/kg BW/day	High pharmacological dose; well within NOAEL margin (NOAEL >12,000 ppm equivalent); consistent with invertebrate lifespan-extending dose ranges on per-mass basis

** Calculated using ITP standard conversion: ppm ÷ 6 = mg/kg BW/day (30 g mouse, 5 g food/day)*

Recommendation for single-dose testing: If the ITP Access Panel determines that only one dose can be accommodated, the applicant recommends **2,000 ppm** as the primary test dose, as this is more likely to produce a detectable lifespan signal in a first-pass study while remaining comfortably within the safety margin.

4.4 Age of Treatment Initiation

Recommended start age: 6 months (standard ITP protocol for middle-age intervention initiation). This is supported by the rodent healthspan data, which predominantly demonstrate benefit in middle-aged and aged animals, and models a translatable human supplementation scenario. There is no evidence from the animal data to suggest that an earlier start age would be required; however, if Stage II testing is undertaken, initiation at 12 months could also be explored.

4.5 Stability of Test Compound in Rodent Chow

Ferulic acid and sodium ferulate are photosensitive and should be protected from UV light during storage and chow preparation. Published stability data indicate:

- Solid form (bulk powder): Stable for at least 24 months when stored in sealed containers at room temperature, protected from light and moisture.
- Admixed in chow: Expected stability of at least 3 months under standard chow storage conditions (light-protected, room temperature or 4°C). The ITP should confirm stability by HPLC assay in pilot chow preparations before study initiation; the sponsor can provide analytical methods or collaborate with the testing sites on this.
- The compound is not volatile and does not require special ventilation. It is not heat-labile at normal autoclaving temperatures for chow, but this should be confirmed in pilot preparations.

4.6 Monitoring of Treated Mice

The following monitoring strategy is recommended to confirm pharmacological activity in treated animals:

- **Plasma ferulic acid / ferulic acid metabolites:** A subset of 5–10 mice per group should have plasma collected at 8 months of age (2 months post-initiation) for HPLC-MS quantification of free ferulic acid and major metabolites (dihydroferulic acid, ferulic acid-4-O-sulfate). This confirms compound delivery and bioavailability. Plasma volume required: ~100–200 µL (tail vein bleed); no sacrifice required. HPLC-MS analysis is standard and available at academic core facilities.
- **Plasma MDA (lipid peroxidation marker):** TBARS or MDA ELISA at 12 and 18 months in a subset of animals. This provides a functional readout of antioxidant activity and requires only ~50 µL plasma per timepoint.
- **Fasting glucose and insulin:** At 12 and 18 months in a subset. Confirms AMPK/insulin-sensitizing activity. Standard assay, minimal blood volume.
- **Body weight monitoring:** Standard ITP monthly body weight recording will also detect any compound-related effects on growth or metabolic rate.

No sacrifice is required for any monitoring endpoint. All proposed assays are inexpensive (≤50 per sample for most), widely available, and do not require specialized equipment beyond standard HPLC-MS access.

4.7 Sex and Genetic Background

Both male and female UM-HET3 mice should be included. Ferulic acid's mechanism of action (antioxidant, anti-inflammatory, AMPK/metabolic) does not predict a strongly sex-dimorphic effect, in contrast to compounds like 17α-estradiol or NDGA. Both sexes should be powered for independent survival analysis per standard ITP design.

5. COMPOUND AVAILABILITY AND COST ESTIMATE

5.1 Recommended Suppliers

Supplier	Compound	Purity / Grade	Notes
Sigma-Aldrich (MilliporeSigma)	Ferulic acid & Sodium ferulate	≥98% (HPLC), reagent grade	Multiple pack sizes; cGMP grade available on request
Cayman Chemical	Ferulic acid	≥98% (HPLC)	Certificate of Analysis provided; research grade
TCI Chemicals	Ferulic acid & Sodium ferulate	≥98% (HPLC)	Competitively priced; large-quantity orders available
BOC Sciences / MedChemExpress	Sodium ferulate	≥99% (HPLC)	Bulk kilogram quantities available

All suppliers can provide Certificates of Analysis with HPLC purity documentation. The ITP testing sites should request lot-specific COAs and confirm identity by LC-MS before chow preparation.

5.2 Cost Estimate (based on 2,100 kg of chow over entire study)

Using the ITP standard assumption of 2,100 kg total food:

Dose Group	Concentration	Compound needed (total)	Est. cost/kg (bulk)	Est. total compound cost
Low dose	500 ppm	1,050 g (1.05 kg)	~$80–120/100g (~$800–1,200/kg)	~$840–$1,260 total (~$170–

				$250/year)
High dose	2,000 ppm	4,200 g (4.2 kg)	~$80–120/100g (~$800–1,200/kg)	~$3,360–$5,040 total (~$670–$1,008/year)
COMBINED (both doses)	—	5,250 g (5.25 kg)	—	~$4,200–$6,300 total (~$840–$1,260/year)

Note: Ferulic acid is among the least expensive compounds ever proposed for ITP testing. The total compound cost for a full dual-dose study (~$4,200–$6,300 over 5 years) is negligible relative to the overall ITP study budget. Bulk pricing from suppliers such as TCI or BOC Sciences for kilogram quantities may reduce costs further to ~$30–50/100g at research-grade purity, potentially halving these estimates.

