In a few years, with the development of biotechnology, human organs can be constantly transplanted so that (people) can live younger and younger, and even become immortal (Vladimir Putin). The prediction is that in this century humans may live to 150 years old (Xi Jinping). Informal dialog between the two heads of state during an international conference in Beijing, September 3, 2025. Hoping that these discussions spread to the most democratic states. *Source*.

This month's theme: Compounds for Longevity

Introduction

Most humans would love a pill without negative effects and largely extending healthy life. Sadly, until today, there is no product making a far longer healthier life possible for humans. This newsletter is about the compounds for longevity that are the most studied at the moment.

Metformin

A widely prescribed drug for type 2 diabetes has garnered significant interest for its potential role in promoting longevity and healthy aging. Beyond its glucose-lowering effects, metformin influences multiple cellular pathways associated with aging, including activation of AMPK, inhibition of mTOR, reduction of oxidative stress, and improvement of mitochondrial function. These actions collectively mimic some of the effects of caloric restriction, a well-established intervention for lifespan extension in model organisms. Preclinical studies in mice and other animals have shown that metformin can extend healthspan, reduce the incidence of age-related diseases such as cancer and cardiovascular disease, and improve metabolic and cognitive function. Observational studies in humans, particularly among individuals with diabetes, suggest that metformin use is associated with lower all-cause mortality and a reduced risk of age-related conditions compared to non-users. However, randomized controlled trials specifically evaluating longevity in non-diabetic populations are sadly not yet startedongoing, most notably the TAME (Targeting Aging with Metformin) trial.

mTOR Inhibitors

Rapamycin and its analogs (rapalogs such as everolimus, temsirolimus, and ridaforolimus), are among the most validated pharmacological interventions for extending lifespan across model organisms and are now showing promise in humans. These drugs primarily inhibit mTORC1, slowing growth and enhancing stress resistance, but dose and context are critical: while moderate dosing improves longevity, excessive inhibition can impair fertility, immunity, or metabolism. Beyond aging, rapalogs are being investigated in oncology, reproductive health (reducing endometriosis progression and preserving ovarian function), and neuro-ophthalmology (protecting against glaucoma through autophagy). Recent advances such as RapaLinks—next-generation compounds targeting both mTORC1 and mTORC2—offer stronger, more durable inhibition and may overcome drug resistance seen in cancer. Overall, rapalogs remain central to longevity research, with evidence pointing to sex-specific, tissue-specific, and dose-dependent benefits that make them promising, though nuanced, tools for extending healthspan.

NMN

By replenishing NAD^+, NMN has been shown in animal studies to improve insulin sensitivity, vascular function, and cognitive performance, while extending healthspan and in some cases lifespan. Recent work highlights the role of NMN transporters and extracellular NAMPT in systemic aging regulation, leading to the "NAD World 3.0" framework that emphasizes multi-tissue communication in longevity control. NMN supplementation has also been found to restore NAD^+ levels and reduce inflammation through pathways like TLR4/NF-κB/MAPK, suggesting protective effects against age-related ovarian decline. Human clinical data remain limited but show that NMN is generally safe and well-tolerated, capable of raising blood NAD^+ levels. Overall, NMN represents a leading candidate among NAD^+ boosters, with strong mechanistic rationale and encouraging early results, but confirmation from large-scale clinical trials is still needed.

Senolytics

Dasatinib combined with quercetin (D+Q) is one of the most studied senolytic strategies in the context of longevity. Aging is partly driven by the accumulation of senescent cells, which stop dividing but secrete pro-inflammatory factors known as the senescence-associated secretory phenotype (SASP), contributing to tissue dysfunction, chronic inflammation, and age-related diseases. Dasatinib, a tyrosine kinase inhibitor originally used in leukemia, selectively induces apoptosis in senescent preadipocytes and endothelial cells, while quercetin, a natural flavonoid, targets senescent endothelial cells and fibroblasts. Together, they provide a broader spectrum of senescent cell clearance than either agent alone. Preclinical studies in mice have shown that intermittent administration of D+Q reduces senescent cell burden in fat, liver, and kidney, improves physical function such as grip strength and endurance, reduces age-related pathologies, including fibrosis and atherosclerosis, and enhances healthspan. Early human pilot studies, including in patients with idiopathic pulmonary fibrosis and age-related dysfunction, suggest that intermittent D+Q therapy can decrease senescence markers and

systemic inflammation, potentially improving physical performance and tissue function. While these results are promising, long-term effects on human lifespan and healthspan are still unknown, and dasatinib carries potential serious side effects, so its use requires medical supervision.

