Geroprotectors

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Next Frontier in Fight Against Aging

As longevity scientists look to target and stop aging, many researchers are focusing on **geroprotectors**, compounds capable of preventing or even reversing aging ***at the cellular level***. **Senescent cells** are particularly troublesome when they enter the stage in which they can no longer properly divide and function. As cells become ***dysfunctional***, organ health markedly deteriorates. Another problem caused by **cell senescence** is release of ***proinflammatory cytokines*** that systemically damage tissues.

Compounds capable of identifying and eliminating **senescent cells** are categorized as **senolytics**. Clinical research on **geroprotectors** and **senolytics** is complicated by the fact that *many decades of time* may be required to determine human longevity benefits.

A novel way to accelerate the research is via the strategic use of high-speed computer programs employing **artificial intelligence biomedical algorithms**. This technology has advanced to where it can *identify* natural compounds that activate *anti-aging pathways* throughout the body.

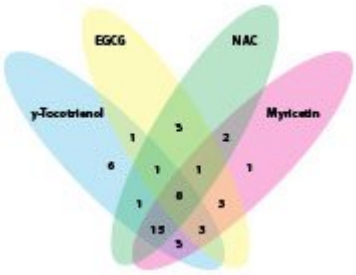
Seeing the enormous potential of this kind of deep-learning artificial intelligence, **Life Extension®** has partnered with **Insilico Medicine** to identify nutrient cocktails that function as **geroprotectors**. The objective is to develop better ways to potentially slow or even stop certain aspects of aging processes.

This scientific collaboration has resulted in the identification of a **geroprotector** formulation consisting of four nutrients with various complementary and reinforcing properties. These include effects on cell ***signaling***pathways with the potential to *prevent* the degenerative progression of damaged cells to a senescent state—and *eliminate* those that have reached irreversible senescence.[1,2]

With the discovery of geroprotective compounds, there are now greater opportunities to more effectively intervene into cellular aging processes.

By harnessing **artificial intelligence** advances with existing scientific data, a powerful new weapon to combat degenerative aging has emerged.

Using Artificial Intelligence to Solve Aging



Overlap and Unique Pathway Activation - Figure 1.
The numerals within the diagram indicate the number of pathways activated by the four short-listed nutrients.

Life Extension and **Insilico Medicine** researchers ran computer simulations of more than 200 potential geroprotective compounds and narrowed the list down to four.[1,2] While most of these candidates were known natural nutrients, their full potential as geroprotectors remained elusive. Scientists found that all four of these nutrients work together, but in very different ways, to beneficially influence key anti-aging pathways. Together, they combat numerous aging factors throughout the body.

These compounds all *modulate* specific biological pathways responsible for keeping us young and healthy.
When combined, these ingredients promote anti-aging mechanisms at the cellular level throughout the body, acting by multiple pathways, some unique, and some overlapping.

Together, these four natural compounds represent the beginning of the future: anti-aging cocktails identified using artificial intelligence under expert human supervision.

Geroprotectors and Senolytic Agents Extend Lifespan

The concept of ***geroprotection***, meaning prevention of cells from entering an aged, senescent, inflammation-promoting state, originated in Soviet-era Russia in the late 1970s.

Modern science has uncovered a variety of natural substances capable of extending healthy lifespan, and these agents have been called ***geroprotectors***.

Scientists then discovered that several of these nutrients function as ***senolytic***agents.
The term ***senolytic*** means the removal of useless senescent cells from tissues.[3,4] **Cellular senescence** is characterized by the aged cell's inability to divide, yet the senescent cell continues to generate a variety of *proinflammatory compounds* as well as other harmful cellular mediators that can potentiate damage to healthy tissues.

Cancer researchers were first intrigued by the idea of developing **senolytic** drugs that could selectively kill malignant cancer cells without damaging normal cells in the body.[5,6]
Based on this research, scientists have realized that **senolytics** can enhance healthspan by ***eliminating***aging cells from our tissues, making room for newer, active cells that support youthful tissue, organ, and systems functioning. The result is a younger, healthier and better-functioning body.

