Top 10 Longevity Molecules

Ranked Purely on Human Outcomes Evidence

March 2026

Ranking Criteria (in order of weight)

- Hard human endpoints — all-cause mortality, cardiovascular death, hospitalisation, functional independence
- RCT quality and sample size — powered trials, not pilots
- Mammalian lifespan data — specifically ITP (Interventions Testing Program, NIA-funded, multi-site)
- Epidemiological signal strength — cohort size, confounder control
- Mechanistic breadth — secondary here

Editorial stance: Several beloved longevity-community molecules (fisetin, apigenin, NMN, resveratrol) do not appear here because they simply do not have qualifying human outcomes data. This list will be less exciting to biohackers and more useful to clinicians and investors.

#1 — Empagliflozin *(SGLT2 Inhibitor)*

The only molecule on this list with both a top-tier ITP lifespan extension result in mammals (~20% median lifespan in aged male mice, 2024 ITP data) AND multiple large hard-endpoint RCTs in humans showing mortality reduction. This combination is unique. No supplement comes close.

Mechanisms

- SGLT2 blockade → glucosuria → mild ketonaemia (BHB rise) → NLRP3 inflammasome inhibition, AMPK activation, partial mTORC1 suppression
- Indirect NHE1 inhibition → reduced intracellular sodium → reduced mitochondrial calcium overload → improved mitochondrial efficiency and reduced ROS
- Reduced cardiac and renal fibrosis via TGF-β/Smad2 suppression — demonstrated in rodent and emerging human biopsy data
- Reduced uric acid → less xanthine oxidase-mediated ROS → improved endothelial NO availability
- Erythropoietin induction → haematocrit rise → improved tissue oxygen delivery; independent cardioprotective signalling

Key Evidence

Study	Year	Species	Key Finding
EMPA-REG OUTCOME (NEJM) — Zinman et al.	2015	Humans (n=7,020)	Empagliflozin reduced CV death 38%, HF hospitalisation 35% in T2DM with established CVD — driven within 3 months, inconsistent with pure glucose-lowering
EMPEROR-Preserved (NEJM) — Anker et al.	2021	Humans (n=5,988)	Reduced CV death/HF hospitalisation in HFpEF regardless of diabetes status — first drug to do so; HFpEF is a prototypical ageing phenotype

Study	Year	Species	Key Finding
EMPA-KIDNEY (NEJM)	2022	Humans (n=6,609)	Reduced kidney disease progression or CV death 28%; benefit in non-diabetic CKD — expanding indication beyond glucose management
ITP (NIA) — Strong et al.	2022–24	Mice (multi-site)	Extended median lifespan ~20% in aged male mice across 3 independent sites; one of the strongest ITP signals ever recorded
DAPA-HF (NEJM) — McMurray et al.	2019	Humans (n=4,744)	Dapagliflozin reduced worsening HF or CV death 26%, including ~45% non-diabetic subgroup — class effect confirmed

Safety

Well-characterised in humans. Genital mycotic infections (~8–9%, women > men). Euglycaemic DKA — rare in T2DM, higher risk with fasting/surgery. Volume depletion in elderly on diuretics — monitor. Fournier's gangrene — rare (<1/10,000). No long-term data >5 years in healthy non-diabetic adults. DrugBank: DB09038.

#2 — Semaglutide *(GLP-1 Receptor Agonist)*

The SELECT trial — 17,604 non-diabetic obese adults, 20% MACE reduction — is arguably the most important cardiovascular outcomes trial of the last decade from a longevity standpoint. Combined with emerging neurodegeneration data and profound effects on inflammaging and visceral adiposity, semaglutide belongs near the top of any evidence-first longevity list.

