

Senolytic Fisetin

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✓ Fact Checked

STORY AT-A-GLANCE

- > Fisetin has been shown to reduce the burden of COVID-19 in the lab and an animal model with significant results; researchers are now testing it in skilled nursing facility residents
- > Fisetin is a flavonoid with known senolytic properties, which help reduce the number of senescent cells in the body. These cells have lost the ability to proliferate and are resistant to apoptosis
- > The foods highest in fisetin are strawberries; yet you need to eat 37 strawberries each day to get the benefits. The compound also extended the health span of animals used in the study
- > Fisetin has been shown to have anti-inflammatory and antitumorigenic properties, to inhibit bone-damaging glycation, to maintain glutathione levels, and to protect brain function

Fisetin is a flavonoid molecule that's found in fruits and vegetables. An animal study published in July 2021¹ demonstrated that it may help reduce the mortality rate in older adults with COVID-19. A human study² is underway to analyze the effect it may have on elderly patients with COVID-19.

There are nearly 6,000 flavonoids³ found in fruits, vegetables, herbs and medicinal plants. Flavonoids are also antioxidants and have a number of subclasses, including flavanols, flavones and flavanones.⁴ During 2020, there was a growing focus on the value of antioxidants in the fight against infectious diseases.

As the science grows, researchers are becoming interested in individual flavonoids for the positive effect they can have on human health. Past research has suggested that fisetin may help extend a healthy life span by acting as a senolytic.⁵

These are a class of molecules that can selectively induce the death of senescent cells. Currently, there are 16 research studies registered with ClinicalTrials.gov studying fisetin.⁶ Of these, 13 are in the initial stages, either enrolling, recruiting or not yet recruiting participants.

Flavonoid compounds are well-known for their antioxidant, anti-inflammatory, anticarcinogenic and antimutagenic properties.⁷ They have become indispensable in a variety of applications including the pharmaceutical, nutraceuticals and cosmetic industries. Although scientists are continuing to study the mechanism of action flavonoids' use in the body, the plant derivatives have been widely used for centuries.

Fisetin Reduced the Burden of COVID in the Lab

Many of the biological effects that flavonoids have on the human body are related to modulating cell signaling cascades.⁸ This is how they protect against inflammation, thrombogenesis, diabetes and cancer development. Past studies have shown promising results when supplementation is used to improve glycemic control, enhance cognitive function, or in the prevention of cancer.

Fisetin is being studied to help reduce the severity of COVID-19 in elderly patients.⁹ In an animal study¹⁰ published in July 2021, researchers studied the response to stress signals that were associated with senescent cells known to increase in number with age.

They demonstrated that senescent cells increase the risk of severe COVID-19. Since the senescent cells secrete proinflammatory factors, they hypothesized these may heighten the proinflammatory response and raise the risk of cytokine storms and multi-organ failure.

To test the hypothesis, the researchers used human cells in a lab study and old mice that were challenged with lipopolysaccharide. The results demonstrated that senescent cells increased the susceptibility to SARS-CoV-2 and induced hyperinflation. When the researchers used senolytic compounds to reduce the burden of senescent cells, the mortality declined.

The senolytic compound they used to induce the death of senescent cells was fisetin. They believe the data suggests "senolytics might protect others vulnerable to adverse COVID-19 outcomes in whom increased SnCs [senescent cells] occur (such as in obesity or numerous chronic diseases)."¹¹

In one of the studies, the researchers found older mice exposed to a normal microbial environment, including SARS-CoV-2-related mouse beta coronavirus, experienced 100% lethality within 2 weeks. By comparison, those exposed to the same microbes but treated with fisetin had a significant improvement in survival – 64% of the male mice and 22% of the females survived long-term with an extension in lifespan for both sexes.¹²

Fisetin Being Tested Against COVID in an Aging Population

Announcement of a human trial was published in August 2021 in the Journal of the American Geriatrics Society,¹³ in which researchers plan to evaluate supplementation with fisetin in elderly adults residing in skilled nursing facilities. Past research has demonstrated that fisetin was a senolytic in animal models.