Why should we care about getting rid of these senescent cells? Because they contribute to virtually all known age-associated disorders: heart disease, stroke, cancer, diabetes, obesity, liver and kidney disease, osteoporosis, and neurodegeneration.[4,7-22] In fact, senescent cells have recently been labeled "…***drivers of age-related pathologies***."[22]

There's already evidence that removing senescent cells from old animals through nutrients and drugs promotes longevity and improves the function of aging body systems.[4]
Using sophisticated genetic engineering, scientists in **2011** showed they could identify and eliminate senescent cells in mice that naturally age rapidly.[23] After lifelong administration of this therapy, senescent cells were swept clean from fat, muscle, and eye tissues, resulting in delayed onset of age-related disorders in those areas. Furthermore, treating mice late in life slowed the progression of such disorders that had already appeared.

Following up on this initial research, the same group in **2016** showed that clearing senescent cells using this approach delayed cancer development and slowed age-related deterioration of kidney, heart, and fat tissues, and extended median lifespan in mice.[24]
Similar findings resulted from a **2015** study using existing drugs and nutrients, in this case the combination of**dasatinib** (a cancer drug) plus the polyphenol nutrient **quercetin**.[4] Lab studies showed that this combination reduced the numbers of senescent cells in normally aged mice and in age-accelerated mice, as well as in those exposed to radiation.[4]

This study showed that in the living animals, healthspans were also improved, as determined by scores of age and wellbeing and by individual symptom scores for common symptoms of aging.

The Remarkable Potential of Geroprotectors

- The discovery of ways to counteract ***cellular senescence*** is ushering in a new era in health promotion and disease prevention.
- Senescent cells are old cells that have lost the ability to replicate, but instead of dying, they hunker down in tissues and secrete proinflammatory substances that promote aging throughout the body.
- Many stimuli trigger cells to become senescent, including oxidative stress, DNA damage, mitochondrial dysfunction, elevated blood glucose, and others.
- Because the senescence-promoting stimuli are the same throughout the body, and because those stimuli operate via a number of known biochemical signaling pathways, it has now become possible to slow aging in all tissues of the body at once.
- This ability is especially pronounced in a handful of nutrients called ***geroprotectors***.
- These geroprotective nutrients were characterized through a computer algorithm that compared senescence-promoting pathways with those modulated by each of hundreds of candidate compounds.
- The "final four" compounds, myricetin, NAC, gamma tocotrienol, and EGCG each modulate a different but overlapping set of signaling pathways.
- Separately and together, these compounds work to slow cellular aging in all tissues in the body.
- Supplementing with these nutrients in combination seems likely to reduce the body's burden of senescent cells, promoting youthful function and preventing not one or two, but literally all of the known age-related disorders that threaten human lifespan and healthspan.

What Are Signaling Pathways?

Researchers from Insilico Medicine identified nutrients based on their abilities to modulate certain biochemical ***signaling pathways*** that control development of cellular senescence.[1,2] To grasp the breakthrough nature of this approach, it's vital to understand what biologists mean by "***signaling pathways***."

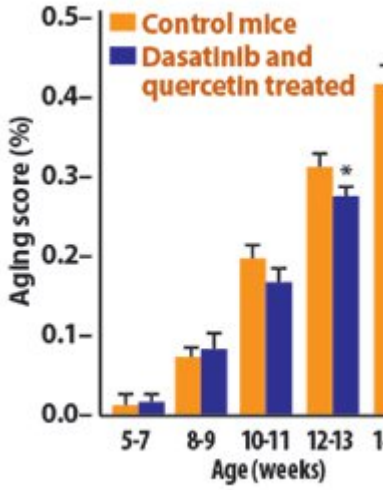
Cells need to send and receive information about their environment, nutrient status, stress level, and many other important factors. Without this constant communication, cells could not perform their various life-sustaining duties.

Cells communicate by producing and sending vast amounts of ***signaling molecules***, and receiving other molecules at specific receptors on their membranes and in their nuclei. This network of molecular events is called a ***signaling pathway***.[25] When beneficial pathways fail, or destructive ones prevail, cells are pushed toward the senescent state,[26] and degenerative aging processes begin to unfold.