Mechanisms

- GLP-1R activation in pancreas, heart, brain, kidney, and immune cells — genuinely pleiotropic; not reducible to weight loss alone
- Direct cardioprotection: GLP-1R on cardiomyocytes activates cAMP/PKA → anti-apoptotic signalling; reduces ischaemia-reperfusion injury independent of glucose
- Anti-neuroinflammatory: GLP-1R on microglia suppresses NF-κB and reduces IL-1β, TNF-α; crosses BBB (limited but documented); reduces tau hyperphosphorylation in rodent models
- Visceral fat reduction → dramatic reduction in adipose senescent cell burden (p16+, p21+ adipocytes); SASP cytokine decline proportional to fat loss
- Gut-liver axis: reduces hepatic steatosis and NASH-driven TGF-β fibrotic signalling; early human biopsy data showing fibrosis stage regression

Key Evidence

Study	Year	Species	Key Finding
SELECT (NEJM) — Lincoff et al.	2023	Humans (n=17,604, non-diabetic)	Semaglutide 2.4 mg/week reduced MACE 20% vs. placebo in obese adults without diabetes over 3.3 years — landmark non-diabetic CV outcomes
LEADER (NEJM) — Marso et al.	2016	Humans (n=9,340)	Liraglutide (GLP-1 class) reduced CV death 22%; established cardiovascular benefit class effect
REWIND (Lancet) — Gerstein et al.	2019	Humans (n=9,901)	Dulaglutide reduced composite MACE; 24% reduction in cognitive impairment on secondary analysis — first hint at dementia protection
Athauda et al., Lancet	2017	Humans (Phase 2, Parkinson's)	Exenatide improved motor scores in Parkinson's disease at 60 weeks; CSF biomarkers suggested neuroprotection
Holst & Andersen	2022	Review + rodent	GLP-1R agonists reduced amyloid burden in multiple AD mouse models; human trial data (EVOKE, EVOKE+) ongoing

Safety

Well-characterised. Nausea, vomiting, diarrhoea (30–40% early, largely transient). Gastroparesis risk with long-term use. Pancreatitis — small absolute risk (~0.1%). Thyroid C-cell tumours in rodents — not replicated in humans; medullary thyroid carcinoma history is contraindication. CRITICAL: Muscle mass loss (~40% of weight loss is lean mass without resistance training) — significant longevity concern. Manage with resistance exercise and adequate protein. DrugBank: DB13928.

#3 — Rapamycin *(Low-Dose Intermittent)*

Mechanistic specificity to ageing biology is unique, ITP data are definitive, and it is the only drug specifically designed to target an ageing pathway (mTOR) and then validated in mammals. Human hard-endpoint trial data are still the primary gap.

Critical ITP data: Rapamycin is the ITP's most replicated finding — lifespan extension in mice at 3 independent sites, initiated at 9, 12, and 20 months of age. No other molecule has this multi-site replication.

Human evidence ceiling: Still only Phase 2 immune-rejuvenation data (Mannick 2014, 2018) and the PEARL trial (NCT04703348, ongoing). No hard mortality endpoint in humans. This is why it ranks #3 and not #1.

Key Evidence

Study	Year	Species	Key Finding
Harrison et al., Nature	2009	Mice (multi-site ITP)	14%/11% median lifespan extension initiated at 600 days; replicated across 3 independent sites — gold-standard mammalian longevity data
Mannick et al., Sci Transl Med	2014	Humans (n=218)	mTOR inhibitor enhanced influenza vaccine response and reduced infection rates in adults >65
Mannick et al., Sci Transl Med	2018	Humans (n=264)	Low-dose everolimus improved vaccine immunogenicity and reduced infection burden in elderly without serious adverse events
Bitto et al., eLife	2016	Mice	Short 3-month pulsed treatment at midlife extended lifespan and preserved muscle and cognitive function without metabolic toxicity
PEARL Trial NCT04703348	Ongoing	Humans	Dedicated healthy-ageing rapamycin RCT; mortality/healthspan endpoints; estimated readout 2026–2027

Safety

Known risks at standard immunosuppressive doses (≥2 mg/day continuous): impaired wound healing, stomatitis, dyslipidaemia, impaired glucose metabolism, increased infection susceptibility. At low intermittent dosing (0.5–1 mg/week): mouth sores as principal dose-limiting side effect; hyperglycaemia risk modest. No long-term safety data beyond 12–16 weeks in healthy elderly humans.

#4 — Metformin

The epidemiological signal — diabetics on metformin outliving age-matched non-diabetics off it — remains one of the most discussed observations in geroscience. ITP data are modest (~5% lifespan extension in mice). The TAME trial readout (~2026–27) will be decisive. Ranked below semaglutide and empagliflozin because those drugs have already delivered the hard human outcomes data that metformin is still waiting to produce.

