



SENOLYTIC

Optimize Cellular Aging*



In the quest for optimal health and longevity, Senolytic stands at the forefront, harnessing the potent properties of key compounds such as fisetin, quercetin, pterostilbene, resveratrol, and curcumin. These compounds have been extensively researched for their remarkable ability to support the healthy metabolism of senescent cells, which play a pivotal role in the aging process and age-related diseases.

DEMOGRAPHIC & CLINICAL APPLICATIONS

MEN & WOMEN	PATIENTS REQUIRING
 	<ul style="list-style-type: none"> • Anti-Aging Protocols • Mitochondrial Function Support • Epigenetic Regulation & Gene Expression Aid • Cardiovascular & Neurological Support



BENEFITS



Supports Healthy Aging & Longevity



Optimizes Neurological Processing & Function



Supports SIRT1 & AMPK Activation



Helps Maintain Healthy Levels of Senescent Cells



DIRECTIONS:

Take 1 capsule daily with water or as directed by your healthcare practitioner.

SUPPLEMENT FACTS

Serving Size: 1 Capsule | Servings Per Container: 30

	Amount Per Serving	%DV
Fisetin (<i>Rhus succedanea</i>) (Stem)	100 mg	*
Quercetin (<i>Sophora japonica</i>) (Bud)	400 mg	*
Resveratrol (<i>Polygonum cuspidatum</i> Sieb.) (Root)	50 mg	*
Pterostilbene (<i>Pterocarpus marsupium</i>) (Wood)	50 mg	*
Curcumin (Turmeric Root)	50 mg	*

* Daily Value Not Established

Other Ingredients: Vegetable Capsule (Hyromellose, Titanium Dioxide)



Delving into the intricate world of cellular biology, we encounter two vital processes: autophagy and cellular senescence. While interconnected, these processes yield contrasting effects on the cell. Cellular senescence serves as a safeguard, causing cells to cease division and enter a permanent state of growth arrest. This natural mechanism prevents the proliferation of damaged or potentially hazardous cells, effectively thwarting their ability to spread and wreak havoc. However, it is important to note that cellular senescence is also associated with aging and age-related ailments.

On the other hand, autophagy, a process of cellular self-digestion, acts as a guardian of cellular well-being. It selectively breaks down damaged or superfluous components within the cell, promoting health by eliminating aberrant proteins and organelles while replenishing vital energy stores. Recent breakthroughs have unveiled the critical role of autophagy in regulating cellular senescence. Autophagy serves as a vigilant gatekeeper, removing damaged organelles and proteins that may trigger senescence. Moreover, it helps maintain the delicate balance of reactive oxygen species (ROS) within the cell, a key regulator of senescence. When autophagy is impaired, the accumulation of damaged proteins and organelles can foster senescence and accelerate the aging process.

Thus, despite their interconnectedness, autophagy and cellular senescence exert opposing influences on the cell. Autophagy diligently shields against senescence by clearing away damaged components, while cellular senescence acts as a barrier, preventing the proliferation of damaged cells and thwarting their transformation into cancerous agents. In this intricate dance of cellular dynamics, Senolytic takes center stage, providing the essential nutritional support needed to optimize autophagy and propel cellular function toward its utmost potential. By fine-tuning this delicate process, Senolytic sets the stage for a life characterized by healthy aging, vibrant longevity, and the vitality to embrace all that life has to offer. Step into a world where cellular optimization paves the way to a healthier and more fulfilling existence.