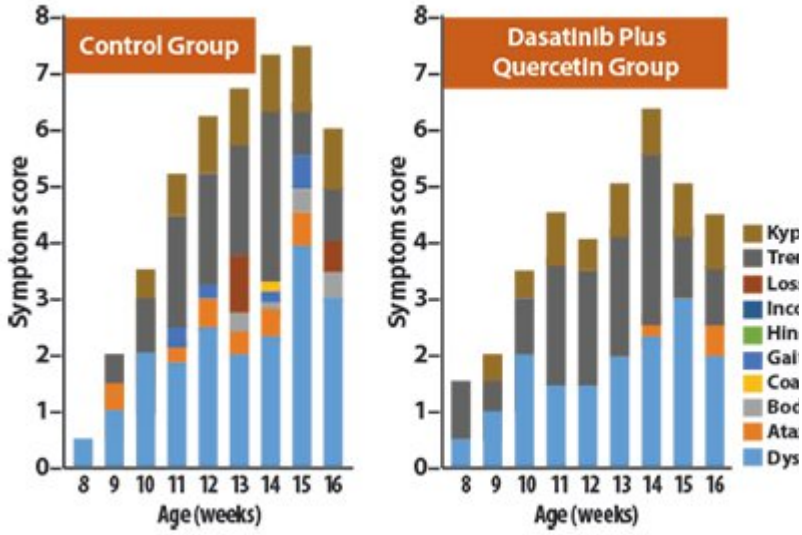
By studying signaling pathways that influence development of cellular senescence, scientists can target specific pathways to slow progression of senescence and decrease the number of senescent cells. With the help of artificial intelligence and technology, we can determine which pathways are modulated by a single nutrient—and how nutrients can modulate multiple pathways.[1,2]
Attacking cellular senescence by modulating multiple independent and overlapping pathways is a broad-spectrum approach to ***geroprotection*** and the ***removal of senescent cells***.

EFFECTS OF SENOLYTIC TREATMENT ON MICE

Aging Scores Symptom Scores



Aging scores of control mice vs. those of mice treated with dasatinib+quercetin. Significant reductions in score are seen at 12-13 and 14-15 weeks, indicated by "*."



Symptom scores for multiple signs of aging. Kyphosis = humped back; Ataxia = poor balance; Dystonia = loss of muscle tone.4

Identifying Geroprotective Nutrients

The basic idea behind *geroprotector screening* is to compare large numbers of molecular profiles of human tissues of patients of all ages as well as tissues that contain various diseases to identify the changes implicated in degenerative aging.
Unlike studies done in the glass dishes of a laboratory (*in vitro* studies), or those done in living animals (*in vivo* studies), research done inside a computer exists purely in virtual form, in the silicon chips of the processor, and is referred to as an "*in silico*" study.
Searching for natural compounds that could work on many different levels to halt the aging process, researchers resorted to this innovative "*in silico*" type of study and identified four age-reversing substances.[1,2]

How the Selected Nutrients Perform as Geroprotectors

Each of the nutrients identified using *in silico* type of research showed an impressive record at ***geroprotection***.[1,2]

- **Myricetin**, a plant-derived polyphenol, is revealing a wide array of pathway modulation in age-related disorders.
  In particular, myricetin is known to regulate the ***p38 MAPK*** family of stress-responsive signaling molecules that are known to regulate aging in many tissues.[27,28]

Myricetin also promotes cell differentiation and self-repair, and regulates pathways involved in metabolic processes.[29-32]

- **N-acetyl-cysteine (NAC)** is a natural sulfur-containing molecule best known for its free-radical scavenging capabilities.
  NAC is proving useful for its ability to upregulate signaling pathways that boost natural, cellular protections against oxidative stress that promotes cellular senescence.[33]
  In addition, NAC has shown powerful effects on reducing pathways that promote inflammation, adding further anti-aging benefits to this versatile molecule.[33,34]
- **Gamma tocotrienol** is now showing a wide range of signaling pathway modulation that produces health benefits that far exceed those of simple oxidant-reducing nutrients.[35-38]
  A unique pathway modulated by gamma tocotrienol is the ***mevalonate*** pathway that controls cholesterol production, cancer promotion, and bone formation.[35-37]
- **Epigallocatechin-gallate** (EGCG) is a polyphenol with known anti-inflammatory properties, but new studies are showing that EGCG also regulates multiple pathways that influence aging in a broad range of tissues.
  EGCG uniquely regulates the ***Wnt*** pathway, which is vital in determining developing cells' proper fate and preventing cancer.[39]
  EGCG also prevents sugar-induced damage to tissues throughout the body, helping to suppress their pro-aging effects.[40]

