

Fisetin & Senolytics

A Practical Guide to Cellular Senescence
and the Compounds That Target It

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What Is Cellular Senescence?

As cells age or accumulate damage, some stop dividing but refuse to die — a state called cellular senescence. These “zombie cells” don't just sit inertly; they secrete inflammatory signaling molecules collectively known as the senescence-associated secretory phenotype (SASP), which damages surrounding healthy tissue and drives chronic, low-grade inflammation.

Research from the Mayo Clinic and Unity Biotechnology, published across multiple peer-reviewed journals since 2015, has linked senescent cell accumulation to age-related conditions including osteoarthritis, pulmonary fibrosis, cardiovascular disease, and cognitive decline. Compounds that selectively clear senescent cells — called senolytics — are among the most actively studied interventions in longevity science.

Where Fisetin Fits In

Fisetin is a flavonoid found naturally in strawberries, apples, persimmons, and cucumbers. In a 2018 study published in *EBioMedicine* by researchers at the Mayo Clinic and Scripps Research, fisetin was screened against ten candidate senolytic compounds and emerged as the most potent at clearing senescent cells in both cell culture and aged mice — outperforming quercetin, another commonly studied flavonoid senolytic.

How Fisetin Works

Senescent cells rely on specific survival pathways — collectively called SCAPs (senescent cell anti-apoptotic pathways) — to resist the normal cell-death process. Fisetin appears to inhibit several of these pathways (including PI3K/AKT and BCL-2 family proteins), tipping senescent cells into apoptosis while largely sparing healthy, non-senescent cells.

The 2018 Mayo Clinic study found that intermittent dosing — not continuous daily use — was the effective protocol: senescent cells are cleared in short pulses, after which the treatment is stopped for weeks. This “hit-and-run” approach is a defining feature of the senolytic model and distinguishes fisetin from typical daily-use supplements.

Human Evidence So Far

Human trials remain early-stage relative to the animal data. A 2023 Mayo Clinic pilot trial (published in *eBioMedicine*) of intermittent fisetin dosing in elderly women with frailty found reductions in senescence and inflammatory biomarkers, alongside a good safety profile, over a two-day dosing protocol repeated monthly. Larger randomized controlled trials are ongoing; as of this writing, evidence in humans should be considered promising but preliminary compared to the extensive rodent literature.

Common Dosing Protocols

RESEARCH DOSE (MAYO PILOT)

20 mg/kg body weight, 2 consecutive days per month

COMMON SUPPLEMENT DOSE

500–1000 mg per day, 2 consecutive days, repeated monthly

BIOAVAILABILITY NOTE

Fisetin has poor solubility — take with a fat source to improve absorption

CYCLING PATTERN

2 days on, then 4–6 weeks off before repeating

Stacking Considerations

Some protocols pair fisetin with quercetin (500mg) for broader senolytic coverage, since the two compounds act on overlapping but not identical pathways. Others combine intermittent fisetin with daily NAD+ precursors (NMN or NR) on the theory that clearing senescent cells and supporting mitochondrial function address longevity from two different angles. There is limited direct clinical evidence for these combinations — they are extrapolated from the separate evidence bases for each compound individually.

Safety Notes

- Fisetin has a generally favorable safety profile in the studies conducted to date, with no serious adverse events reported at typical supplemental doses.
- Avoid combining with blood thinners (warfarin, etc.) without medical supervision — flavonoids can have mild anticoagulant interactions.
- Pregnant or breastfeeding individuals should avoid use, as no safety data exists for these populations.
- Consult a physician before starting if you take any prescription medication metabolized by the liver, since flavonoids can affect certain CYP450 enzyme pathways.

Quick Reference Checklist

- ☐ Choose a fisetin supplement with third-party testing (NSF, USP, or Informed Choice)
- ☐ Take with a meal containing fat to improve absorption
- ☐ Follow an intermittent protocol — 2 days on, weeks off, not daily use
- ☐ Track how you feel and any bloodwork changes over a 3–6 month period
- ☐ Check with your physician if on any prescription medication