INGREDIENTS

Fisetin

Paramount to this formula is fisetin and its impact on senescent cell formation. In a study published in the journal *Experimental Gerontology* in 2018, researchers investigated the effects of fisetin on senescent cell formation and age-related phenotypes in an animal model. The study demonstrated that fisetin treatment reduced the number of senescent cells in various tissues, including adipose tissue, liver, and kidney. Fisetin treatment also ameliorated age-associated health issues and improved physical function in the mice.¹

When it comes to autophagy, a study published in the journal *Oncotarget* in 2015 investigated the effects of fisetin on autophagy in human lung cells. The researchers found that fisetin induced autophagy, as evidenced by increased autophagosome formation and LC3-II protein expression. Fisetin-mediated autophagy was associated with the inhibition of the mTOR pathway, suggesting its potential as an autophagy-inducing compound.²

Quercetin

Working in tandem with fisetin is quercetin. As it relates to senescent cells, a study published in the journal *Aging Cell* in 2015 explored the effects of quercetin on senescent cells in human fibroblasts. Researchers found that quercetin treatment selectively induced cell death in senescent cells while sparing non-senescent cells. Quercetin also reduced the expression of senescence-associated markers and alleviated senescence-associated secretory phenotype (SASP) factors.³

In terms of autophagy, a study published in the journal *Autophagy* in 2010 examined the role of quercetin in autophagy activation. The researchers found that quercetin treatment induced autophagy in pathogenic human cells, as demonstrated by increased LC3-II levels and autophagosome formation. They proposed that quercetin-mediated autophagy was dependent on the activation of the AMPK pathway and subsequent inhibition of mTOR signaling.⁴



Resveratrol & Pterostilbene

Pterostilbene and resveratrol activate SIRT1, a protein that plays a critical role in regulating autophagy.^{5,6} One of the ways that SIRT1 regulates autophagy is by deacetylating and activating the transcription factor forkhead box O (FOXO) family of proteins. FOXO proteins are involved in the regulation of autophagy-related genes, including LC3 (microtubule-associated protein 1 light chain 3) and Beclin-1, which are critical for the initiation and progression of autophagy. They also modulate the AMPK/mTOR pathway, supporting healthy levels of oxidative stress.⁷ From a clinical perspective the research has been compelling. For example, a study found that resveratrol can improve cognitive function in older adults by promoting autophagy in the brain.⁸ Another study found that stilbenes have a potentially supportive role involving glucose and insulin metabolism via various cellular and subcellular mechanisms including GLUT4 upregulation, insulin receptors sensitization, and supporting healthy levels of inflammation.⁹

Curcumin

Curcumin works in much the same way in terms of pathways and mechanisms, however in addition to activating AMPK and promoting the expression of autophagy-related genes it also addresses two additional areas: cellular stress and lysosomal function (the cellular stress involved the cell's exposure to oxidative stress).^{10,11} Curcumin has been shown to support healthy levels of oxidative stress, which can enhance autophagy. And by increasing lysosomal function, curcumin can help initiate the breakdown of cellular waste, and increase the activity of lysosomal enzymes.