Scientists found that these compounds *reduced* cellular aging and various processes that contributed to aging by beneficially modulating a group of ***signaling pathways*** that led to the formation of senescent cells.[1,2]
Most of these pathways are known to contribute to, or protect against, development of senescent cells, and all have been shown to protect against aging at the cellular level.

Table 1 (below) illustrates these pathways in context, showing both considerable overlap (e.g., antioxidant and anti-inflammatory pathways) as well as several pathways unique to each nutrient.

Table 1. How Geroprotective Nutrients Team Up To Slow Aging

Part 1

Nutrients ⟶	**NAC**		**Myricetin**	
↓Body System orCondition↓	**Pathways Modulated**	**Health Impact**	**Pathways Modulated**	**Health Impact**
Bone (Target: Slowing Osteoporosis by ↑Bone Formation and/or ↓Bone Resorption)	↑Antioxidant ↓Inflammatory	↓Death of bone-producingcells ↓Birth of bone-resorbing cells	↑P38-MAPK[28] ↓MMP (Protein-melting enzymes)[53]	↑Birth of bone-formingcells[28] ↓Birth of bone-resorbing cells[53]
Cancer (Target: Reduce Incidence and Severity)	↑Antioxidant ↓Inflammatory[57] ↓Cancer cell telomerase[58] ↓Growth factors[59] ↑ER-stress[60]	Sensitizes cancer to chemo[57] ↑Cancer cell death[58,60]↓Cancer growth[59]	↑Antioxidant ↑P38-MAPK[61,62] ↓VEGF[63] ↓Akt[46]	↑Cancer cell death[61-63] ↓Replication[61,62] ↓Malignant transformation[46] ↓New blood vessels[46,63]

Cardiovascular (Target: Slow Atherosclerosis)	↑Antioxidant ↓Inflammatory[68]	↓Hypertension[69] ↓Arrythmia[70]	↑Antioxidant ↑Self-repair[29,30,71] ↓Activity of calcium channels[72]	↓Vessel constriction[72,73]
Diabesity (Targets: ↓Weight, body fat, lipid glucose, ↓tissue damage, inflammation)	↑Antioxidant ↓Inflammatory ↓PPAR-gamma ↑FXR ↑Adiponectin[43]	↓Obesity ↓Atherosclerosis ↓Blood sugar ↑Insulin sensitivity ↑Fat burning ↓Liver fat[43] ↓Cataracts ↑Wound healing[85,86]	↓Inflammatory[87,88] ↑IRS-1-associated PI3-kinase ↑GLUT4[31] ↓NFkB, STAT1, NrF2[89] ↓CCAAT/Enhancer-binding protein PPAR-gamma[42]	↑Insulin sensitivity ↑Glucose uptake ↓Insulin[87,88] ↓Fat cell maturation[42] ↓Body weight[90] ↓Fat storage[91]
Liver and pancreas (Targets: ↓Liver fat, ↓Inflammation, ↑Liver function, ↓Cancer risk) ↓Fibrosis	↑Antioxidant[103] ↑Mitochondrial function[104]	↓Fatty liver disease, toxic damage[105-107] ↓Liver cancer formation[108]	↓Oxidation, inflammation[91] ↑Detox enzymes[109] ↓DNA damage, ↑DNA repair, ↓JAK1-STAT, CDK1, PAK1[45-47]	↓Fatty liver disease[91] ↓Fibrosis[110] ↓Liver cancer formation[45,46] ↑Cancer cell death[47]
Neuroprotection (Targets: Cognition, Memory, ↓Alzheimer's, Parkinson's) Strok protection	↑Antioxidant, ↓Inflammatory ↓Toxic protein accumulation ↑Mitochondrial function[121-124] ↑Brain cell survival path-ways[125,126]	↑Cognitive function[122-126]	↓Excitotoxicity by ↓calcium overload, ↓glutamate stimulation, ↓capase-3[127] ↓Glutamate release[52] ↓Deposits of toxic beta-amyloid protein[128] ↑GABA protective pathways[129]	↓Cognitive deficts, ↓decrease depressive behavior[130,131] ↑Learning and memory[132]
Kidney (Targets: ↓kidney failure, stone formation, ↑kidney function)	↑Oxidant protection ↓Inflammation[33,138,139]	↓Urine protein loss[33] ↓Kidney stones[138] ↓Uremic anemia[139]	↑Antioxidant[140] ↓SREBP, VEGF ↑PPAR[141]	↓Glomerular thickening (↑Kidney filtering function)[141] ↓Diabetic kidney damage[140]