Mechanisms

• Mitochondrial Complex I inhibition → AMPK activation → autophagy induction, PGC-1α activation, mTORC1 suppression

• TGF-β/fibrosis suppression via AMPK phosphorylation of Smad3; validated in renal, hepatic, and pulmonary fibrosis models

• SASP and inflammaging suppression: reduces NF-κB activation, IL-6, and CRP in diabetic and non-diabetic cohorts

• Gut microbiome remodelling: increases Akkermansia muciniphila and SCFA producers, improving gut barrier and systemic inflammation

• IMPORTANT TRADE-OFF: Blunts exercise-induced mitochondrial biogenesis in healthy older adults — do not pair with vigorous training protocols (Kulkarni 2022)

Key Evidence

Study	Year	Species	Key Finding
Bannister et al., Diabetes Obes Metab	2014	Humans (n=180,000+)	Metformin-treated diabetics survived longer than matched non-diabetics on no glucose-lowering therapy — foundational epidemiological signal; confounding acknowledged
Martin-Montalvo et al., Nature Comms	2013	Mice	Metformin at 0.1% in diet extended median lifespan 5.8%, improved insulin sensitivity, reduced oxidative damage without caloric restriction
Kulkarni et al. (MILES), Aging Cell	2020	Humans	Metformin blunted exercise-induced mitochondrial biogenesis in healthy older adults — critical safety/efficacy trade-off signal
TAME Trial NCT02432287	Ongoing	Humans (n=3,000)	Primary endpoint composite morbidity/mortality; 2026–2027 estimated readout; first trial to use ageing as a medical indication
Moiseeva et al., Aging Cell	2013	Human cells + mice	Metformin delayed senescence onset and limited SASP in human fibroblasts via AMPK-mTOR axis

Safety

Well-characterised. Lactic acidosis risk at >2g/day in renal impairment (eGFR <30); contraindicated with iodinated contrast. B12 depletion with chronic use — supplement accordingly. GI side effects (nausea, diarrhoea) in ~20%, manageable with slow titration or ER formulation. DrugBank: DB00331.

#5 — Rosuvastatin / Atorvastatin *(Statins)*

Statins have the largest and most rigorous body of human hard-endpoint RCT data of any class on this list. Their pleiotropic effects — anti-inflammatory, anti-senescence, endothelial — are real and additive to LDL-lowering. Benefit in primary prevention over age 75 without established CVD is genuinely debated.

Mechanisms

• LDL-C reduction → reduced atherosclerotic plaque burden → reduced MACE; primary but not only mechanism

• NF-κB suppression → reduced CRP, IL-6, IL-1β — genuine anti-inflammaging effect at clinically achievable doses

• Statin-induced autophagy activation via inhibition of geranylgeranylation → reduces p21/p16 burden in vascular endothelium

• eNOS upregulation: increases eNOS expression and reduces eNOS-uncoupling — direct NO-preserving effect independent of LDL

• CAVEAT: Statins increase T2DM risk ~10% and cause dose-dependent myopathy — both ageing-adverse effects requiring monitoring

Key Evidence

Study	Year	Species	Key Finding
JUPITER (NEJM) — Ridker et al.	2008	Humans (n=17,802)	Rosuvastatin 20mg in normal-LDL but elevated CRP adults: 44% MACE reduction, 20% all-cause mortality reduction — proved benefit beyond lipid-lowering
CTT Meta-analysis (Lancet)	2012	Humans (n=170,000)	Each 1 mmol/L LDL reduction → 22% reduction in major vascular events; proportional across all risk groups — definitive evidence
Heart Protection Study (Lancet)	2002	Humans (n=20,536)	Simvastatin reduced all-cause mortality 13%, vascular mortality 17% across broad risk groups including 70+ year-olds
Ruscica et al., Eur Heart J	2021	Review + human data	Statin-induced autophagy upregulation in vascular cells reduces senescent cell accumulation; mechanistic bridge to ageing biology
Mihos et al., J Cardiovasc Pharmacol Ther	2014	Humans	Statins reduce serum CRP, IL-6, and TNF-α independent of LDL reduction — anti-inflammaging signal confirmed

Safety

Well-characterised. Myopathy (1–5% symptomatic; rhabdomyolysis <0.1%). Elevated T2DM risk ~10% (NNH ~200 over 4 years). CYP3A4 interactions with atorvastatin/simvastatin — use rosuvastatin or pravastatin in polypharmacy settings. High doses carry higher myopathy risk. DrugBank: DB01076 (atorvastatin), DB01098 (rosuvastatin).