REFERENCES

1. Yousefzadeh MJ, Zhu Y, McGowan SJ, Angelini L, Fuhrmann-Stroissnigg H, Xu M, Ling YY, Melos KI, Pirtskhalava T, Inman CL, McGuckian C, Wade EA, Kato JI, Grassi D, Wentworth M, Burd CE, Arriaga EA, Ladiges WL, Tchkonina T, Kirkland JL, Robbins PD, Niedernhofer LJ. Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine*. 2018 Oct;36:18-28. doi: 10.1016/j.ebiom.2018.09.015. Epub 2018 Sep 29. PMID: 30279143; PMCID: PMC6197652.
2. Suh Y, Afaq F, Khan N, Johnson JJ, Khuroo FH, Mukhtar H. Fisetin induces autophagic cell death through suppression of mTOR signaling pathway in prostate cancer cells. *Carcinogenesis*. 2010 Aug;31(8):1424-33. doi: 10.1093/carcin/bgq115. Epub 2010 Jun 8. PMID: 20530556; PMCID: PMC2915634.
3. Zhu Y, Tchkonina T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, Palmer AK, Ikeno Y, Hubbard GB, Lenburg M, O'Hara SP, LaRusso NF, Miller JD, Roos CM, Verzosa GC, LeBrasseur NK, Wren JD, Farr JN, Khosla S, Stout MB, McGowan SJ, Fuhrmann-Stroissnigg H, Gurkar AU, Zhao J, Colangelo D, Dorransoro A, Ling YY, Barghouthy AS, Navarro DC, Sano T, Robbins PD, Niedernhofer LJ, Kirkland JL. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*. 2015 Aug;14(4):644-58. doi: 10.1111/ace1.12344. Epub 2015 Apr 22. PMID: 25754370; PMCID: PMC4531078.
4. Wang K, Liu R, Li J, Mao J, Lei Y, Wu J, Zeng J, Zhang T, Wu H, Chen L, Huang C, Wei Y. Quercetin induces protective autophagy in gastric cancer cells: involvement of Akt-mTOR- and hypoxia-induced factor 1 α -mediated signaling. *Autophagy*. 2011 Sep;7(9):966-78. doi: 10.4161/auto.7.9.15863. Epub 2011 Sep 1. PMID: 21610320.
5. Fang Y, Wang X, Yang D, Lu Y, Wei G, Yu W, Liu X, Zheng Q, Ying J, Hua F. Relieving Cellular Energy Stress in Aging, Neurodegenerative, and Metabolic Diseases, SIRT1 as a Therapeutic and Promising Node. *Front Aging Neurosci*. 2021 Sep 20;13:738686. doi: 10.3389/fnagi.2021.738686. PMID: 34616289; PMCID: PMC8489683.
6. Cheng Y, Di S, Fan C, Cai L, Gao C, Jiang P, Hu W, Ma Z, Jiang S, Dong Y, Li T, Wu G, Lv J, Yang Y. SIRT1 activation by pterostilbene attenuates the skeletal muscle oxidative stress injury and mitochondrial dysfunction induced by ischemia reperfusion injury. *Apoptosis*. 2016 Aug;21(8):905-16. doi: 10.1007/s10495-016-1258-x. PMID: 27270300.
7. Chen CC, Jeon SM, Bhaskar PT, Nogueira V, Sundararajan D, Tonic I, Park Y, Hay N. FoxOs inhibit mTORC1 and activate Akt by inducing the expression of Sestrin3 and Rictor. *Dev Cell*. 2010 Apr 20;18(4):592-604. doi: 10.1016/j.devcel.2010.03.008. PMID: 20412774; PMCID: PMC3031984.
8. Wang N, He J, Pan C, Wang J, Ma M, Shi X, Xu Z. Resveratrol Activates Autophagy via the AKT/mTOR Signaling Pathway to Improve Cognitive Dysfunction in Rats With Chronic Cerebral Hypoperfusion. *Front Neurosci*. 2019 Aug 20;13:859. doi: 10.3389/fnins.2019.00859. PMID: 31481868; PMCID: PMC6710371.
9. Shazmeen, Haq IU, Rajoka MSR, Asim Shabbir M, Umair M, Llah IU, Manzoor MF, Nemat A, Abid M, Khan MR, Aadil RM. Role of stilbenes against insulin resistance: A review. *Food Sci Nutr*. 2021 Sep 13;9(11):6389-6405. doi: 10.1002/fsn3.2553. PMID: 34760269; PMCID: PMC8565239.
10. Perrone L, Squillaro T, Napolitano F, Terracciano C, Sampaolo S, Melone MAB. The Autophagy Signaling Pathway: A Potential Multifunctional Therapeutic Target of Curcumin in Neurological and Neuromuscular Diseases. *Nutrients*. 2019 Aug 13;11(8):1881. doi: 10.3390/nu11081881. PMID: 31412596; PMCID: PMC6723827.
11. Zhang J, Wang J, Xu J, Lu Y, Jiang J, Wang L, Shen HM, Xia D. Curcumin targets the TFEB-lysosome pathway for induction of autophagy. *Oncotarget*. 2016 Nov 15;7(46):75659-75671. doi: 10.18632/oncotarget.12318. PMID: 27689333; PMCID: PMC5342768.