Table 1. How Geroprotective Nutrients Team Up To Slow Aging

Part 2

Nutrients →	**Gamma Tocotrienol**		**EGCG**	
↓Body System or Condition↓	**Pathways Modulated**	**Health Impact**	**Pathways Modulated**	**Health Impact**
Bone (Target: Slowing Osteoporosis by	↓Mevalonate[35,36]	↑Activity of bone-forming cells[35,36]	↑Wnt[39] ↓HSP27	↑Birth of bone-forming cells[56]

↑Bone Formation and/or ↓Bone Resorption)		↓Activity of bone-resorbing cells[35,36,54] ↑Bone quality[36]	↓GSK-3beta ↓Akt[55]	
Cancer (Target: Reduce Incidence and Severity)	↓Mevalonate[37,38] ↓Inflammatory[64]	↓Replicaton[37,38] ↓New blood vessels[37] ↑Cancer cell death[37,38]	↓Growth factors[65] ↓NFkB[66] ↑miRNA[67]	↓Cell division[65] ↑Cancer cell death[66] ↓Cancer growth[67]
Cardiovascular (Target: Slow Atherosclerosis)	↓Inflammatory[74] ↑Antioxidant[75] ↓Mevalonate[76] ↑Autophagy[50]	↓Plaque[75] ↓Cholesterol[76] ↓Ischemic damage[50]	↓Inflammatory ↑Antioxidant[77] ↑AMPK[49]	↓Lipids ↓DNA Damage ↑Fat burning ↓Fat storage ↑Endothelial function ↓BP[78-84]
Diabesity (Targets: ↓Weight, body fat, lipid glucose, ↓tissue damage, inflammation)	↑Autophagy ↑AMPK ↓PPAR gamma[44] ↑Fat cell death[92] ↓NFkB[93-95]	↓Fat cell formation ↑Fat burning[44] ↓Body fat ↓Risk of diabetes ↓Impact on tissues[92]	↑AMPK[96] ↑Cellular antioxidants[97] ↓DNA Damage[97]	↓Fat accumulation ↑Fat burning ↓Blood sugar ↓Body weight, BMI, Waist circumference.[78,98-102]
Liver and pancreas (Targets: ↓Liver fat, ↓Inflammation, ↑Liver function, ↓Cancer risk) ↓Fibrosis	↑Mitochondrial failure in senescent pancreas cells[111] ↓NFkB[112]	Improved NAFLD[113] **Senolytic** in pancreas[111]	↑AMPK, oxidant protection ↓Inflammation.[114-116]	↓Fibrosis ↑Markers of liver function ↑Liver regeneration after injury.[114,117-120]
Neuroprotection (Targets: Cognition, Memory, ↓Alzheimer's, Parkinson's) Strok protection	↑Antioxidant, ↓Inflammatory[133]	Improved cell viability[133]	↓Inflammation ↓Oxidant stress ↑DNA damage repair[48,134] ↑Cleanup of toxic proteins[51]	↑Learning and memory in neurodegenerative disease, stroke, aging[135-137]
Kidney (Targets: ↓kidney failure, stone formation, ↑kidney function)	↓TGF-beta[142] ↓Inflammation (↓NFkB)[94] ↓Oxidative stress[143] ↑Mitochondrial function[144]	↓Diabetic kidney damage[94] ↑Kidney function, filtering efficiency[143] ↓Structural damage from toxins[143]	↓Thromboxane[145] ↓RAGE, AGEs[40] ↓DNA damage[48] ↑Oxidative stress protection[146] ↓NFkB[147]	↑Lifespan in rats by ↑kidney function[147] ↑Kidney function[145] ↓Kidney stone formation[146] ↑Kidney structure, function[148] ↓Kidney fibrosis[149]