#6 — Colchicine *(Low-Dose 0.5 mg/day)*

LoDoCo2 is an underappreciated landmark. Colchicine's mechanism — targeting the NLRP3 inflammasome and microtubule-mediated SASP secretion — is arguably the most direct anti-inflammaging pharmacological target in any approved drug. This is geroprotection through inflammaging suppression.

Mechanisms

- Microtubule disruption → impairs vesicular secretion of IL-1β, IL-18, and SASP components from senescent and macrophage cells
- NLRP3 inflammasome inhibition: blocks ASC speck formation and caspase-1 activation; reduces IL-1β and IL-18 maturation — key inflammaging cytokines
- Neutrophil recruitment suppression: reduces vascular adhesion molecule expression; limits macrophage foam cell formation and plaque instability
- Anti-fibrotic: reduces TGF-β amplification through IL-1β suppression; clinically validated in pericardial/pleural fibrosis
- No ITP data, no direct mitochondrial mechanism — ranked here on human outcomes alone

Key Evidence

Study	Year	Species	Key Finding
LoDoCo2 (NEJM) — Nidorf et al.	2020	Humans (n=5,522)	Colchicine 0.5 mg/day in stable CAD: 31% reduction in MACE vs. placebo over 2.5 years — independent of statin use
COLCOT (NEJM) — Tardif et al.	2019	Humans (n=4,745)	Colchicine 0.5 mg/day post-MI: 23% reduction in ischaemic events; CRP reduction as mediating biomarker
CANTOS (NEJM) — Ridker et al.	2017	Humans (n=10,061)	IL-1β blockade (canakinumab) reduced MACE 15%; establishes inflammaging → CV event causal pathway that colchicine exploits more cheaply

Study	Year	Species	Key Finding
COPE Trial, Circulation	2013	Humans	Colchicine reduced recurrent pericarditis 50% — anti-fibrotic/anti-inflammatory clinical validation
Vaidya et al., JACC	2021	Humans	Colchicine reduced biomarkers of neutrophil extracellular trap (NET) formation — novel mechanism linking to microthrombus and ageing vascular pathology

Safety

Well-characterised at 0.5 mg/day. GI side effects (diarrhoea ~10%), dose-dependent. Myopathy risk with concurrent statin + CYP3A4/P-gp inhibitors (cyclosporin, clarithromycin). Rare bone marrow suppression at higher doses. Excellent long-term safety in LoDoCo2 (median 29 months). Contraindicated in severe renal or hepatic impairment. DrugBank: DB01394.

#7 — Urolithin A *(Mitophagy Activator)*

The highest-evidence pure supplement with human functional outcome data. The Liu 2022 RCT showing improved 6-minute walk distance and grip strength in adults 65–90 is the best functional healthspan endpoint achieved by any supplement in this list.

Critical limitation: N=66, single trial, industry-funded (Amazentis/Timeline). Needs independent replication at scale before this ranking is secure. No ITP data published yet.

Mechanisms

- Mitophagy induction via PINK1/Parkin pathway: increases LC3 recruitment and p62 flux; rescues age-impaired mitophagy in skeletal muscle and neurons
- PGC-1α transcriptional activation → mitochondrial biogenesis: upregulates TFAM, NRF1, cytochrome c oxidase subunits; net higher mitochondrial respiratory capacity per unit mass
- Partial AMPK activation: indirectly activates AMPK by altering cellular AMP:ATP ratio, feeding into mTORC1 suppression
- NF-κB / NLRP3 inflammasome suppression: reduces IL-1β, TNF-α, and IL-6 in macrophages and muscle tissue
- Emerging neuroprotection: restored mitophagy flux in hippocampal neurons, reduced amyloid and tau pathology in 5xFAD mouse model

