



*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

## Fisetin

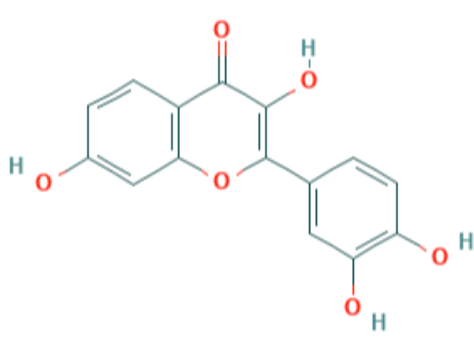
### Evidence Summary

Some evidence for benefits for Alzheimer's and longevity in preclinical studies, but poor bioavailability makes dosing uncertain.

**Neuroprotective Benefit:** Some evidence suggests fisetin may be beneficial for Alzheimer's disease, but it has poor bioavailability.

**Ageing and related health concerns:** There is some evidence as a potential senolytic, but it has poor bioavailability.

**Safety:** There is no evidence that fisetin would cause side effects, but no studies in humans have been conducted.

<b>Availability:</b> Available as a supplement	<b>Dose:</b> 20mg/kg/day for five days as a senolytic in clinical studies underway	<b>Chemical formula:</b> C <sub>15</sub> H <sub>10</sub> O <sub>6</sub> <b>MW:</b> 286.2363g/mol  <b>Source:</b> <a href="#">PubChem</a>
<b>Half-life:</b> 3.12 hrs (in mice)	<b>BBB:</b> Yes (mice)	
<b>Clinical trials:</b> 5 ongoing	<b>Observational studies:</b> none	

### What is it?

Fisetin is a naturally occurring flavonoid found in low levels in many fruits and vegetables such as apples, persimmon, grapes, onions and cucumbers. The highest concentration is found in strawberries (160ug/g). It is hydrophobic and penetrates the cell membrane where it exerts antioxidant effects.

Fisetin is reported to have low oral bioavailability (44.1%) due to poor aqueous solubility (10.45ug/ml) and high lipophilicity (logP 3.2). Additionally, it is highly metabolized when taken orally or intravenously. Efforts are being made to improve its bioavailability with novel delivery mechanisms or modifications to the structure. Therefore, some of the preclinical studies, especially *in vitro* studies, may not effectively translate the human studies. ([Mehta et al, 2018](#)).

**Neuroprotective Benefit:** Some evidence suggests fisetin may be beneficial for Alzheimer's disease, but it has poor bioavailability.

### Types of evidence:

- 6 *in vivo* studies
- 4 *in vitro* studies



Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None

Human research to suggest benefits to patients with dementia:

None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Multiple mechanisms of action have been reported through numerous animal and cell culture studies including increasing antioxidant capacity through increased glutathione expression, reduction of inflammation, increased neuroprotective signaling (e.g. increased BDNF expression), reduced amyloid fibril formation, and increased autophagy.

In an animal model of Alzheimer's disease, early treatment with fisetin improved cognition and decreased soluble A $\beta$ , but not insoluble A $\beta$  or plaque number. It also decreased oxidative stress, increased synaptic density, and decreased astrocytic inflammation ([Currais et al, 2014](#)). In an animal model of intracerebroventricular injections of A $\beta$ 42, two weeks of fisetin treatment (20mg/kg/day) started 24 hours after amyloid injections reduced levels of amyloid-beta, BACE1 expression, tau phosphorylation, and the expression of inflammatory proteins (TNF $\alpha$ , IL-1 $\beta$ , NFkB). It also increased the expression of synaptic markers and improved cognition ([Ahmad et al, 2017](#)). In a SAMP8 mouse model of accelerated aging, fisetin slightly improved cognition and reduced markers of inflammation and cellular stress ([Currais et al, 2017](#)).

The plant yielding flavonoid-rich ethyl acetate fraction (PREF) from the bark *Rhus verniciflua* (which contains high levels of fisetin) improved cognition and increased the expression of CREB-BDNF signaling in a scopolamine-induced cognitive deficit model, reduced expression of inflammatory markers in LPS-activated microglia, and improved cell viability in an *in vitro* model of glutamate-induced neurotoxicity ([Cho et al, 2013](#)). [Maher et al \(2006\)](#) and [He et al \(2018\)](#) reported that fisetin increased LTP in hippocampal slices *in vitro* and increased LTP and improved cognition in healthy mice *in vivo* through an ERK-dependent mechanism.

In a mouse model of L-methionine-induced hyperhomocysteinemia endothelial dysfunction, two-week treatment with fisetin, improved cognition, decreased serum homocysteine and cholesterol, increased serum nitrite levels, and increased the brain expression of anti-oxidants such as GSH and SOD. Additionally, it reduced thickening of the aortic wall, reduced the volume of necrosis in the brain, and reduced the number of infiltrating leukocytes in the brain ([Kumar et al, 2016](#)).