GLP-1

Glucagon-like peptide-1 is a hormone primarily known for its role in glucose metabolism and appetite regulation, but emerging evidence suggests it may also influence longevity and healthy aging. GLP-1 receptor agonists, such as liraglutide and semaglutide, improve insulin sensitivity, reduce systemic inflammation, and promote weight loss, all of which are key factors in mitigating age-related metabolic and cardiovascular diseases. Beyond metabolic effects, GLP-1 signaling has been shown in preclinical studies to protect against oxidative stress, improve endothelial function, and enhance mitochondrial health, mechanisms that are closely linked to cellular aging. Animal studies indicate that GLP-1 receptor activation can improve cardiovascular outcomes, reduce neurodegeneration, and extend healthspan. Human observational and clinical data suggest potential benefits in reducing the incidence of type 2 diabetes, cardiovascular events, and possibly cognitive decline. Although direct evidence for lifespan extension in humans is still limited, GLP-1–based therapies appear to target several hallmarks of aging, making them a promising avenue for promoting longevity and metabolic resilience.

Glucosamine

This naturally occurring amino sugar commonly used as a dietary supplement for joint health, has recently drawn attention for its potential role in longevity. Beyond its effects on cartilage and osteoarthritis, preclinical studies suggest that glucosamine may influence aging through several mechanisms, including reducing chronic inflammation, modulating nutrient-sensing pathways such as mTOR and AMPK, and promoting autophagy, all of which are linked to extended healthspan. Epidemiological studies, particularly large cohort studies in humans, have observed associations between regular glucosamine supplementation and lower overall mortality, reduced risk of cardiovascular disease, and decreased incidence of some age-related diseases. While the exact mechanisms are still being elucidated, glucosamine appears to act as a mild caloric restriction mimetic, supporting cellular homeostasis and potentially contributing to healthier aging. Its safety profile is generally favorable, making it an attractive candidate for longevity research, though randomized controlled trials specifically targeting aging outcomes are still limited.

Lesser-known therapeutic compounds

SGLT2 inhibitors (ex : dapagliflozin, canagliflozin)

SGLT2 inhibitors, such as dapagliflozin and canagliflozin, offer significant benefits for kidney, heart, and metabolic health. These medications help improve glucose control while also reducing cardiovascular and renal risks. Interestingly, canagliflozin has even been shown to extend lifespan in male mice but not female and to slow the development of age-related lesions in the heart, kidneys, liver, and adrenal glands in genetically heterogeneous male mice.

Urolithin A

Urolithin A is a natural mitophagy activator that helps promote the removal of damaged mitochondria, thereby improving cellular energy and health. It is well tolerated in humans and has shown promising effects on mitochondrial function in clinical studies. Ongoing trials are investigating its potential in Alzheimer's disease, where it has been shown to restore mitophagy and lysosomal function (which involves the cell's "recycling centers" that break down and clear waste, helping maintain healthy cellular homeostasis and neuronal function).

TNIK

TNIK(Traf2- and Nck-interacting kinase) inhibitors are an emerging class of compounds being explored for longevity because of their role in pathways linked to cellular senescence, inflammation, and fibrosis. Recent AI-driven and robotics-lab studies identified the inhibitor INS018_055 which reduced markers of senescence such as the senescence-associated secretory phenotype (SASP) while preserving healthy cell function. Early clinical data in patients with idiopathic pulmonary fibrosis, a disease strongly tied to aging, showed that TNIK inhibition was safe and improved lung function. Howeverthere is still no evidence that TNIK inhibitors extend lifespan in animal models or humans, and long-term safety data remain limited.

The good news of the month. GLP-1 Receptor Agonist Use Reduces Heart Failure Mortality.

Some longevists affirm that GLP-1 can be considered the first real longevity drug useful for most people. Actually, it could be useful because most people have an unbalanced diet.

GLP-1 receptor agonist has various positive effects. It was recently established that patients initiating semaglutide or tirzepatide had a more than 40% lower risk of hospitalization for heart failure or all-cause mortality compared with sitagliptin (a glucose-lowering drug with no effect on heart failure end points).

For more information

- Heales, Longevity Escape Velocity Foundation, International Longevity Alliance, Longecity, and Lifespan.io
- Heales Monthly Science News
- Heales YouTube channel
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