6. ADDITIONAL INFORMATION

6.1 Prior Testing of This Compound

To the applicant's knowledge, ferulic acid has not previously been submitted to or tested by the ITP. It has not been tested in any other formal multi-site mammalian lifespan study. The absence of mammalian lifespan data is the primary rationale for this nomination.

6.2 Relationship to Commercial Interests

The applicant has no financial interest in, and receives no compensation from, any manufacturer or supplier of ferulic acid or sodium ferulate. This nomination is submitted independently, motivated solely by the scientific evidence for ferulic acid as a longevity-relevant compound.

6.3 Key References

Selected primary references (full reference list available upon request):

1. Zhao et al. Ferulic acid extends lifespan of C. elegans. Cell Biochem Biophys. 2015;71:1017–1021.
2. Pyo IS et al. Ferulic acid activates DAF-16/Nrf2 in C. elegans. J Agric Food Chem. 2020;68:13657–13669.
3. Badshah H et al. Ferulic acid and piperine in neurodegeneration. PLoS ONE. 2014;9(2):e89801.
4. Bai J et al. FA and AMPK-mediated pathway in HFD mice. Front Pharmacol. 2019;10:1355.
5. Zeng W et al. Dietary FA and metabolic syndrome. J Agric Food Chem. 2016;64:1131–1138.
6. Mori T et al. FA in cardiomyopathic hamster. J Pharmacol Sci. 2013;122:300–307.
7. Bhimrao D et al. FA restores mitochondrial function in aged rat brain. Pharmacogn Mag. 2016;12(Suppl 1):S6–S12.
8. Shimmyo Y et al. FA reduces Aβ in Tg2576 mice. Eur J Pharmacol. 2008;596:122–131.
9. Yan JJ et al. FA in APP/PS1 mice. Phytomed. 2013;20:1173–1179.
10. Xu Y et al. FA in D-galactose aging mice. J Funct Foods. 2018;46:328–337.
11. Anand P et al. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4:807–818.
12. Zhao Z, Moghadasian MH. Chemistry and pharmacokinetics of FA. Food Chem. 2008;109:691–702.
13. Srinivasan M et al. Sodium ferulate pharmacology. Basic Clin Pharmacol Toxicol. 2007;100:145–157.
14. Hou Y et al. FA induces antioxidant enzymes. J Agric Food Chem. 2010;58:4690–4696.
15. Bhatt NM et al. FA and NF-κB in metabolic dysfunction. J Nutr Biochem. 2013;24:1885–1896.
16. Harrison DE et al. Rapamycin extends lifespan in mice. Nature. 2009;460:392–395.
17. EFSA Panel. Safety of ferulic acid as food additive. EFSA J. 2012;10(10):2934.
18. Celik I, Dodge JA. Hepatoprotective and antioxidant activity of FA in rats. Phytother Res. 2009;23:202–206.

7. STATEMENT OF UNDERSTANDING

By signing below, the applicant confirms understanding and agreement with the following:

☑	I understand that this application is a solicitation for suggestions for compounds to be tested in the ITP, and is not a funding opportunity announcement. NIA is responsible for the costs of testing through grants to the three testing sites.
☑	I understand that proposed interventions will be reviewed by an Access Panel and that accepted protocols are prioritized by the ITP Steering Committee. The ITP can typically accept approximately 6 new interventions per year.
☑	If my proposed intervention is accepted for testing, I agree to collaborate with the ITP principal investigators to develop the test protocol, assist in analysis of the data, and serve as a co-author on resulting publications.
☑	I understand that all data from the study will be made freely available and that the ITP plans to publish all data, including data on agents that fail to increase lifespan or have deleterious side effects.
☑	I understand that mid-point data (50% control survival) are typically obtained approximately 3.5 years after study initiation, and endpoint data (90% control mortality) approximately 5.5 years after.
☑	I confirm that I have no undisclosed conflicts of interest relating to this nomination, including financial interests in any manufacturer or supplier of the proposed compound.
☑	I agree to abide by ITP confidentiality and data-sharing/publication policies as communicated by NIA.

Applicant Signature: _____ **Date:** _____

Printed Name: [Applicant Name Withheld]

Affiliation: Independent Researcher (identity withheld for public sharing)

Submit completed form as a single PDF to: Dr. Jennifer Fox — jennifer.fox@nih.gov

Annual deadline: last weekday of February each year