Some key points about the information presented in Table 1:

- All four nutrients excel at protecting cells against oxidative stress, as well as against inflammation. These processes are known to promote formation of **senescent** cells.[26,41]
- Myricetin, NAC, and gamma tocotrienol all prevent energy from being stored as fat through the PPAR-gamma pathway.[42-44]
- Myricetin and EGCG excel at preventing senescence-inducing DNA damage and promoting its repair.[45-48]
- Gamma tocotrienol and EGCG activate the AMPK pathway that promotes youthful cellular function, reduced fat storage, and improved entry of glucose into cells.[44,49]
- Gamma tocotrienol and EGCG both promote ***autophagy***, the removal of debris (junk proteins) that accumulates inside of aged cells.[50,51]
- Myricetin reduces the effects of glutamate, the ***excitatory*** neurotransmitter implicated in brain aging.[52]

These nutrients have also shown the potential to be ***senolytic*** agents, meaning that they not only prevent cellular senescence, but may contribute directly to removal of age-accelerating senescent cells from tissues.[1,6]

Combining Geroprotectors to Slow Aging

The discovery and characterization of ***geroprotective*** nutrients is changing the ways we think about aging. The new paradigm is to look at ***signaling pathways*** that effect aging at cellular, and indeed, subcellular levels.
By utilizing this technology, whether aging is occurring in the brain, the heart, the intestinal tract, the muscle, or anywhere else in the body is irrelevant. Instead, we can see how myriad biochemical ***signaling pathways*** are operating in every cell in the body, ultimately contributing to accumulation of ***senescent cells*** that produce symptoms of aging and degenerative illnesses.
These advances mean that we can begin to identify specific nutrients, the pathways that they modulate, and their long-term effects in cells. This data is then used to develop anti-aging mixtures capable of defeating **cellular senescence** wherever it occurs.

NAC, myricetin, gamma tocotrienol, and EGCG are demonstrating the ability, between them, to modulate more than a score of ***signaling pathways*** that prevent cells from deteriorating into age-promoting, ***senescent cells***, while also preventing those cells from taking the alternate route of becoming malignant.

As a result, these nutrients have been combined into the first-ever ***geroprotective formulation based on artificial intelligence*** with far-reaching effects on age-related disorders to which senescent cells contribute. This improves our ability to develop strategies aimed at preventing cellular aging throughout the body.

The real world upshot is an opportunity to lengthen healthy human lifespans.

Summary

Senescent cells lose the ability to contribute meaningfully to body function. Instead of dying they go into an abnormal secretory state, pumping out destructive pro-inflammatory molecules that contribute to destructive aging throughout the body.

In partnership with researchers at Insilico Medicine, **Life Extension** scientists reviewed the biochemical pathways that push aging cells into senescence, and then screened hundreds of drugs and nutrients capable of favorably modifying those pathways.

The result was a short-list of four specific nutrients, myricetin, NAC, gamma tocotrienol, and EGCG, all of which modify senescence-inducing pathways, slowing down the development of senescent cells and exhibiting characteristics of senolytics.

Each nutrient not only has its own unique set of pathways that it regulates, but also overlaps with similar pathways modulated by the others, providing comprehensive protection against aging at the cellular level.

That ability, now known as ***geroprotection***, makes it possible to better prevent or decelerate aging ***throughout the body***, rather than on an organ-by-organ, or disease-by-disease basis. This work is only the beginning.

Future studies will no doubt identify other cocktails with geroprotective properties and will fine-tune our understanding of how manipulation of senescence-inducing pathways can operate.

In time, new studies will produce further evidence of the intriguing notion of ***senolytic*** compounds, those capable of sweeping the body clean of existing senescent cells – a possibility that could facilitate meaningful **age reversal**.

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