*In vitro* studies suggest that in mouse and rat neurons, fisetin reduces p-tau levels by increasing autophagic flux ([Kim et al, 2016](#)). *In vitro* studies also suggest that fisetin and analogs of fisetin can reduce beta-amyloid fibril formation and increase antioxidant capacity through an induction of glutathione (GSH) expression ([Kim et al, 2005](#); [Ushikubo et al, 2012](#)). Studies suggest that fisetin has a high EC50 (i.e. it is not very potent) and poor bioavailability, and SAR studies are underway based on the chemical scaffold of fisetin to make better molecules ([Chiruta et al, 2012](#)).

A study using two-photon excitation fluorescence imaging reported that fisetin was readily detectable in the blood vessels after 40 minutes and in the brain parenchyma after 2 hours ([Krasieva et al, 2015](#)).

**Aging and related health concerns:** There is some evidence as a potential senolytic, but it has poor bioavailability.

Types of evidence:

- 3 *in vitro* studies for lifespan or as a senolytic
- 1 *in vivo* study as a senolytic
- 1 review in cancer

Lifespan

Fisetin was reported to activate SIRT1 and extend yeast lifespan by 55% (compared to resveratrol ~ 70%) ([Howitz et al, 2003](#)). Fisetin also activated sirtuins in worms and flies and increase fly lifespan by 23%. Interestingly, the ability of different sirtuin activating compounds (STACs) to activate sirtuins was species-dependent. Fisetin was also reported to improve the reprogramming efficiency of primary mouse fibroblasts to iPSCs by 3.2-fold ([Chen et al, 2011](#)).

*In vitro* studies suggest that fisetin is a senolytic for human umbilical vein endothelial cells (HUVECs), but not human lung fibroblasts (IMR90 cells) or primary human preadipocytes ([Zhu et al, 2017](#)). In contrast, a follow up study reported that fisetin did reduced senescent cells in human lung fibroblasts (IMR90 cells) ([Yousefzadeh et al, 2018](#)).

Fisetin also reduced senescent cells in a mouse model of progeria (in fat, spleen, liver, kidney, and immune cells). When administered for 5 days to 20-month-old mice, fisetin reduced senescent mesenchymal stem/progenitor cells, T lymphocytes, and natural killer T cells and endothelial cells in



subcutaneous fat (but not senescent macrophages or dendritic cells). It also reduced senescent cells in human adipose explants. Finally, fisetin treatment (500ppm) at 20 months of age extended median and maximum (~12%) lifespan, improved pancreatic and liver homeostasis, reduced age-related lesions in brain and kidney tissue, reduced inflammation markers in fat, spleen, liver, kidney and immune cells, reduced circulating MCP-1 (a pro-inflammatory cytokine), and reduced oxidative stress ([Yousefzadeh et al, 2018](#)).

The dose of fisetin used in the acute study was 100mg/kg.

### Cancer

Fisetin is also being investigated as a potential cancer therapeutic. It is reported to induce apoptosis, prevent cell proliferation, prevent metastatic signaling, and reduce inflammation *in vitro* in numerous cancer cell lines. *In vivo* fisetin in combination with other cancer drugs (e.g. cyclophosphamide, cisplatin, and sorafenib) reduced tumor size, reduced angiogenesis, and reduced metastasis greater than either drug alone ([Kashyap et al, 2018](#)).

**Safety:** There is no evidence that fisetin would cause side effects, but no studies in humans have been conducted.

### Types of evidence:

- Two studies of food intake from Japanese women

There is no safety data for fisetin supplementation in humans, though no toxicity in animals has been reported. Two studies in Japanese women suggest an average daily intake of 400-800mg was safe; however, this was conducted from food surveys ([Kimira et al, 1998](#); [Arai et al, 2000](#)). There are no studies on intake of fisetin supplements.

### **Drug interactions:**

Fisetin is metabolized by glucouronidation, so may potentiate the effects of warfarin ([Zhu et al, 2017](#)). Other drug interactions have not been explored.

### **Sources and dosing:**

Fisetin is available from many vitamin sources online. The senolytic clinical trials are using 20mg/kg/day for five days.



### Research underway:

Although there are no clinical trials using fisetin reported as completed on clinicaltrials.gov, five trials are ongoing, including three from the Mayo Clinic looking at alleviation of frailty in elderly or reduction of inflammation ([link](#)). All are likely based on Kirkland's work with fisetin as a senolytic (and two are sponsored by Kirkland) and are using a protocol of 20mg/kg/day for two consecutive days.

### Search terms:

Pubmed, Google:

**fisetin + alzheimer, cognition, longevity, cardiovascular, cancer, atherosclerosis**

Websites visited for

- Clinicaltrials.gov
- Drugs.com (0)

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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality's Rating page](#).*