However, until recently, the only senolytic therapy that had demonstrated effectiveness in humans was a combination of quercetin and dasatinib.¹⁴ Dasatinib goes by the trade name SPYRCEL, which is a targeted therapy used in the treatment of chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia.¹⁵

The promising senolytic results of fisetin in animal studies increases the potential for senolytic treatments in humans without using chemotherapy-targeted drugs. The new clinical trial using fisetin in older patients is being funded by the National Institutes of Health and conducted by Mayo Clinic researchers.¹⁶

The researchers are engaging residents in skilled nursing facilities who were PCR positive for SARS-CoV-2 and age 65 or older. Data collection was estimated to start in October 2021 and primary completion is estimated to be by December 2023.¹⁷ The primary outcome measure is a change in severity of COVID-19.

The researchers are seeking to assess whether fisetin can help prevent the disease progression and alleviate complications. They plan to enroll 150 patients who will receive either a placebo with no active ingredients or fisetin.

The scientists mention clinical trials that are also ongoing evaluating the efficacy of fisetin against multiple disorders associated with aging, such as frailty, osteoporosis, cardiovascular and lung diseases, and obesity and diabetes.¹⁸

Reducing Senescent Cells May Be Key to Healthier Aging

Researchers believe that a larger number of senescent cells, which develop as an individual ages, contributes to a susceptibility of chronic disease and infections, such as COVID-19.¹⁹ Senescent cells are metabolically active and resist apoptosis.

However, they don't divide, and researchers have found higher numbers of senescent cells in older adults with chronic disease. The study that used a combination of dasatinib and quercetin was performed in Rochester, Minnesota, by the Mayo Clinic researchers.

The team engaged participants who had diabetes-related kidney disease. James Kirkland, Ph.D., was the senior author. He talked about senescent cells and the importance of the research on a range of human illnesses:²⁰

“Senescent cells can develop in all mammals in response to disease, injury, or cancerous mutations. Senolytic drugs do not interfere with generation of senescent cells, which could lead to cancer. However, once formed, senescent cells can contribute to developing cancers, multiple other diseases, and consequences of aging.

By targeting senescent cells with senolytics in mice, we can delay, prevent, or treat multiple diseases and increase health and independence during remaining years of life. As we increase our understanding of these drugs and their effects, we hope there may be benefits for a range of human diseases and disorders.”

Historically, cellular senescence was thought to be irreversible.²¹ Senescent cells are resistant to apoptosis.²² This mechanism of programmed cell death protects against the development of cancer.

Senescent cells have also lost their ability to proliferate. There is a multifunctional nature of cellular senescence that has a greater effect than tumor suppression. It may also be involved in wound healing, tissue repair and visible signs of aging.²³

Your body uses apoptosis to remove damaged cells harmed through injury or disease. However, as cells become resistant to apoptosis, it can contribute to a weakened immune system.²⁴ Scientists at UC San Francisco²⁵ have been investigating alternatives to senolytic therapies by approaching it from an immunotherapy standpoint.

They have been researching invariant natural killer T (iNKT) cells which function as a surveillance system. When these become less active with age, it can also lead to a reduction in function to eliminate cells with irreparable DNA damage. Using this alternative pathway, scientists found that by removing senescent cells through an activation of iNKT cells they could affect positive change on diabetes and lung fibrosis.²⁶

More Health Benefits Associated With Fisetin

As a senolytic, fisetin may have even greater health benefits. While the compound is naturally occurring in fruits and vegetables, you likely cannot get a therapeutic amount from food alone. As scientists continue to work out the proper dosing for fisetin, there is likely much benefit to adding some of these fisetin-containing foods to your diet.²⁷