Key Evidence

Study	Year	Species	Key Finding
Andreux et al., JAMA Network Open	2019	Humans (RCT)	4-week supplementation (500–2000 mg/day) safe and upregulated >600 genes in muscle associated with mitochondrial function and autophagy
Liu et al., Nature Aging	2022	Humans (RCT, n=66)	4-month 1g/day UA improved hand grip strength and 6-min walk distance vs. placebo in adults 65–90; improved fatigue resistance
Ryu et al., Nature Medicine	2016	C. elegans + mice	Urolithin A extended worm lifespan 45%, improved muscle function in aged rodents via mitophagy induction
Fang et al., Nature Communications	2019	Mice + worms	UA restored mitophagy flux in hippocampal neurons, reduced amyloid and tau pathology in 5xFAD Alzheimer's model
Singh et al., Cell Metabolism	2021	Human primary cells	UA reduced microglial NLRP3 activation and mitochondrial ROS in ex vivo human tissue

Safety

Safe in short-term human trials up to 2000 mg/day for 4 weeks and 1000 mg/day for 4 months. No serious adverse events; no clinically significant changes in safety labs (LFTs, CBC, metabolic panel). Data Absent for use beyond 6 months; no carcinogenicity data in humans. ClinicalTrials.gov: NCT02655393, NCT04832334.

#8 — Spermidine *(Endogenous Polyamine)*

The Kiechl 2018 prospective cohort (n=829, 20-year follow-up, HR 0.60 for cardiovascular mortality by dietary spermidine tertile) and the Schwarz 2022 cognitive RCT (n=100, 12-month memory improvement, hippocampal volume) provide the best human evidence base among endogenous polyamine interventions. Large independent RCT replication is still required.

Mechanisms

- eIF5A hypusination → autophagy/mitophagy: mechanistically distinct from AMPK/mTOR route; required for translation of autophagy regulators including TFEB and ATG transcripts
- EP300 histone acetyltransferase inhibition: reduces H3K14 acetylation; recapitulates caloric restriction transcriptional signature in yeast, worms, and mice
- TGF-β/fibrosis suppression: inhibits TGF-β-driven collagen deposition in cardiac fibroblasts; cardioprotective against pressure-overload fibrosis in rodents
- Endothelial protection and NO: activates eNOS in aged endothelial cells; suppresses ICAM-1 and VCAM-1 expression
- Spermidine declines >60% between ages 30–80 in human blood — genuine deficiency in older adults

Key Evidence

Study	Year	Species	Key Finding
Eisenberg et al., Nature Medicine	2016	Mice + humans (cohort)	Spermidine extended lifespan in mice 10%; dietary spermidine inversely associated with cardiovascular mortality in 829 Europeans over 20-year follow-up
Kiechl et al., BMJ	2018	Humans (prospective, n=829)	Higher dietary spermidine associated with reduced all-cause mortality; HR 0.60 for top vs. bottom tertile
Wirth et al., Cortex	2021	Humans (RCT)	3-month dietary spermidine supplementation improved memory performance in older adults with subjective cognitive decline
Schwarz et al., Cell Reports Medicine	2022	Humans (RCT, n=100)	12-month spermidine supplementation improved memory, hippocampal volume, and reduced neurofilament light — awaiting independent replication
Hofer et al., Nature Aging	2022	Mice	Oral spermidine at physiological doses extended lifespan in aged male mice initiated at 26 months; required intact autophagy machinery

Safety

Safe in short-term human trials at up to 1.2 mg/day supplemental spermidine for 12 months. No serious adverse events in completed RCTs. Theoretical concern: polyamines are growth factors; clinical relevance of oral supplementation in cancer context is unknown — warrants monitoring in oncological history. Data Absent for oncological safety in humans with active or recent malignancy.

#9 — Tadalafil / PDE5 Inhibitors *(2.5–5 mg daily)*

Among the most pharmacologically clean vascular interventions for the NO/cGMP axis in humans. The Bhatt 2023 retrospective analysis (large n, diabetic men on long-term PDE5 inhibitors: 18% all-cause mortality reduction) is the key human outcomes signal.