Food	Fisetin in micrograms/gram (g)
Strawberry	160
Apple	26.9
Persimmon	10.6
Lotus root	5.8
Onion	4.8
Grape	3.9
Kiwi	2.0
Peach	0.6
Cucumber (with skin)	0.1

As you can see, strawberries have the greatest amount of fisetin. However, scientists have suggested you would need approximately 37 strawberries each day to get the benefits from fisetin.²⁸ Paul Robbins, Ph.D., is a professor of biochemistry, molecular biology and biophysics at the University of Minnesota medical school.²⁹

He believes that knowing it can have a positive impact on human health is good news, but more work continues to be needed. “These results suggest that we can extend the period of health, termed health span, even towards the end of life,” Fisetin told MediBulletin Bureau. “But there are still many questions to address, including the right dosage, for example.” Fisetin has been shown to:

Encourage anti-inflammatory action – Fisetin has been shown to suppress the production of inflammatory cytokines. While noting a flavonol-rich compound containing fisetin could be a potential therapeutic agent in the treatment of inflammatory conditions, one group of study authors noted:³⁰

“In experimental inflammation-related models, flavonol-rich RVHxR (Rhus verniciflua Stokes) and fisetin have shown significant anti-inflammatory activities on vascular

permeability, leukocyte migration and cellular immunity.

Also, flavonol-rich RVHxR and fisetin treatments significantly reduced the incidence and severity of [the] collagen-induced arthritis model.

These results suggest RVHxR and its major compound fisetin have shown potent suppressive effects on some inflammatory cytokines/chemokines and angiogenic factor in [Interleukin 1 beta]-stimulated rheumatoid arthritis FLS (fibroblast-like synoviocytes) and inflammatory in vivo models.”

Help prevent cancer – Given its well-known anti-inflammatory, antioxidant and antiproliferative properties, fisetin can play a role in helping to prevent cancer. To date, among other effects, fisetin has been shown to:

- Activate particular signaling pathways to induce cell death (apoptosis) in cervical cancer cells³¹
- Exhibit antigrowth potential against lung cancer cells³² and prostate cancer cells³³
- Inhibit melanoma cell growth³⁴
- Induce apoptosis in colon cancer cells by inhibiting certain signaling pathways³⁵

Inhibit bone-damaging glycation – Glycation, a process in which sugar molecules bond to certain proteins and lipids in your body, results in bone-damaging Advanced Glycation End (AGE) products.

According to Vivian Goldschmidt, founder of the Save Institute, a branch of which focuses on osteoporosis prevention, these molecules destroy collagen, the cartilage-like material that gives your bones tensile strength.³⁶ Due to its beneficial interaction with proteins found in your body, one study indicates fisetin arrests the glycation process.³⁷

Maintain your glutathione levels – According to a 2009 study, fisetin has been shown to help maintain your glutathione levels, particularly during times of increased oxidative stress.³⁸

The study authors stated, “Fisetin not only has direct antioxidant activity, but it can also increase the intracellular levels of glutathione, the major intracellular antioxidant.”³⁹ Glutathione is also known as the “master antioxidant.”⁴⁰

Protect brain function – A 2014 study⁴¹ published in *Aging Cell* suggests fisetin may have the ability to stave off age-related memory associated with Alzheimer’s disease and other types of

dementia in an animal model. The researchers suggested fisetin can act on many of the target pathways implicated in Alzheimer's disease.

They also found oral administration in mice aged 3 to 12 months prevented the development of learning and memory deficits. The study authors suggested "our results demonstrate fisetin, a compound that activates multiple, well-defined neuroprotective pathways, may provide a new approach to the treatment of [Alzheimer's disease]."⁴²

Stabilize resveratrol – Similar to other flavonoids, fisetin has been shown to inhibit the hepatic and duodenal sulphation of resveratrol,⁴³ thus improving the bioavailability of this powerful anti-inflammatory polyphenol found in red wine and the skins of certain fruits.