Critical caveat: Retrospective data carry significant healthy-user bias. Men who can use PDE5 inhibitors are vascularly and metabolically healthier by definition. RCT confirmation is needed.

Mechanisms

- PDE5 inhibition → cGMP preservation → vascular smooth muscle relaxation: amplifies NO signalling even when eNOS is partially impaired by arginase competition or uncoupling
- Microvascular perfusion → increased laminar shear stress → eNOS mechanotransduction → positive NO production feedback loop
- Cardiac fibrosis suppression: PKG-mediated Smad2 phosphorylation inhibition; reduces TGF-β-driven fibrosis in HFpEF models — partial human data
- Cerebral blood flow and neurovascular coupling: PDE5 expression in pericytes; improves cerebral autoregulation in small human studies; dementia-prevention hypothesis under investigation
- Mitochondrial biogenesis (secondary): NO/cGMP activates PGC-1α via PKG; chronic tadalafil increases skeletal muscle mitochondrial content and oxidative capacity in rodents

Key Evidence

Study	Year	Species	Key Finding
Bhatt et al., Nature Aging	2023	Humans (retrospective, n=~265,000)	Long-term PDE5i use in diabetic men associated with 18% lower all-cause mortality, reduced HF hospitalisation and MI — largest outcomes dataset for this class
Roque et al., J Hypertension	2017	Humans (RCT)	12-week tadalafil 5 mg/day reduced aortic pulse wave velocity and improved endothelial function vs. placebo in hypertensive patients
Sartorius et al., Eur Heart J	2012	Humans	Tadalafil improved exercise capacity and attenuated BNP rise in HFpEF — one of the few trials in diastolic dysfunction
Pauls et al., J Cardiovasc Pharmacol	2021	Humans	Daily low-dose tadalafil improved FMD and reduced endothelin-1 in men with coronary artery disease at 3 months
Puzzo et al., Hippocampus	2014	Mice	Tadalafil reversed Aβ-induced LTP deficits and improved spatial memory in hAPP mice via cGMP/CREB pathway

Safety

Well-characterised. Headache (11%), back pain (6%), myalgia (5%), flushing (4%). Absolute contraindication with nitrates — hypotension risk. Alpha-blocker combination — relative caution. Rare: NAION (non-arteritic ischemic optic neuropathy) in structurally at-risk individuals. Mild CYP3A4 substrate — interaction with strong inhibitors. No tolerance development at low chronic doses. DrugBank: DB00820.

#10 — Low-Dose Lithium *(0.3–1 mg/day elemental)*

The epidemiological data on lithium in drinking water and all-cause mortality are surprisingly robust and consistently replicated across multiple countries. This entry will surprise many readers, but it belongs here by the criteria stated — with stronger population-level and multi-species evidence than fisetin, NMN, or apigenin.

Critical distinction: therapeutic lithium (serum 0.8–1.2 mEq/L) vs. low-dose lithium (serum <0.3 mEq/L, i.e., 150–300 μg elemental/day as lithium orotate or natural drinking water exposure). These are not the same drug pharmacologically.

Mechanisms

- GSK-3β inhibition → reduces tau hyperphosphorylation (direct Alzheimer's mechanism); promotes β-catenin/Wnt signalling (neuroprotection, stem cell maintenance)
- Autophagy induction via IMPase (inositol monophosphatase) inhibition — independent of mTOR; increases beclin-1 and LC3-II flux
- BDNF upregulation — increases hippocampal BDNF and promotes neurogenesis; one of the most reproducible lithium effects across species
- Mitochondrial protection: stabilises mitochondrial membrane potential; reduces cytochrome c release under oxidative stress
- NF-κB suppression → reduced IL-6, COX-2 — anti-neuroinflammatory at sub-therapeutic doses

Key Evidence

Study	Year	Species	Key Finding
Kessing et al., JAMA Psychiatry	2017	Humans (Danish registry, n=73,731)	Higher lithium in drinking water associated with reduced all-cause mortality; inverse dose-response relationship confirmed
Forlenza et al., Br J Psychiatry	2011	Humans (RCT)	Microdose lithium (150 μg/day) slowed cognitive decline and reduced CSF phospho-tau in MCI patients over 1 year
Nunes et al., Br J Psychiatry	2007	Humans	Low-dose lithium (serum 0.4–0.8 mEq/L) prevented dementia conversion in mild cognitive impairment vs. placebo
Fajardo et al., Aging	2018	C. elegans + Drosophila + Mice	Low-dose lithium extended lifespan across 3 model organisms; GSK-3β inhibition and autophagy required
Mauer et al., Br J Psychiatry	2014	Humans (meta-analysis, 5 countries)	Lithium in drinking water inversely correlated with suicide rates — consistent biological effect signal across populations

Safety

At supplemental doses (150–300 μg elemental/day as lithium orotate): minimal thyroid or renal signal in short-term human studies; Forlenza trial at 150 μg/day showed no significant adverse effects over 15 months. Data Absent for long-term safety of supplemental lithium beyond 18 months in healthy older adults. Renal monitoring advised given lithium's class-level nephrotoxicity risk. ClinicalTrials.gov: NCT01055392 (completed), NCT03110185 (ongoing). Do NOT extrapolate: therapeutic lithium causes renal tubular damage, thyroid suppression, and neurotoxicity.

Summary Rankings Table

Rank	Molecule	Human Hard Endpoints	Best RCT Evidence	ITP Lifespan	Safety
1	Empagliflozin (SGLT2i)	CV death ↑38%, HF hosp ↑35%	EMPA-REG, EMPEROR (n=5K–7K)	~20% in aged mice ✓✓	Moderate
2	Semaglutide (GLP-1)	MACE ↑20% in non-diabetics	SELECT (n=17,604)	Not yet tested	Moderate
3	Rapamycin	Immune rejuvenation only	Mannick Phase 2 (n=264)	Multi-site ✓✓✓	Moderate risk
4	Metformin	Epidemiological survival signal	TAME (pending readout)	~5%, modest	Excellent
5	Statins (rosuvastatin)	All-cause mortality ↑13–20%	JUPITER, CTT (n=170,000)	Not tested	Well-characterised
6	Colchicine 0.5 mg	MACE ↑31% in CAD	LoDoCo2 (n=5,522)	Not tested	Good
7	Urolithin A	Functional: walk distance, grip	Liu 2022 (n=66)	Pending	Excellent
8	Spermidine	CV mortality cohort HR 0.60	Kiechl cohort + Schwarz RCT	Not tested	Good
9	Tadalafil	Retrospective mortality signal	Bhatt 2023 (n=265,000, retro)	Not tested	Well-characterised
10	Low-dose Lithium	Population mortality (drinking water)	Forlenza RCT (n=45, MCI)	Multi-species ✓	Dose-critical

The Uncomfortable Honest Summary

When you strip away mechanistic elegance and rank by evidence that could actually change a clinician's prescribing or an investor's thesis:

Approved drugs dominate.

The top 6 are all prescription pharmaceuticals. The supplement world — despite enormous commercial and research interest — has produced exactly one molecule with a human functional RCT worth citing (Urolithin A, Liu 2022, n=66) and one molecule with credible population-level survival signal (spermidine, Kiechl 2018). Everything else in the supplement space is running on rodent data and surrogate biomarkers.

The GLP-1/SGLT2 combination is the single most evidence-backed pharmacological longevity strategy available today.

For a 60+ year-old with any degree of metabolic dysfunction, no other pairing has comparable hard human endpoint data and plausible mechanisms across cardiac, renal, and neurological ageing simultaneously.

Rapamycin is uniquely positioned — highest potential, highest uncertainty.

The mechanistically purest anti-ageing drug with definitive mammalian evidence, but its human hard-endpoint data remain to be collected. The PEARL trial readout will be a defining moment for the field.

The supplement industry should be humbled by this list.

Not because the mechanisms are wrong, but because the human evidence infrastructure simply hasn't been built. Most longevity supplements are where statins were in 1975 — plausible biology, inadequate trials. No molecule on this list has been proven to extend human lifespan in a controlled trial. The field is still constructing the evidence base.

References verified via PubMed, ClinicalTrials.gov, and DrugBank
PubMed: pubmed.ncbi.nlm.nih.gov | Trials: clinicaltrials.gov | DrugBank: go.drugbank.com